THE MINISTRY OF HEALTHCARE OF THE REPUBLIC OF KAZAKHSTAN
NSEE "KAZAKHSTAN-RUSSIAN MEDICAL UNIVERSITY"

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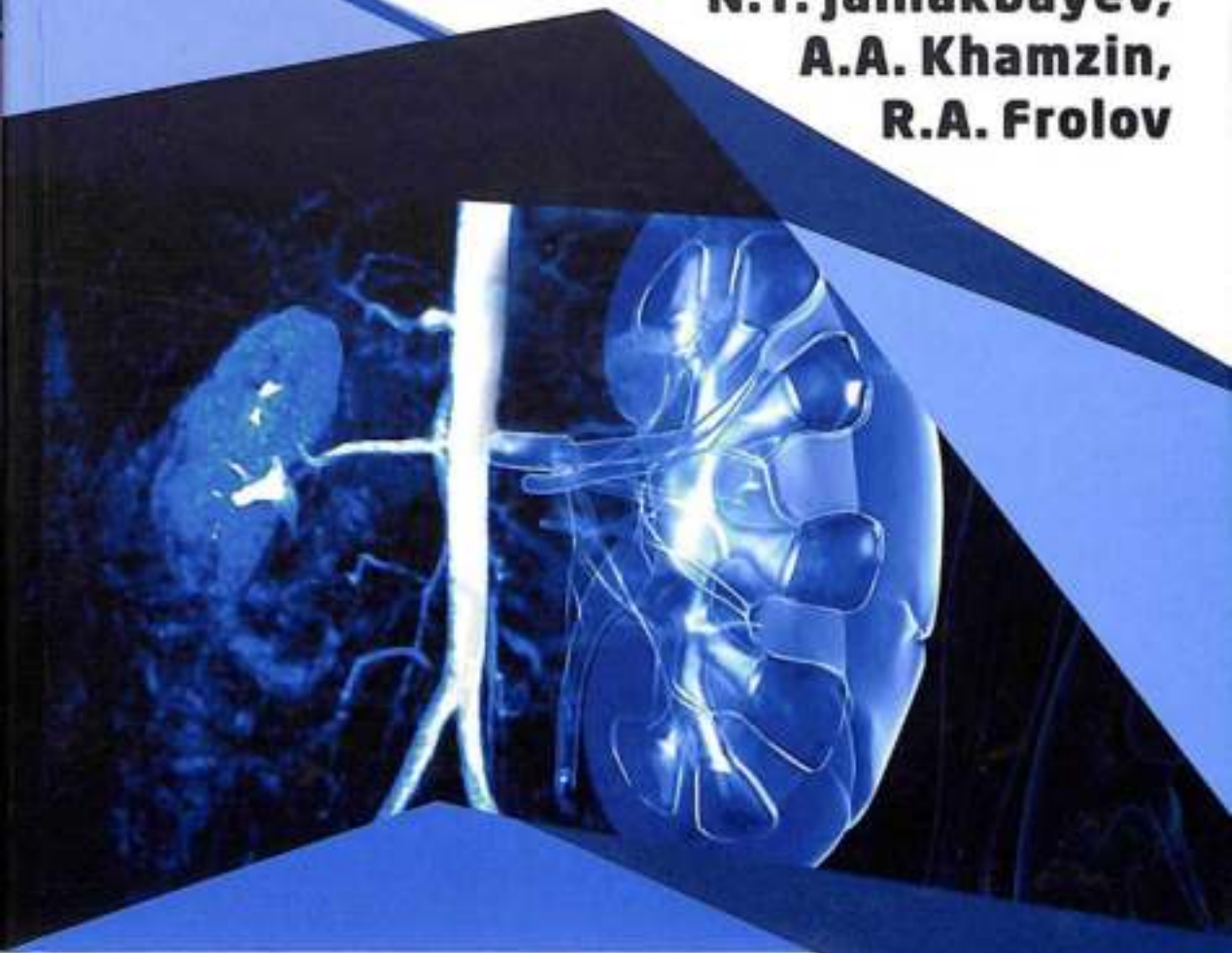
R.A. Frolov



UROLOGY

Textbook

Almaty 2019

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The textbook contains material on the basic concepts in urology, andrology and urogynecology, touches on the pathogenesis, clinical picture, diagnosis, treatment and prevention of the most common diseases in these disciplines. The material is presented in accordance with the State Standard and the Model Curriculum for Urology and Andrology. The textbook was compiled using the recommendations of the European Association of Urology 2014, 2015, 2016, as well as data from the educational site medscape.com.

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The Republican state enterprise on the right of economic management "Republican Center for Healthcare Development" of the Ministry of Healthcare of the Republic of Kazakhstan (№1110 from 14.06.2019) recommends this book as a textbook for higher education institutions.

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List of abbreviations

5-ARIs – 5-alpha-reductase inhibitors

ADT – androgen deprivation therapy

BC – bladder cancer

BCG – bacillus Calmette-Guérin

BPE – benign prostatic enlargement

BPH - benign prostatuc hyperplasia

CT – computed tomography

DRE – digital rectal examination

GFR – glomerular filtration rate

HIFU – high-intensity focused ultrasound of the prostate

HoLEP – Holmium laser enucleation of the prostate

HoLRP - Holmium laser resection of the prostate

HUs – Hounsfield units

IVC – inferior vena cava

LDH – lactate dehydrogenase

LESS – laparoendosopic single-site surgery

LUTS – lower urinary tract symptoms

MIS – minimally-invasive surgery

MRI – magnetic resonance imaging

NOTES – natural orifice transluminal endoscopic surgery

NS – needlescopic surgery

PCa – prostate cancer

PET – positron-emission tomography

PSA – prostate-specific antigen

QoL – quality of life

RCC – renal cell carcinoma

RP – radical prostatectomy

TRUS – transrectal ultrasound

TUIP – transurethral incision of the prostate

TUNA – transurethral needle ablation of the prostate

TURB – transurethral resection of the bladder

TURP – transurethral resection of the prostate

UC – urethral carcinoma

UPJ – ureteropelvic junction

US – ultrasound

UTI – urinary tract infection

VCUG – voiding cystourethrography

VUR – vesicoureteral reflux

Introduction

About a hundred years ago, at the beginning of the twentieth century, urology was an integral part of surgery. Then, with the discovery of X-rays and its properties, the development of diagnostics, urology separated from surgery and became an independent area of medicine. Despite this, a significant component in the treatment of urogenital diseases belongs precisely to surgery. According to the WHO, in the structure of mortality of the population of economically developed countries, diseases of the genitourinary system occupy the 7th place and constitute 2.5–3% of all causes of death. But at the same time, they afflict people of all ages, and especially the able-bodied population, causing temporary disability and disability of a significant number of the able-bodied population, and thus causing enormous economic damage to the country.

Urology should take its rightful place, since urological diseases account for 10–12% of the total morbidity of the population, is one of the leading causes of declining quality of life, disability and mortality, creates a number of social and economic problems.

Continuous medical education requires providing information in the form of modern textbooks and textbooks containing both complete information on the main problems and in the form of brief information for better mastering the material. The special attractiveness of this method of training lies in the most optimal conditions, not only for practical use and assimilation of useful achievements of technical progress, but also for self-monitoring.

The proposed textbook on urology contains the most modern information on new methods of diagnosis and treatment of urological diseases. Some of them are only beginning to be applied in practical activities, but their wide introduction is a matter of the next few years.

The textbook is intended for students (bachelors), and can also be used for interns, residents and medical practitioners.

N.T. Jainakbayev - Doctor of Medical Sciences, Professor,

Rector of the NSEE "Kazakhstan-Russian Medical University"

Theme # 1: Urology as a scientific and clinical discipline. History of urology. Subdisciplines of urology. Minimally-invasive urological surgery

1.1 Urology as a scientific and clinical discipline

Urology, as a clinical discipline, is one of the rapidly improving branches of medicine. A feature of modern urology is the availability of a wide choice of high-tech diagnostic methods, allowing to establish a diagnosis regardless of the stage of the disease, and then to select adequate and effective methods of treatment (conservative and/or operational). Another important point is the fact that urology deals with both prevention and metaphylaxis of diseases of the genitourinary system [3].

It is as a clinical discipline that it will be more correct to call this branch urogenital surgery, although often specialists resort only to medical treatment of diseases of the female urinary and male urinary tract. Thus, unlike nephrology, urology is a surgical discipline. The organs of the urinary system, of which urology is involved, includes the upper (kidneys, ureters) and the lower urinary tract (urinary bladder, urethra), as well as the male genital organs (testicles with appendages, seminal vesicles, prostate, penis). In most countries, urologists are also engaged in adrenal gland surgery.

In addition, there is a special discipline - andrology, which deals only with diseases of the male genital organs.

Urology as an independent discipline was separated from surgery in the second half of the 19th century. However, descriptions of diseases of the genitourinary organs and some methods of treatment (stone-cutting, stone crushing, catheterization) are found in literary archives of Ancient India and the Roman Empire.

Urologic pathologies occur in people of all ages. Eating low-quality foods, sedentary lifestyle, hypothermia, and other unfavorable factors contribute to the development of many diseases of the genitourinary system. Modern methods allow quick and effective solution of the problem associated with various disorders of the genitourinary system.

XX century was marked by the wide introduction of new methods of diagnosis and treatment of urological diseases into medicine. The introduction of equipment based on X-ray radiation, endoscopic equipment, the oncomarker coverage has made its corrections in the diagnosis of diseases of the urogenital organs.

Modern methods have deservedly begun to occupy a leading position in the urology practice. Brachytherapy, endovideosurgical interventions, HIFU of the prostate and robotic operations have become a serious addition to the already available and successfully used minimally invasive techniques in urology.

The urgency of urology is the wide spread of diseases of the urogenital system. So, according to global studies, there are 830 000 deaths per year (1.4% of all causes of death and 1.0% of all disabilities) for kidney and urinary tract diseases [2].

The main urologic diseases are:

1. Inflammatory diseases:

- **Pyelonephritis** (from Greek πύελο|ς pýelos, "basin" + νεφρ|ός nephrós, "kidney" + suffix –itis suggesting "inflammation") is an inflammation of the kidney tissue, calyces, and renal pelvis;
- **Cystitis** (from Greek κύστις — bladder + suffix –itis suggesting "inflammation") is an inflammation of the urinary bladder;
- **Prostatitis** is an inflammation of the prostate gland;
- **Vesiculitis or spermatocystitis**, is a disease that is characterized by inflammation of the seminal vesicles;
- **Urethritis** is an inflammation of the urethra;
- **Balanoposthitis** is an inflammation of the glans of penis;
- **Orchitis** is an inflammation of the testicle;
- **Epididymitis** is an inflammation of the epididymis;
- **Orchiepididymitis** is an inflammation of the testicle and its epididymis.

2. Traumatic injuries of the urogenital system;

3. Oncological diseases of the urogenital system;

4. Benign prostatic hyperplasia;

5. Urolithiasis;

6. Urogenital abnormalities.

1.2 History of urology

Urinary and genital diseases have been around since time immemorial [1].

We know this from the evidence left behind – urinary stones discovered in Egyptian mummies and alongside numerous skeletal remain sand in vestiges of ancient civilisations such as paintings and writing tablets (Fig. 1).

From historical sources, it is known that in the ancient times such urological operations as castration for the purpose of punishment and circumcision for religious reasons were performed, but sometimes they were performed for medical reasons, for example, cystolithotomy by ancient Greeks or catheterization of the bladder in case of urine retention in ancient India.

The famous Greek physician and philosopher Hippocrates in the 5th century BC first documented the basic

Fig. 1 - Urology in Ancient Egypt
(illustration from http://www.circlist.de/bescheidung.jpg)

principles of medical practice, and described the symptoms of many diseases. Later, after 7 centuries, Galen continued research and gave descriptions and urological diseases, and also left recommendations for treatment.

In the Middle Ages in Europe, in connection with the misuse of religion, like other industries, medicine has suffered a decline. However, at that time, its apogee reached the Arab medicine led by Avicenna, which, among other things, described urological diseases [1].

Shortly before the beginning of the Renaissance, barbers were known who, along with the main activity, were also engaged in extracting stones from the bladder (cystolithotomy was performed) (Fig. 2).

Then, with the discovery of the Bacon circulatory system in the 17th and 18th centuries and the invention of the microscope by Leeuwenhoeck, even without becoming an independent discipline, urology took these inventions into its arsenal.

However, these innovations were not widely used, and the spectrum of operations included a catheterization of the bladder, cystolithotomy, and later the doctors of Lusitano and Laguna began trying to bougie the urethra under strictures.

Fig. 2 – Lithotomy in Middle Ages
(illustration from
https://pics.livejournal.com/byzantine_way/pic/002bsc21)

In most cases, in the detection of urological diseases, conservative treatment was prescribed, primarily phytotherapy.

Marianus Sanctus describes a set of tools necessary for the production of stone-cutting, under the name of "large set" ("le grand appareib) (Fig. 3). The latter consists of: a conductor, a razor, a probe, dilators of the wound, stone forceps, a spoon for stones and others.

The novelty of this technique was that he used a conductor inserted into the urethra and a bladder for orientation when producing a cut on the perineum to the left of the midline, whereas before, before the introduction of the conductor, the orientation was performed with the help of fingers inserted into the rectum.

Fig. 3 – "Large set" for stone-cutting
(illustration from http://medwiki.org.ua/article/4212%20184835d3c-1a184835475d383a-69.png)

And only at the beginning of the XIX century were introduced the first tools for conducting urethroscopy and cystoscopy by such scientists as Benique, Lewis and Ficher [1].

However, they faced a huge problem - there was no high-quality lighting to improve the visibility of the area under investigation.

And only in 1877, when electric lighting fixtures began to be introduced, Max Nitze performed the world's first qualitative cystoscopy using a lighting element (lamp). This was a huge breakthrough in urology and endoscopy as a whole, since from that moment the diagnosis of lower urinary tract diseases was much easier. (Fig. 4).

Fig. 4 - M. Nitze's cystoscope
(illustration from http://www.ai-kras.narod.ru/student/1st/endo/endos_000.htm)

This was followed by a series of important modifications of endoscopic instruments. So, after several decades, Albarran invented a special mechanism for adjusting the tip of the cystoscope, as a result of which it became possible to catheterize the ureters (Fig. 5, Fig. 6).

As a consequence, doctors were given the opportunity to receive a portion of urine from each kidney separately, by conducting its microscopy. In particular, this was very important for determining the localization of the inflammatory process (for example, tuberculosis).

Then came the era of X-ray diagnostics:

- 1895 - the discovery of X-rays (Roengten);

- the beginning of the 20th century - visualization of the urinary tract by introducing X-ray positive probes and catheters (Chevassu);

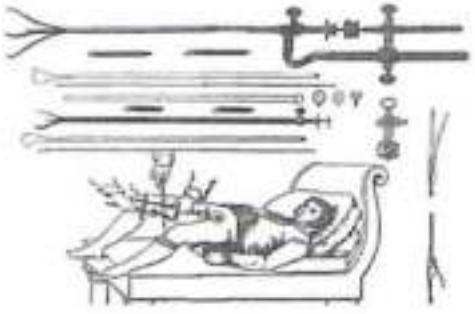


Fig. 5 - First endoscopic operations in urology

(illustration from https://vinnflies.net/preview/3547765/)

- 1929 - introduction of renal arteriography and aortography (Santos);

- 1923 (Rowntree), 1929 (Litchenberg) - development of a technique for intravenous excretory urography.

In parallel with the diagnosis, treatment methods developed, in particular urogenital surgery, and in 1869 a radical nephrectomy (Simon) was performed for the first time, and in 1900 - a prostatectomy (Freyer).

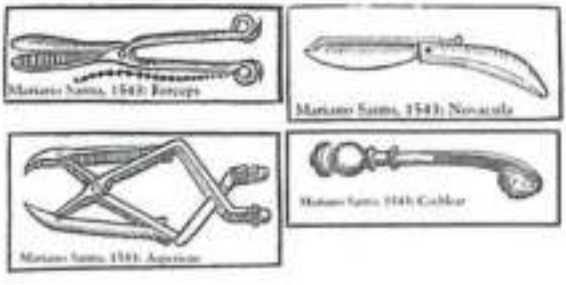
In 1929, with the discovery of penicillin by Fleming, the medical treatment of diseases of the urogenital system began to develop actively.

From the same time, hormone, enzyme, and hemotherapy were rapidly introduced, and many drugs began to be injected intravenously.

Since that moment, urology has become one of the first disciplines to separate from general surgery, taking into account the features of diagnosis and treatment (X-ray diagnostics and endoscopy). So, in 1926, M. Stern performed the first transurethral resection of the prostate, and since then, endoscopic surgery has taken a leading position in urology.

Over the past 3 decades, a number of high-tech diagnostic and treatment methods, presented by urodynamic studies, magnetic resonance and computer tomography, ultrasound diagnostics, the use of radioisotopes, genetic and immunological tests, have been invented and put into practice.

The surgery in urology has undergone tremendous changes. Laparoscopic and robotic surgery was introduced (1991, for the first time



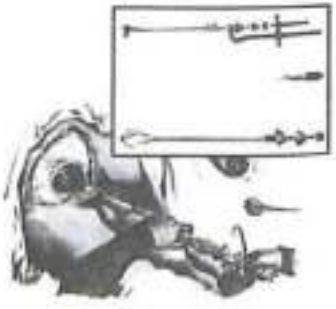


Fig. 6 - First instruments for endourological operations

(illustration from https://www.shermedical.com/images/news/2015-03-12_001_news.jpg)

laparoscopic nephrectomy was performed by Clayman), remote and contact laser lithotripsy in urolithiasis became available, prosthetics (in particular, with severe erectile dysfunction) were actively used.

The newest antibiotics allow us to overcome the resistance of microorganisms to preparations in patients with inflammatory urological diseases.

Kidney transplantation and dialysis therapy for chronic renal failure have become a huge achievement, and oncourology has also made progress by introducing gene, immune, radiotherapy and many other methods into treatment.

In connection with the general availability of the Internet, telemedicine is gaining in speed in urology, making it possible to diagnose diseases and treat patients living far from large settlements. We would especially like to note the fact that urologists were one of the first to use robotic surgery in the treatment (Fig. 7) [7].

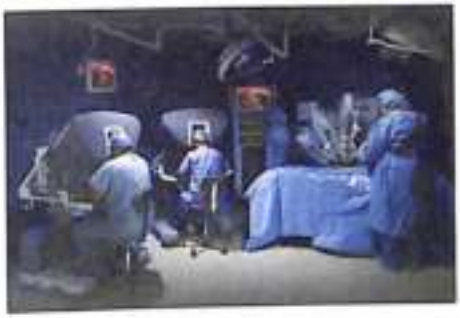


Fig. 7 - Robotic-assisted urology

(Illustration from https://bme-israel.org/sites/default/files/uploads/da_vinci_si_dual_console_or_layout_2_-_low_res.jpg)

And in our opinion, this is only the beginning, because there are still many unresolved problems that will soon be solved by rapid progress in urology.

1.3 Subdisciplines of urology

Narrow specialists of each branch sharpen their skills, improve their qualifications in accordance with their sub-discipline, which allows to achieve good results in the diagnosis and treatment of diseases of the genito-urinary tract [3, 8].

Endourology is a surgical branch of urology, the main feature of which is conducting operations by introducing instruments through the urethra.

At the moment it is one of the main branches used in urology. This technique allows you to perform surgery for BPH, urethral tumors, bladder, prostate, for stones in the urinary tract [4].

Laparoscopy - a branch of urology, the main feature of which is the carrying out of operations by special instruments that are inserted through little skin incisions (0,5-1,0 cm in length). Accordingly, due to the minimal invasiveness, many open

operations have been replaced by laparoscopic ones.

Recently, the introduction of robots has come to the aid of this technique.

Oncourology is involved in the treatment of tumors of the urogenital tract, such as prostate cancer, bladder tumors, penile and testicular cancer, kidney tumors.

Recently oncourologists use in their arsenal of minimally invasive operations, which will be written below.

Neurourology a narrow branch of urology, engaged in the diagnosis and treatment of diseases of the nervous system, causing problems with urination.

For example, traumatic spinal cord injury, Parkinson's disease or stroke are often accompanied by incontinence or urinary retention.

One of the main diagnostic methods in this industry is urodynamic research. According to the diagnosed diagnosis, adequate treatment is prescribed, so, with incontinence urine is used anticholinergic drugs, and if ineffectiveness resorts to botulinum toxin, which is injected into the wall of the bladder.

Pediatric urology deals with the diagnosis and treatment of diseases of the genitourinary system in children.

The most common diagnoses in pediatric urology are hydrocele, cryptorchidism, varicocele, hypospadias, epispadias, enuresis, and vesicoureteral reflux.

Andrology (in our opinion, an independent discipline) stands out as part of urology, engaged in the diagnosis and treatment of diseases of the male sexual system.

The main topics that andrology deals with are: male hypogonadism, male infertility, erectile dysfunction and premature ejaculation, inflammatory diseases of male genital organs [5, 6].

Reconstructive urology is a special branch of urology, whose task is to restore the structure and function of the organs of the genitourinary system.

In such operations and manipulations may need patients who have suffered trauma, iatrogenic damage, as well as severe birth, which leads to a defect in the organs of the urinary tract.

Female urology is the unit of urology, which deals with the diagnosis and treatment of urinary incontinence, prolapse of pelvic organs and a hyperactive bladder.

The female pelvic floor has some differences from the male pelvic floor, therefore, taking into account the physiological and anatomical features, specific diagnostics and then treatment are necessary. A highly specialized specialist in female urology will be able to select adequate treatment according to a specific diagnosis.

Transplant urology. To date, the most frequently transplanted organ is the kidney. For the first time kidney transplantation was conducted in the 50th years of the twentieth century. The essence of this operation is to remove the healthy donor kidney and further transplant it to a recipient suffering from chronic renal failure.

Phthisiourology. Tuberculosis of the genitourinary system is the most frequent extra-local localization of a specific process. According to the data of Brazilian colleagues published in 2008, in patients with tuberculosis of the genitourinary system, a dysfunctional kidney is diagnosed in 27% of cases, and a total renal failure of 7.5%. According to Iranian experts, half of the patients showed ureteral strictures and bladder lesions, as well as lack of kidney function. In Japan, where there is little genitourinary tuberculosis in general, doctors for a long time make an erroneous diagnosis, unable even to admit that in their country someone can get tuberculosis of the kidneys or genitals. As a result, each third patient is removed kidney due to irreversible damage to her tuberculosis.

Thus, urology is an independent clinical discipline dealing with a wide range of diseases of the genitourinary system. More details will be given in the following lectures.

1.4 Minimally-invasive urological surgery

In recent years, every medical discipline has sought to provide survey and treatment services as painlessly as possible. No exception is urology, including, being a surgical branch [7].

Thus, minimally invasive surgery (MIS) is preferred, which includes a huge set of procedures and manipulations, as a result of which open cavity operations are replaced by closed and local procedures with minimal trauma.

The main goal of minimally invasive surgery is to reduce pain during surgery and during the postoperative period, reduce tissue and organ trauma, and shorten hospitalization times, which is important in economic terms. In addition, the gross cosmetic defect observed after open interventions is also eliminated.

Applicable to urology, MIS is represented by laparoscopy, endoscopy, as well as by robotic techniques that allow the diagnosis and treatment of diseases of the urinary tract.

Laparoscopic technique of operations originates from endoscopy, when using a tool and a light source, the mucous membrane of the rectum, the uterine cavity and the bladder were examined. Pioneers in the field of laparoscopy are gynecologists and surgeons who began to perform operations as early as the beginning of the 20th century, and only in June 1990 the first urological laparoscopic operation was performed -

nephrectomy for kidney cancer. And now, after 3 decades, laparoscopic urology is being introduced more and more and becomes more and more standard for diagnosis and treatment.

The constantly improved technique of conducting such operations aims to reduce the percentage of complications, shorten the period of rehabilitation after surgery, and to achieve the best cosmetic result. Instead of the traditionally used 3-6 trocars necessary to provide access to internal organs and tissue dissection, trocars, laparoscopes and surgical instruments of smaller sizes and diameters are increasingly being used to minimize trauma to organs and tissues. The smallest cosmetic defect remains after operations through natural openings, the so-called transluminal surgery or NOTES - natural orifice transluminal endoscopic surgery.

The topic of minimally invasive surgery in urology is so urgent that a special working group was created that combined NOTES and laparoendosopic single-site surgery (LESS) concepts under one term in order to clarify the experts.

Below, the main subtypes of minimally invasive urology will be described in detail.

NOTES (natural orifice transluminal endoscopic surgery). An amazing technique, the basic principle of which is to conduct operations through natural openings, that is, without cutting the skin of the abdominal wall.

Historically, the first was access through the incision of the stomach wall, but at present access to the abdominal cavity and retroperitoneal space is increasingly carried through the incision of the vaginal wall, bladder and rectum. Thus, first, a cosmetic defect is eliminated, because there are no gross scars left on the surface of the body, and secondly, complications such as a hernia or suppuration of a postoperative wound that often occur after traditional laparoscopic operations are absent after the operation. This is especially important for patients in the high-risk group.

Similar operations began to be introduced relatively recently (only 2 decades). Then nephrectomy was performed through transvaginal access (in laboratory animals). Of course, most transluminal operations are performed in gynecology and surgery, for example, transvaginal tubal ligation, partial hysterectomy, and cholecystectomy.

Given the success in the conducted operations on animals, several groups of scientists began to apply such accesses in humans (peritoneoscopy, cholecystectomy, appendectomy and others).

A highly progressive and promising industry could not stop development, and due to the rapid pace of improvement, a special consortium was organized (the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) Working

Group) whose task was to develope tactics for conducting transluminal patients undergoing surgery.

So, a number of issues solved by this community consisted of prevention of infection, ways of wound closure and suturing, as well as treatment of possible complications. Thus, a number of recommendations have been made about antibiotic prophylaxis, and even special devices have been designed to cover the defect of the hollow organ. An interesting fact is that some researchers allowed an independent closure of the defect.

The working group led by Clayman conducted a unique operation - nephrectomy using a single port, introduced through transvaginal access (in laboratory animals). The diameter of the installed port was only 1.2 cm, through which the four-channel platform (TransPort Multi-Lumen Operating Platform) was introduced.

Another technique was suggested by a group of scientists led by Lima, who performed nephrectomy through 2 accesses (transvesical and transgastric).

Having gained great experience in this field, the members of the working group of the consortium became not only the authors of new terminology and techniques, but also gave the opportunity to learn this branch of surgery to other specialists from around the world.

Undoubtedly, there are unanswered questions, for example, there is no reliable data on the level of pain reduction in the area of a postoperative wound, as well as the occurrence of an infectious process in the abdominal cavity as a result of perforation of the hollow organ.

A special issue is for people with obesity, because they have difficulty accessing the body due to the large amount of visceral fat. In addition, transluminal surgery requires special skills, special tools, and, of course, technically difficult. Therefore, there is a wide field for research, and perhaps one of the readers of this textbook will become a high-level specialist in minimally invasive surgery.

LESS (laparoendoscopic single-site surgery). Standard laparoscopic operations are performed using 3 or more ports, one of which is reserved for the camera and several ports for instruments.

Fig. 8 – Laparoendoscopic single-port surgery
(illustration from http://www.journalofeau.com/articles/2011/7/1/images/JMin Access-2010-7-1-a-73368_f15.jpg)

But the dynamically developing industry of medical equipment

production brings to the attention the newest tools, the use of which reduces the traumatization. At the moment, a technique is being introduced to introduce several tools via 1 port (Fig. 8).

Pioneers in this area performed cholecystectomy and appendectomy, using just one port, introducing it transabdominally. The first to introduce single-port laparoscopy in urology were Rana and colleagues who performed nephrectomy and ureterolithotomy (transperitoneally) using the R-Port® SPA system.

This system was successfully used by a group of researchers led by Desai, who twice performed nephrectomy and pyeloplasty, introducing the port transumbilically. Undoubtedly, not standard laparoscopic instruments were used, but special, in particular, a two-millimeter needle port for suturing. Later, the same working group performed a partial nephrectomy using a similar one-port technique.

Implemented in practice laparoscopic (single-port) Uni-X system, a team of specialists led by Kaouk conducted 4 sacrocolpopexies, 1 wedge-shaped resection of the kidney, 1 radical nephrectomy, 4 renal cryotherapies and 4 radical prostatectomies.

To date, Desai and others have reported successful single-port transvesical enucleations of the prostate with a volume greater than 80 cm^3.

Explicit advantages of LESS - in carrying out the operation using only one port, however, the range of movement of tools is substantially limited. The scar after such an operation is hidden in the navel opening and is almost invisible, which is of considerable importance when performing operations for young women.

A comparative study of single-port and standard laparoscopic nephrectomy revealed the same efficacy of both types of operations. Of course, taking into account the cosmetic effect LESS is more preferable, while a larger study is needed to identify all the advantages and disadvantages of this technique.

NS (needlescopic surgery). Modified laparoscopy, which uses not 5-10 mm ports, but ports with a diameter of less than 3 mm. Initially, this technique was used by gynecologists, but primarily for diagnosis, but later it was also used for therapeutic purposes.

Of course, the technique loses its meaning when performing radical operations with the removal of the organ, to extract which it is necessary to expand the incision.

Such operations minimize the risks of forming postoperative hernias, leave behind wounds that do not require suturing, and, as a result, do not leave a gross cosmetic defect. Among the shortcomings, it can be noted that instruments of this diameter (less than 3 mm) are very fragile and require special skills from the surgeon.

With the help of the NS, Soble and Gill successfully carried out nephrerethectomy and adrenalectomy

(standard + acupuncture ports). Thus, during the carrying out of the needleoscopic adrenalectomy, blood loss, operation time and hospitalization time were reduced in comparison with standard laparoscopy.

Unfortunately, due to technical difficulties and expensive equipment, this method was not widely implemented in urological practice, but some instruments are successfully used in LESS.

FR (flexible robots). Conducting minimally invasive operations requires the surgeon to have sharpened technical skills. In conditions of limited review, lack of tactile perception, when precise coordination of hands and eyes is needed, robotic surgery comes to the rescue.

Flexible robots seem to feel the environment, thereby facilitating the fulfillment of tasks.

Urology

Urology, as a clinical discipline, is one of the rapidly improving branches of medicine. A feature of modern urology is the availability of a wide choice of high-tech diagnostic methods, allowing to establish a diagnosis regardless of the stage of the disease, and then to select adequate and effective methods of treatment (conservative and/or operational). Another important point is the fact that urology deals with both prevention and metaphylaxis of diseases of the genitourinary system.

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Endourology is a surgical branch of urology, the main feature of which is conducting operations by introducing instruments through the urethra.

Laparoscopy - a branch of urology, the main feature of which is the carrying out of operations by special instruments that are inserted through little skin incisions (0,5-1,0 cm in length).

Urologic oncology. Oncourology is involved in the treatment of tumors of the urogenital tract, such as prostate cancer, bladder tumors, penile and testicular cancer, kidney tumors.

Neurourology a narrow branch of urology, engaged in the diagnosis and treatment of diseases of the nervous system, causing problems with urination.

Pediatric urology deals with the diagnosis and treatment of diseases of the genitourinary system in children.

Andrology stands out as part of urology, engaged in the diagnosis and treatment of diseases of the male sexual system. (in our opinion, andrology is an independent discipline (Khamzin A., Frolov R.)).

Reconstructive urology is a special branch of urology, whose task is to restore the structure and function of the organs of the genitourinary system.

Female urology is the unit of urology, which deals with the diagnosis and treatment of urinary incontinence, prolapse of pelvic organs and a hyperactive bladder.

Transplant urology. To date, the most frequently transplanted organ is the kidney.

Phthisiourology. Tuberculosis of the genitourinary system is the most frequent extra-local localization of a specific process.

Minimally-invasive urological surgery

Minimally invasive surgery (MIS) is preferred, which includes a huge set of procedures and manipulations, as a result of which open cavity operations are replaced by closed and local procedures with minimal trauma. The main goal of minimally invasive surgery is to reduce pain during surgery and during the postoperative period, reduce tissue and organ trauma, and shorten hospitalization times, which is important in economic terms.

NOTES (natural orifice transluminal endoscopic surgery). An amazing technique, the basic principle of which is to conduct operations through natural openings, that is, without cutting the skin of the abdominal wall.

LESS (laparoendoscopic single-site surgery). At the moment, a technique is being introduced to introduce several tools via 1 port.

NS (needlescopic surgery). Modified laparoscopy, which uses not 5-10 mm ports, but ports with a diameter of less than 3 mm.

FR (flexible robots). In conditions of limited review, lack of tactile perception, when precise coordination of hands and eyes is needed, robotic surgery comes to the rescue.

Theme # 2: Anatomy and physiology of the urogenital system.

Urogenital apparatus includes the urinary (organa urinaria) and genital (organa genitalia) organs. These organs are closely related to each other in terms of their development anatomical and functional state, which is the reason for their unification under the name "genitourinary apparatus" [9].

2.1 Kidneys

The kidneys (Fig. 9) are a paired organ of the bean-shaped form, which is located in the retroperitoneal space (the lumbar region) [9, 10].

Skeletaltopia of the kidneys: the right one is at the level of Th XII – L III, and the left one is located at the level of Th XI - L II. Thus, the right kidney is below the left (in connection with the location of the liver): the left kidney is split in half by 12th rib, and on the right it is on the border of the upper and middle third.

Speaking about the location, it can be noted that, first, the left kidney is above the right kidney, secondly, the upper poles are located closer to the spine (medially) and posteriorly than the lower ones.

The average size of the kidneys is 100-120 mm in length, 50-60 mm in width and 30-40 mm in thickness. In women, the weight of the kidneys is about 135, and for men it is 150 g.

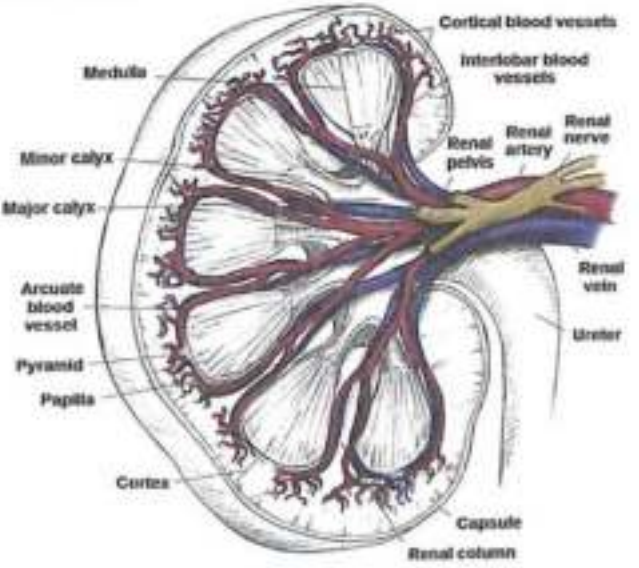

Fig. 9 - Kidney anatomy

(illustration from https://www.ebmconsult.com/content/images/Anatomy/Kidney%20renal%20section%202.6.jpg)

Kidneys are a multifunctional organ, details of which functions will be written in the next chapter.

There are the following main functions:

1. Filtration and isolation of slags formed in the course of metabolism;

2. Regulation of basic electrolytes (potassium, sodium, chlorine), water and constancy of the pH of the internal environment;

3. Regulation of hemopoiesis;

4. Regulation of blood pressure;

5. Reverse absorption of amino acids and glucose;

6. Participation in hormonal metabolism (erythropoietin, vitamin D, calcitriol).

The kidney is divided into segments, which is due to the peculiarities of renal artery branching.

There are following segments (Fig. 10):

- the upper segment (segmentum superius);
- upper front segment (segmentum superius anterius);
- the lower segment (segmentum inferius);
- lower front segment (segmentum inferius anterius);
- posterior segment (segmentum posterius).

A place where the kidney contains elements of the kidney , (the renal artery, vein and ureter) is called the hilus (portal) of the kidney.

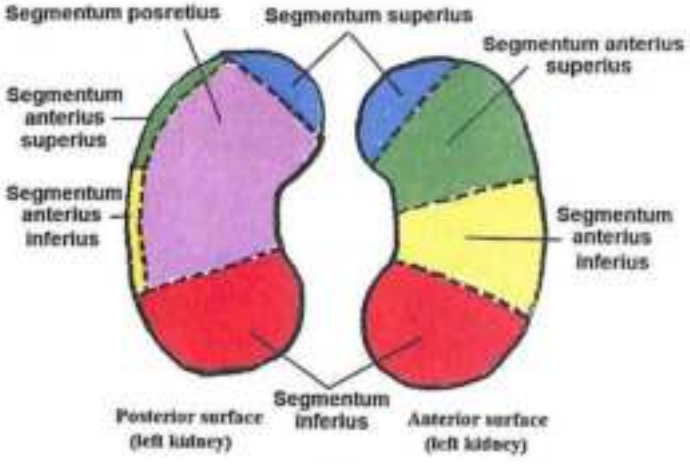

Fig. 10 - Kidney segments

(Illustration from http://vmede.org/sait/content/Anatomija_topograficheskaja_nikolis_2009_2/7_files/mb4_013.jpeg)

The fixing apparatus of the kidney includes:

- Peritoneal folds - ligaments. The right kidney is supported by the duodenum-kidney and hepatic-renal ligaments, and the left kidney by the diaphragmatic-ligament ligament.
- Vascular renal pedicels, but they do not play a special role in fixing the kidneys, because when the kidneys are lowered, they can lengthen.
- Rear-spine and prefences and fascia - with their help the kidneys are attached to the diaphragm.
- Fatty capsule of the kidney, which, together with the fascia, performs both fixative and protective functions.
- Mesentery of descending and ascending colon.
- Kidney receptacles are funnel-shaped indentations.

The kidneys are quite mobile, and the amplitude of their movement is on the average 3.5 centimeters, but within the limits of the norm can reach 5 centimeters.

Outside, each kidney is surrounded by a special layer of connective tissue (the renal capsule), which creates a framework that limits the soft spongy parenchyma. And outside the kidney capsule is an adipose (fat) capsule, which creates additional protection and fixation [10, 11, 13].

Kidney syntopy (their relationship to neighboring organs) (Fig. 11):

- Above the kidneys are the adrenal glands (above the upper poles);
- In front of the upper pole of the left kidney is the spleen, from which there are splenorenal (lienorenal) ligaments;
- Even more medial, in front of the upper pole of the left kidney is the greater curvature of the stomach;
- On the border of the upper and middle third of the left kidney in front (near the gate of the kidney) is the tail of the pancreas;
- In front of the lower pole of the left kidney is a jejunum;
- Near the edge (margo) of the left kidney, on the border of the middle and upper third of it is the left bend of the colon, and just below - its descending part;
- Almost the entire upper pole of the right kidney (front) covers the liver;
- The area of the hilus of the right kidney is bordered by the duodenum;
- The anterior surface of the lower pole of the right kidney is bordered by the loops of the small intestine;

- Both kidneys seem to sit on the psoas muscle and the quadratus lumborum muscle;
- A diaphragm is located behind the two kidneys.

Each apex connects to a minor calyx, a small hollow tube that collects urine. The minor calyces merge to form 3 larger major calyces, which further merge to form the hollow renal pelvis at the center of the kidney.

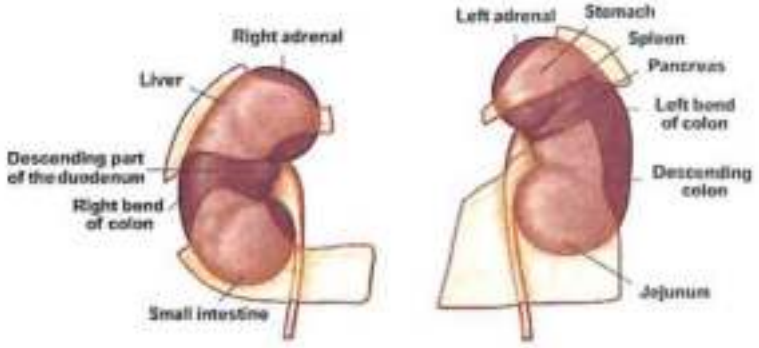

Fig. 11 - Syntopy of kidneys

illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSFTjUhAHgfUsBdbnAtkBJp8dvGq2aiUfvQCEadH0/jVX8/s

There are cortical and medullary substances of the kidneys.The cortex is located on the periphery and between the pyramids (columnae renalis, c. Bertinii), the medulla is located in the center and is represented by pyramids (piramides renalis, Malpigii p.).

Deep to the renal capsule is the soft, dense, vascular renal cortex. Seven cone-shaped renal pyramids form the renal medulla deep to the renal cortex.

The renal pyramids are aligned with their bases facing outward toward the renal cortex and their apexes point inward toward the center of the kidney.

The renal pelvis exits the kidney at the renal hilus, where urine drains into the ureter.

Blood supply, lymphatic drainage and innervation

The renal artery in the kidney sinus is divided into ventral and dorsal branches. They give interlobar arteries located in the renal pillars. At the level of the bases of the pyramids, the interlobar arteries are divided into arc arteries, from which the interlobular arteries radiate at the same distance from each other. Bringing (afferent) arterioles branch off from these vessels, which then disintegrate into capillaries forming the renal glomerulus (Fig. 12).

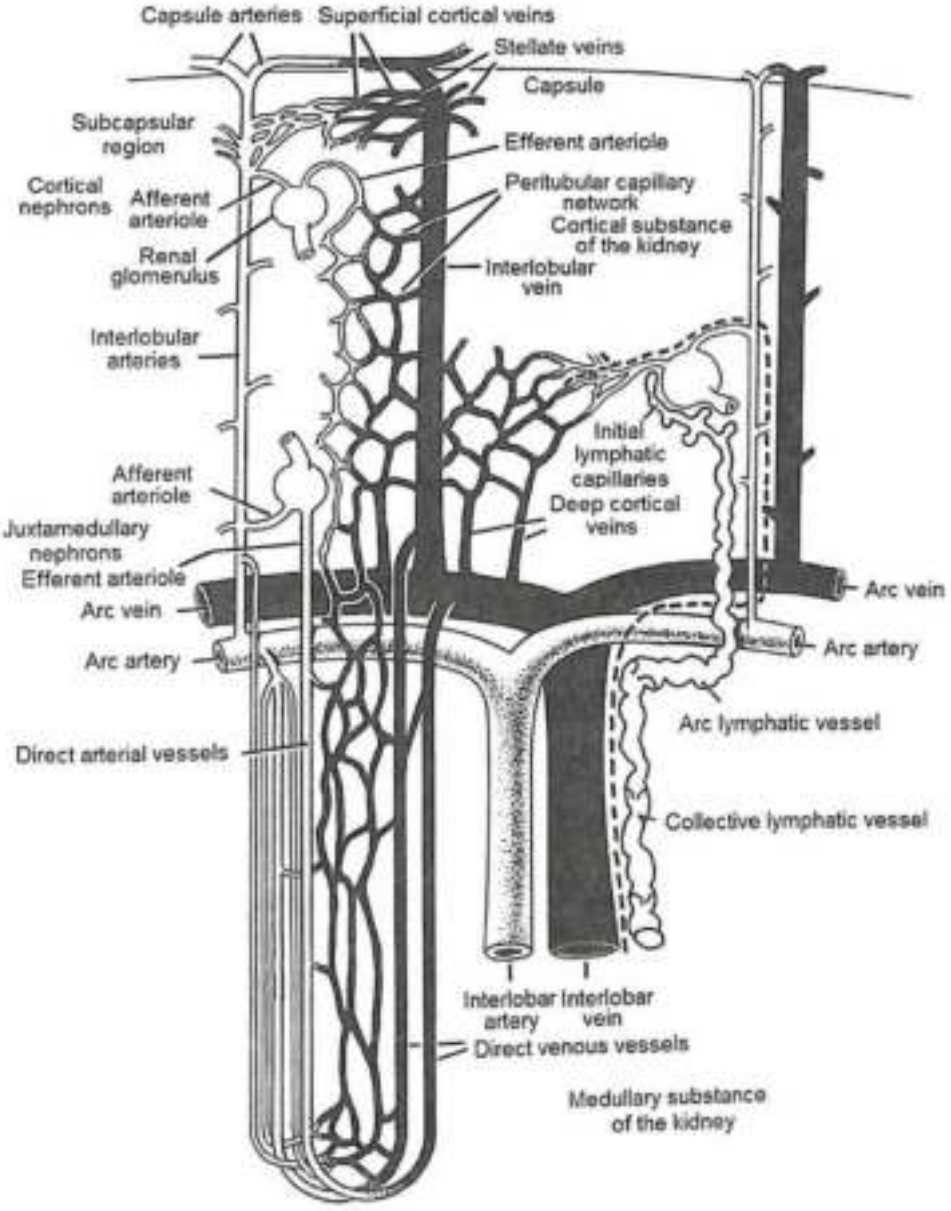

Fig. 12 – Blood supply and lymphatic drainage of the kidney
(illustration from http://[illegible])

The glomerular capillaries, when joined together, form an efferent arteriole.

The outgoing arterioles surround the cortical nephrons, breaking down into the peritubular capillary network that flows into the interlobular vein and radially oriented deep cortical veins. The latter carry blood into the arc vein, which, in turn, flows into the interlobar vein [12].

The carrying arterioles that surround the juxtamedullary nephrons penetrate the medulla at various levels as descending thin-walled non-branching direct arterial vessels. They make a hairpin loop and turn upwards to the cortex, continuing in the form of direct venous vessels flowing into the interlobular and arcuate veins. The interlobular arteries in the subcapsular region pass into an anastomotic-rich capillary network, from which superficial cortical veins eventually form. These veins are combined into stellate veins, which flow into interlobular veins.

Some interlobular arteries penetrate the capsule and supply the organ capsule as capsule arteries. Between them and the interlobular veins there are anastomoses.

Most of the medulla (about 90%) of the kidney is supplied by direct arterial vessels of the juxtamedullary nephrons; the remaining 10% feed on the branches of the arcuate and interlobular arteries — true direct vessels, vasa recta vera, which penetrate the brain substance of the kidney, then form a loop and flow through the direct venous vessels into the arcuate and interlobular veins.

Arc and interlobular arteries are muscular-type arteries that do not form at all or very little anastomoses with adjacent arteries.

Lymph flows mainly in nodi lymphatici lumbales, aortici laterals, cavales laterals, coeliaci, iliaci interni, phrenici inferiors. The initial lymphatic capillaries arise in the cortical substance of the kidney near the juxtamedullary complex. Then they go along with the interlobular blood vessels to the arc blood vessels. The first valves and smooth muscle cells appear in the arc lymphatic vessels at the level of the cortico-cerebral border. Collective lymphatic vessels leave the kidney in the area of the gate, passing in parallel with the interlobar blood vessels.

There are probably no primary lymphatic capillaries in the medulla. Nevertheless, some authors believe that there are several lymphatic vessels that carry the lymph to the arc lymphatic vessels of the outer zone.

In the course of the organ, nerve fibers form the **renal plexus (plexus renalis)**. Afferent innervation is provided by the sensitive fibers of the anterior branches of the lower thoracic and upper lumbar spinal nerves, as well as by the fibers of the renal branches of the vagus nerve (r. renales n. vagi). Parasympathetic innervation occurs from the fibers rr. renales n. vagi, and sympathetic forms from ganglia aortorenalia from plexus coeliacus

(plexus aorticus abdominalis) along the course of the renal arteries.

Function of kidneys

The kidneys play a leading role in the release of nonvolatile end products of metabolism and foreign substances from the blood into the internal environment of the body. In the process of metabolism of proteins and nucleic acids, various products of nitrogen metabolism are formed (urea, uric acid, creatinine, etc.) [11].

The catabolism of purine bases in the human body stops at the level of formation of uric acid, in the cells of some animals there are enzymes that ensure the breakdown of purine bases to CO2 and ammonia. Uric acid in the human kidney is filtered in the glomeruli, and then reabsorbed in the tubules; part of the uric acid is secreted by the cells into the lumen of the nephron. The usually excreted uric acid fraction is quite low (9.8%), which indicates the reabsorption of a significant amount of uric acid in the tubules. The interest in studying the mechanisms of uric acid transport in the renal tubules is due to the sharply increased incidence of gout disease, in which the uric acid metabolism is disturbed.

Creatinine produced during the day, the source of which is creatine phosphoric acid, is excreted by the kidneys. Its daily excretion depends not so much on the consumption of meat from food, but on the muscle mass of the body. Creatinine, like urea, is freely filtered in the glomeruli, with urine all the filtered creatinine is excreted, while urea is partially reabsorbed in the tubules.

In addition to these, there are many different substances that are constantly removed by the kidney from the blood. It is possible to judge what substances the kidney removes or destroys when studying the composition of the blood in people with remote kidneys. In their blood, in addition to urea, creatinine, uric acid, hormones (glucagon, parathyroid hormone, gastrin), enzymes (ribonuclease, renin), indole derivatives, glucuronic acid, etc. accumulate.

It is essential that physiologically valuable substances with their excess in the blood begin to be excreted by the kidney. This applies to both inorganic substances, which were discussed above in the description of the osmosis, the volumo- and ionoregulatory functions of the kidneys, as well and to organic substances - glucose, amino acids. Increased excretion of these substances can be observed under pathological conditions even at normal concentrations in the blood, when the work of cells reabsorbing a particular filtered substance from a canalicular fluid into the blood is disrupted.

Kidney endocrine function. The kidney produces several biologically active substances, allowing it to be regarded as an endocrine organ. Granular cells of the juxtaglomerular apparatus release renin into the blood when the blood pressure in the kidney decreases, the sodium content in the body decreases, and when a person transitions from a horizontal to a

vertical position. The level of renin release from cells into the blood varies depending on the concentration of Na^+ and Cl^- in the area of a dense spot of the distal tubule, providing regulation of electrolyte and glomerular canalone balance. Renin is synthesized in the granular cells of the juxtaglomerular apparatus and is a proteolytic enzyme. In plasma, he cleaves from the angiotensinogen, which is mainly in the ag globulin fraction, a physiologically inactive peptide consisting of 10 amino acids, angiotensin I. In the blood plasma under the influence of the angiotensin-converting enzyme, 2 amino acids are cleaved from angiotensin I, and it turns into angiotenzin II, a vasoconstrictor active. It increases blood pressure due to the narrowing of blood vessels, increases the secretion of aldosterone, increases the feeling of thirst, and regulates the reabsorption of sodium in the distal tubules and collecting tubes. All these effects contribute to the normalization of blood volume and blood pressure.

In the kidney, plasminogen activator, urokinase, is synthesized. In the medulla of the kidney prostaglandins are formed. They are involved, in particular, in the regulation of renal and general blood flow, increase the excretion of sodium in the urine, and reduce the sensitivity of tubule cells to ADH. The kidney cells extract from the blood plasma the prohormone formed in the liver - vitamin D3 and turn it into a physiologically active hormone - the active form of vitamin D3. This steroid stimulates the formation of calcium-binding protein in the intestine, promotes the release of calcium from the bones, and regulates its reabsorption in the renal tubules. The kidney is the site of production of erythropoietin, which stimulates erythropoiesis in the bone marrow. In the kidney, bradykinin is produced, which is a powerful vasodilator.

Metabolic kidney function. The kidneys are involved in the metabolism of proteins, lipids and carbohydrates. The concepts of "kidney metabolism", i.e. the metabolic process in their parenchyma, due to which all forms of kidney activity and the metabolic function of the kidneys are carried out, should not be confused.

This function is due to the participation of the kidneys in ensuring the constancy of the concentration in the blood of a number of physiologically significant organic substances. In the renal glomeruli, low molecular weight proteins and peptides are filtered. The cells of the proximal nephron split them into amino acids or dipeptides and are transported through the basal plasma membrane into the blood. This helps to restore the body of amino acids in the body, which is important when there is a lack of proteins in the diet. With kidney disease, this function may be impaired.

The kidneys are able to synthesize glucose (gluconeogenesis). With prolonged fasting, the kidneys can synthesize up to 50% of the total amount of glucose formed in the body and entering the blood. The kidneys are the site of the synthesis of phosphatidyl inositol, an essential component of plasma membranes. For energy

consumption of the kidney can use glucose or free fatty acids. With a low level of glucose in the blood, kidney cells consume more fatty acids, with hyperglycemia, glucose is predominantly cleaved. The value of the kidneys in lipid metabolism is that free fatty acids in kidney cells can be incorporated into triacylglycerol and phospholipids and in the form of these compounds enter the blood.

Homeostatic kidney functions. There are special systems of reflex regulation, including specific receptors, afferent pathways and nerve centers where information is processed, to maintain the constancy of the volume and composition of the internal environment and, above all, blood. Commands to the kidney come through efferent nerves or humoral.

In general, the restructuring of the kidney, its adaptation to constantly changing conditions are mainly determined by the effect on the glomerular and tubular apparatus arginine-vasopressin [antidiuretic hormone (ADH)], aldosterone, parathyroid hormone and a number of other hormones.

The role of the kidneys in osmosis and volume regulation. The kidneys are the main organ of osmoregulation. They provide the excretion of excess water from the body in the form of hypotonic urine with increased water content (overhydration) or save water and excrete urine, hypertonic in relation to blood, with dehydration of the body (dehydration).

After drinking water or when it excess in the body decreases the concentration of dissolved osmotically active substances in the blood and decreases its osmolality. This reduces the activity of central osmoreceptors located in the supraoptic nucleus of the hypothalamus, as well as peripheral osmoreceptors present in the liver, kidney and other organs, which leads to a decrease in ADH secretion by the neurohypophysis and an increase in water excretion by the kidney. The central osmoreceptors were discovered by the English physiologist Verney (1947), and the concept of the osmoregulating reflex and peripheral osmoreceptors was developed by A. G. Ginetsinsky.

When dehydration of the body or introduction of a hypertonic NaCl solution into the vascular bed, the concentration of osmotically active substances in the blood plasma increases, osmoreceptors are excited, the secretion of ADH increases, water absorption in the tubules increases, urine output is released and osmotically concentrated urine is secreted. In the experiment it was shown that, in addition to osmoreceptors, the secretion of ADH is stimulated by natrioreceptors. When a hypertonic solution of NaCl was introduced into the region of the third ventricle of the brain, an antidiuresis was observed, but if hypertonic sucrose solution was introduced in the same place, then the urine output does not decrease.

Osmoreceptors are highly sensitive to changes in the concentration of osmotically active substances in the blood plasma. With

an increase in plasma concentration of osmotically active substances by 1% (about 3 mosmol/kg H20), the concentration of arginine-vasopressin in human blood plasma increases by 1 pg/ml. Increasing the concentration of osmotically active substances in plasma by 1 mosmol/kg H2O causes, due to the release of ADH, an increase in the osmotic concentration of urine by almost 100 mosmol/kg H2O, and the transition from the state of water diuresis to the maximum osmotic concentration of urine requires a 10-fold increase in the activity of ADH in the blood - from 0.5 to 5 pg/ml.

In addition to osmosis and natrioreceptors, the level of secretion of ADH determines the activity of totaloreceptors that perceive changes in the volume of intravascular and extracellular fluid. Leading in the regulation of secretion of ADH have receptors that respond to changes in the voltage of the vascular wall in the area of low pressure. First of all, these are left atrial receptors, the impulses from which are transmitted to the central nervous system (CNS) via afferent fibers of the vagus nerve. With an increase in the blood supply of the left atrium, the volumoreceptors are activated and the secretion of ADH is inhibited, which causes an increase in urine output. Since the activation of the volume receptors, in contrast to osmoreceptors, is due to an increase in the volume of fluid, i.e., an increased content of water and sodium salts in the body, the stimulation of the volume receptors leads to an increase in kidney excretion of not only water but also sodium. These processes are associated with the secretion of natriuretic hormone, a decrease in the secretion of renin, angiotensin, aldosterone, while the tone of the sympathetic nervous system decreases, resulting in reduced reabsorption of sodium and increased natriuresis and urinary output. Ultimately, the volume of blood and extracellular fluid is restored.

The role of the kidneys in the regulation of the ionic composition of blood. The kidneys are the effector organ of the ion homeostasis system. In the body there are systems for regulating the balance of each of the ions. Specific receptors, such as the natrioreceptors, have already been described for some ions. Reflex regulation of ion transport in the renal tubules is carried out by both peripheral and central nervous mechanisms.

Regulation of reabsorption and secretion of ions in the renal tubules is carried out by several hormones. Sodium reabsorption increases in the end parts of the distal segment of the nephron and collecting tubules under the influence of the hormone of the adrenal cortex, aldosterone. This hormone is released into the blood by reducing the concentration of sodium in the blood plasma and reducing the volume of circulating blood. The natriuretic hormone is involved in enhancing the excretion of sodium by the kidney, one of the places of formation of which is the atrium. With an increase in the volume of circulating blood, an increase in the volume of extracellular fluid in the body, secretion of this peptide hormone into the blood increases.

The secretion of potassium in the distal segment and the collecting tubules increases aldosterone. Insulin reduces potassium excretion. Alkalosis is accompanied by an increase in the excretion of potassium, and in acidosis, kaliuresis decreases.

When the concentration of calcium in the blood decreases, the parathyroid glands secrete parathyroid hormone, which helps to normalize the level of calcium in the blood, in particular due to an increase in its reabsorption in the renal tubules and release from the bone. With hypercalcemia, as well as under the influence of gastrin (or a similar substance) produced in the digestive tract during calcium absorption, the release of para-follicular thyroid cells calcitonin into the blood is stimulated, which contributes to a decrease in plasma Ca^{2+} concentration due to an increase in kidney excretion and Ca^{2+} transition bone. The active forms of vitamin D3, in particular 1.25-(OH) 2-cholecalciferol, are involved in the regulation of Ca^{2+} metabolism, which are formed in the kidney. In the renal tubules, the reabsorption of Mg^{2+}, Cl^{-}, as well as trace elements is regulated.

The role of the kidneys in the regulation of the acid-base state. The kidneys are involved in maintaining constancy of H^{+} concentration in the blood, secreting acidic metabolic products. The active reaction of urine in humans and animals can vary very drastically, depending on the state of the acid-base state of the body. The concentration of H^{+} in acidosis and alkalosis varies almost 1000 times, with acidosis, the pH can drop to 4.5 and with alkalosis, it can reach 8.0. This contributes to the involvement of the kidneys in stabilizing the pH of the blood plasma at the level of 7.36. The mechanism of urine acidification is based on the secretion of H^{+} tubule cells. In the apical plasma membrane and the cytoplasm of cells of different nephron sections, there is an enzyme carbonic anhydrase (CA) that catalyzes the hydration reaction of CO2: CO2 + H2O2 <H2C03> <H + + HCO3-.

When the meat is fed, more acid is formed and the urine becomes acidic, and when the plant food is consumed, the pH shifts to the alkaline side. With intensive physical work from the muscles in the blood enters a significant amount of lactic and phosphoric acids and kidneys increase the excretion of "acidic" products with urine.

Atrial natriuretic peptide (ANP) is a hormone produced by cardiac muscle cells in the atria of the heart. These cells produce ANP in response to high levels of sodium in the blood or increased blood pressure. In the kidneys, ANP increases the glomerular filtration rate so that more blood plasma is forced into the glomerular capsule and into the renal tubules. ANP also removes some solutes from the cells of the renal medulla, making the loop of Henle less efficient in reabsorbing water and ions from the filtrate. The net result of ANP is that more sodium and water end up being excreted into urine, blood volume decreases, and blood pressure decreases as well.

2.2 Ureters

The renal pelvis, narrowing, passes into the ureter (Fig. 13), which is a long, cylindrical tube connecting the renal pelvis to the bladder. There are almost equal two of his department: abdominal (pars abdominalis) and pelvic (pars pelvina) [13].

The length of the ureter 27–32 cm; the right ureter is slightly shorter than the left. About 2 cm of its length falls on the intravesical part. Its diameter is uneven throughout and ranges from 0.5 to 1 cm.

Diameter, it's unequal throughout, extended portions alternate with constrictions. There are three contractions: at the place of transition of the pelvis to the ureter, at the level of the ureter crossing the iliac vessels

In places of narrowing, the diameter of the ureter is 2-3 mm; here, the urinary stones coming out of the pelvis are most often delayed. In dilated areas, the diameter of the ureters is 0.5-1 cm.

Ureters lie on m. psoas with its fascia and in its lower part of the lumbar region cross the vasa testicularis or vasa ovarica, located inwards from them.

At the level of the terminal line, the ureters cross the iliac vessels, located anterior to them. Above the place of the intersection with the iliac vessels, moisers with their posterior surface are in contact with n. Genitofemoralis. This affinity explains the irradiation of pain when a stone passes through the ureter into the groin area, into the scrotum and penis in men, and in the labia majora in women.

The inferior vena cava is located medially from the right ureter, outwards - the inner edge of the ascending colon and cecum, in front and above - the descending part of the duodenum, in front and below - the edge of the mesentery root.

For the rest of the stretch, the ureter is covered in front by the parietal peritoneum of the right intestinal sinus, and between it and the urine pass the vasa ileococlica, colica dextra with the lymph vessels and lymph nodes located along their course.

Medially from the left ureter, the abdominal aorta is located, laterally - the inner edge of the descending colon, in front and above - the parietal peritoneum of the left intestinal sinus, in front and below - the root of the mesentery of the sigmoid colon.

Between the peritoneum and the left ureter, there are branches of the lower mesenteric from vessels with lymph nodes and vessels located along their course.

Blood supply, lymphatic drainage and innervation

The blood supply to the ureter comes from three sources that anastomose among themselves. The upper part of the ureter is supplied with blood by small sprigs extending from a. renalis, medium - from the abdominal aorta or the internal spermatic artery, the lower one - from the superior,

sometimes the inferior cystic, from the hypogastric artery, in women, sometimes from the a system. uterina.

vascular pedicle, for the middle lymph nodes on the vena cava and on the aorta, for the lower lymph nodes on the iliac vessels - vasa iliaca interna.

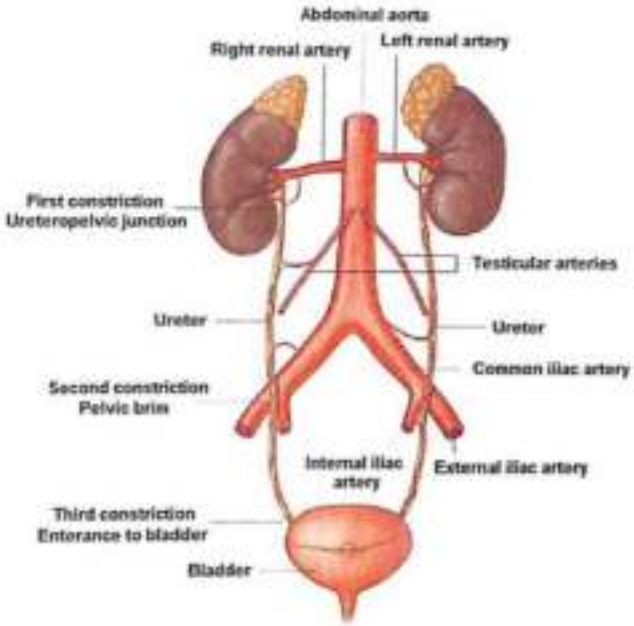

Fig. 13 - Ureter and its constrictions

illustration from https://image.slidesharecdn.com/constrictionsofureter-100618044039-phpapp02/95/constriction-of-ureter-4-728.jpg?cb=1276836100

The arterial vessels supplying the ureter are divided into ascending and descending branches, which around it form a continuous chain of anastomoses. Venous blood flows according to v. renalis, in the middle section of v. testicularis (v. ovarica), in the lower - in the venous plexus of the system v. iliaca interna [13].

Regional lymph nodes for the upper part of the ureter are the lymph nodes at the gates of the kidney and its

The innervation of the ureter is carried out at the top of pi. renalis, in the middle section from the nerve plexus of the seminal vessels (plexus testicularis (pi. ovaricus), in the lower plexus from plexus hypogastricus superior et inferior), and at the place of its entry into the bladder from plexus vesicalis. Experimentally in animals, it was found that the branches of the vagus and pelvic nerves are involved in the innervation of the ureters.

Function of ureters

The main task performed by the ureters is to transport urine from the renal pelvis to the bladder. The presence of the muscle layer in the wall of this organ allows it to constantly change its width under the pressure of the urine tube flowing in the internal cavity, as a result of which it is "pushed" inwards.

In turn, urine cannot return back, since a part of the ureter inside the bladder performs the functions of a valve and a preservative.

The function of the ureter is associated with the work of the sphincter apparatus of the cups, pelvis and bladder. The coordinated function of these parts of the urinary system ensures normal urodynamics.

The passage of urine through the ureter is due, due to the peristaltic contraction, to the longitudinal and circular narrowing of the lumen of the ureter. The frequency of contractions of the ureter is 3-5 per 1 minute, the duration of the wave is 2-5 seconds, the interval between the waves is from 9 to 27 seconds.

2.3 Urinary bladder

The bladder (Fig. 14) is located in the anterior section of the pelvis, behind the pubic bones and symphysis.

Only when the bladder is filled in an adult person goes beyond the pelvic cavity, rising above the pubic bones. It distinguishes the top, body, bottom and neck (part of the bladder, passing into the urethra). The bladder wall has well-defined muscular and submucous layers, as a result of which the mucous membrane forms wrinkles [13].

The bladder, vesica urinaria, is a container for the accumulation of urine, which is periodically excreted through the urethra. The capacity of the bladder an average of 500 - 700 ml and is subject to large individual fluctuations.

The shape of the bladder and its relationship to the surrounding organs vary significantly depending on its content. When the bladder is empty, it lies entirely in the pelvic cavity behind the symphysis pubica, and behind it the seminal vesicles and end parts of the spermatic duct are separated from the rectum in men, and the vagina and uterus in women.

When the urine is filled with urine, the upper part of it, changing its shape and size, rises above the pubis, reaching to the level of the navel in cases of severe stretching.

When the bladder is filled with urine, it has an ovoid shape, and its lower, wider fortified part is the bottom, fundus vesicae, facing down and back towards the rectum or the vagina; narrowing in the form of a neck, cervix vesicae, it passes into the urethra, a more pointed tip, apex vesicae, adjacent to the lower part of the anterior abdominal wall.

The middle part lying between apex and fundus is called the body,

corpus vesicae. From the top to the navel along the back surface of the anterior abdominal wall to its midline goes fibrous cord, lig. umbilicale medidnum.

All three layers of smooth muscle fibers make up the common muscle of the bladder, reducing with its contraction its cavity and expelling urine from it (detrusor).

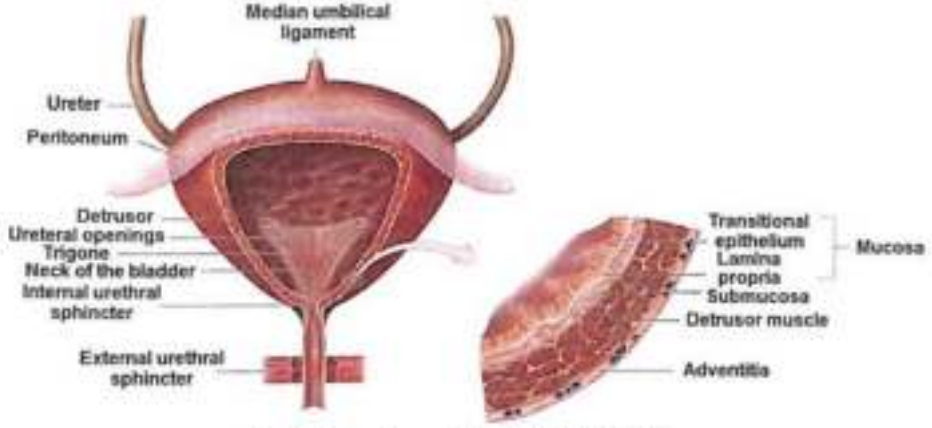

Fig. 14 - Anatomy of the female bladder

(Illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTgwX3Lcq-jnN9o4bbtdAnd5dZykBfTeuSioqKyQOHjRVIzwIhg)

Tunica serosa, which is only partially a part of the bladder wall, covering its back wall and apex, the bladder wall consists of the muscular layer, tunica muscularis (smooth muscle fibers), tela submucosa and tunica mucosa [13].

In tunica muscularis, there are three intertwining layers:

1) stratum externum, consisting of longitudinal fibers;

2) stratum medium - from circular or transverse;

3) stratum internum - from longitudinal and transverse.

The middle layer is most developed, especially in the area of the internal opening of the urethra, ostium urethrae internum, where it forms a bladder constrictor, m. sphincter vesicae. Around each mouth of the ureters also forms a similarity of sphincters due to the strengthening of the circular fibers of the inner muscular layer.

The inner surface of the bladder is covered with a mucous membrane, tunica mucosa, which, with an empty bubble, forms wrinkles due to a rather well-developed sub mucosal base, tela submucosa. When the bladder stretches, these folds disappear. In the

lower part of the bladder there is a noticeable hole on the inside, ostium urethrae internum, leading to the urethra. Directly behind the ostium urethrae internum is a triangular smooth area, trigomum vesicae. The mucous membrane of the triangle fuses with the underlying muscle layer and never forms folds.

Blood supply, lymphatic drainage and innervation

The bladder arteries extend from a iliaca interna and its umbilical artery. The upper part of the bladder is nourished by the branches of a vesicalis superior, the bottom and the lower part - a. vesicalis inferior. The bottom of the bladder is supplied with sprigs a. rectalis media, a pudenda inferior et a. obturatoria. Each lower artery of the bladder supplies the lower section of the ureter, the seminal vesicles, the prostate gland.

Veins of the bladder do not accompany the same arteries, and go independently. They form three plexuses: cortical (plexus venosus pudendalis), cystic (plexus venosus vesicalis) and hemorrhoidal (plexus venosus rectalis). The venous network around the bladder is 15-20 times the arterial, it extends to the prostate gland. Through the venous plexus of the bladder, blood flows from the prostate gland, seminal vesicles and the final part of the vas deferens. The venous plexus of the bladder widely anastases with the veins of the rectum and with the venous plexus.

Lymph drainage from the bladder wall occurs mainly in the hypogastric and iliac lymph nodes. Lymphatic vessels depart anteriorly, vertically and posteriorly. They anastamize with the lymphatic vessels of the seminal vesicles and the prostate gland and through them with the lymphatic vessels of the rectum.

Innervation of the bladder is carried out through the cystic plexus (plexus vesicalis), located mainly at the confluence of the ureters. The nerve plexus is obtained from two sources: from plexus hypogastrici inferioris dexter et sinister - of sympathetic origin and parasympathetic - nn. splanchnici pelvini.

Function of bladder

The main functions of the bladder are:

1) accumulation and retention of urine (continuously flowing from the kidneys through the ureters);

2) urine excretion.

The accumulation of urine in the bladder occurs due to the adaptation of the walls of the bladder to the volume of incoming urine (relaxation and stretching of the walls without a significant increase in intravesical pressure). With a certain degree of stretching of the bladder walls, there is a desire to urinate. A healthy adult can hold urine, despite the urge to urinate. The retention of urine inside the bladder is carried out using the sphincter apparatus (valves), which compress the lumen of the bladder neck and urethra [10, 13].

There are two main sphincter of the bladder: the first is involuntary (consists of smooth muscle fibers), located in the urinary neck at the exit to the urethra, the second is arbitrary (consists of cross-striped muscle fibers), is located in the middle part of the pelvic urethra and is part of pelvic floor muscles.

During urination, which is normal in an adult, performed arbitrarily according to his wishes, both sphincters relax and the walls of the bladder contract, which leads to the expulsion of urine. Impaired functioning of the muscles, expelling urine, and sphincters leads to various disorders of urination.

Frequent diseases of the bladder are infectious inflammation of the mucous membrane (cystitis), stones, tumors and disorders of the nervous regulation of its functions.

2.4 Urethra

Female urethra (Fig. 15) is a short tube (35 mm), which has time to bend, to be under the pubic symphysis, passing through the muscles of the pelvic diaphragm (arbitrary sphincter) [9, 10].

The external opening is located in the perineum between the clitoris and the opening of the vagina. Mucosa forms folds on which ducts of mucous glands open. There is a venous plexus in the submucosal layer and the muscular layer.

Because of such a small length of the urethra, infection is much easier to penetrate into the bladder and continue its development there. That is why women significantly more often have inflammatory diseases of the urinary system.

The following membranes of the urethra can be distinguished:

1. The mucous membrane consists of epithelium and its own plate. The epithelium is transient near the bladder, in the intermediate zone is a multi-layered prismatic, transforming at the end of the urethra into a flat non-squaring epithelium. The epithelium forms small endoepithelial glands. In its own plate are exoepithelial urethral mucous glands.

   The lamina propria of the mucosa is formed by loose connective tissue containing a well-developed venous plexus, formed by a large number of thin-walled veins with intimate pads. The venous plexus of the urethra is regarded as a spongy body due to its ability to swell.

2. The muscular membrane is formed by the inner longitudinal and outer circular layers.

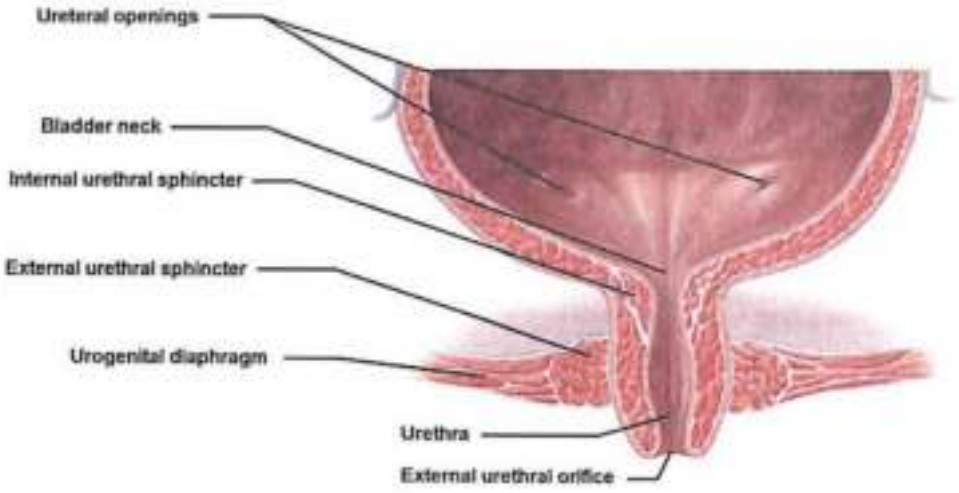

Fig. 15 - Anatomy of the female urethra

(Illustration from
https://lh3.googleusercontent.com/1Wv4Fc6wZQgk&JswFiSGWAmsNWSqdCsKeg_aVZaCJJEJNah3NZzWvUBtIGtoVa_(TcQGvQ=s123)

Circular bundles of smooth muscle cells combine with similar bundles of the bladder wall, forming a muscle sphincter around the inner opening of the urethra. The urethra is surrounded in the intermediate zone by a ring of striated muscle fibers forming the urethral sphincter.

The final part of the urethra is surrounded by the skeletal muscle fibers of the vaginal muscle sphincter.

3. The adventitia is a thin layer of loose fibrous connective tissue that connects the urethra with surrounding organs and contains blood and lymphatic vessels, as well as nerve fibers.

Blood supply, lymphatic drainage and innervation

The blood supply to the urethra comes from a. vesicalis inferior and a. pudenda interna.

The veins are poured through the venous plexus (plexus venosus vesicalis) in v. iliaca interna.

Lymphatic vessels from the upper sections of the canal are directed to the inn. iliaci, from the lower - to the inn. inguinales.

Innervation: from plexus hypogastrics inferior, nn. splanchnici pelvini and n. pudendus.

Male urethra (urethra masculina) (Fig. 16). The male urethra is about 18 cm long, extending from the bladder to the external opening of the urethra on the glans penis. Urethra serves not only for the excretion of

urine, but also for passage of the sperm that enters the urethra through the ductus ejaculatorius.

It is composed of a heterogeneous series of segments: prostatic, membranous, and spongy [10, 13].

Prostatic urethra (pars prostatica). The prostatic urethra is the part of the urethra that traverses the prostate. It originates in the region of the bladder neck.

Fig. 16 - Anatomy of the male urethra

(Illustration from https://daydreamanatomy.com/wp-content/uploads/2017/12/female-anatomy-urethra-female-urethra-anatomy-human-anatomy-diagram-within-human-anatomy.jpg)

Its length is about 30-35 mm. The middle section of the prostatic part is enlarged, and the initial and final parts are narrowed. On the back wall of the prostatic part of the urethra is the seminal hillock, colliculus seminalis, and on the sides of the hillock are numerous excretory ducts of the prostate gland.

It lay in a retropubic location and is bordered superiorly by the bladder and supported inferiorly by the sphincter urethrae externus muscle and the perineal membrane (formerly called the urogenital diaphragm).

The posterior wall of the prostatic urethra contains the urethral crest, which is bordered laterally by prostatic sinuses, into which the prostatic glands drain. The most prominent aspect of this crest is the seminal colliculus, or verumontanum, where the paired ejaculatory ducts and the opening of the prostatic utricle (a small midline paramesonephric duct remnant) meet the lumen of the urethra.

Membranous urethra (pars membranacea). The membranous part, pars membranacea, of the urethra penetrates the urogenital diaphragm 15-20 mm long from the top of the prostate gland to the bulbuspenis. The diameter of the membranous part varies within 3-4 mm.

This is the narrowest part of the urethra, which must be considered when introducing instruments on the urethra into the bladder. The membranous part of the urethra is bounded by tufts of striated and smooth muscles, which form an arbitrary urethra of the urethra, m. sphincter urethrae.

Spongy urethra (pars spongiosa). The spongy part, pars spongiosa, is the longest part of the urethra, its length is 100-120 mm. The urethra is divided into bulbous and

hanging sections, the diameter of the lumen of 6-10 mm. In the onion urethra open numerous urethral glands, gll. urethrales, and ducts of bulbourethral glands, gll. bulbourethral (Cowperi).

The male urethra has three constrictions: at the internal opening, in the membranous part and at the external opening, as well as expansion: in the prostatic part, in the bulb of the male penis and in front of the external opening, in the navicular fossa, fossa navicularis. Along the entire length of the urethra, two bends form in the sagittal plane - upper and lower. In children, the prostatic part of the canal is longer. The lumen of the urethra is straightened with the passage of sperm and urine, and with the introduction into the urethra (catheter, cystoscope).

In clinical practice, the urethra is divided into two sections: the back part is fixed and the front part is mobile. The fixed department, in turn, is divided into the intravesical (5-6 mm long), prostatic (30-35 mm) and membranous (15-20 mm).

Blood supply, lymphatic drainage and innervation

Arteries of the urethra come from the branches of the a. pudenda interna. Different sections of the canal feed from different sources: pars prostatica - from branches a. rectalis media and a. vesicalis inferior; pars membranacea - from a. rectalis inferior and a. perinealis; pars spongiosa - from a. pudenda interna. A. dorsalis penis and a. profunda penis involved in vascularization of urethra's wall [9].

Venous blood flows to the veins of the penis and bladder.

Limphatic drainage occurs from pars prostatica to the lymphatic vessels of the prostate gland, from pars membranacea and pars spongiosa to the inguinal lymph nodes.

The innervation is from nn. perinei and n. dorsalis penis (from n. pudendus), as well as from the plexus prostaticus vegetative plexus.

2.5 Male genital organs

The male genital organs (organa genitalia masculina) include the scrotum and testicles (testes) with their membranes, the vas deferens with seminal vesicles, the prostate gland, the bulbourethral glands, the penis and male urethra.

2.5.1 Scrotum

Scrotum is a separate protrusion of the anterior abdominal wall. It consists of two separate chambers, in which are located the testicles, epididymis and part of the spermatic cord.

The scrotum, scrotum, is a skin-muscular organ that serves as a container for the testicles, their appendages and the distal sections of the seminiferous tubules. The gate performs a thermostatic function for the testicles, which is very important for spermatogenesis [10, 13].

Chronic contracting and relaxing of the scrotal muscles help to maintain the temperature of the testes. The testes need the right temperature to produce healthy sperm. Structurally speaking, the scrotum is divided into two segments.

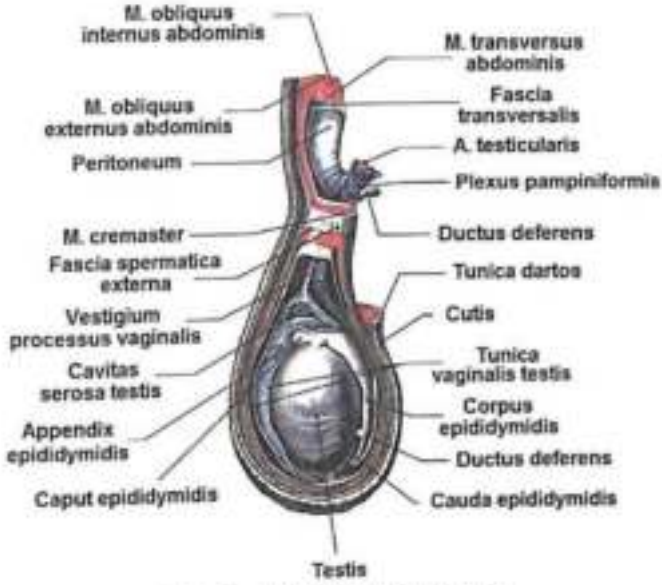

Fig. 17 - Anatomy of the scrotum

(Illustration from http://yamedik.org/content/anatomiya/bil_02/k_files/mb4_027.jpeg)

The exact opposite works as well; whenever the temperature is at a comfortable level, the muscles around the scrotum relax and the scrotum will be hanging much lower than normal, away from the body heat offered at the pelvic region. The scrotum is constantly looking for temperatures which are roughly 3.5 degrees below the body's normal temperature.

The compartments are designed lengthwise and keep their separation through a fibrous scrotal septum. It is this internal segregation which helps protect the testes from infection or damage from the other one. As an added protection against harm, the left testes hangs lower than the right to avoid compression at the moment of impact. The surface of the testes shows evidence of the scrotal septum along

with the appearance of a longitudinal line which runs front to back around the whole testes, except for the part which attaches to the body.

The membranes of the testicle and the spermatic cord, counting from the outside, are as follows (Fig. 17): **skin (cutis), tunica dartos, external fascia spermatica (fascia spermatica externa), fascia cremasterica, m. cremaster, the internal seminal fascia (fascia spermatica interna), tunica vaginalis testis.**

1. The skin (cutis) of the scrotum is thin and has a darker coloration compared to other parts of the body. It is supplied with numerous large sebaceous glands, the secret of which has a characteristic smell.

2. Tunica dartos is located immediately under the skin. It is a continuation of the subcutaneous connective tissue from the groin and perineum, but is devoid of fat. It contains a significant amount of smooth muscle tissue. Tunica dartos forms for each testicle one separate sac that joins along the middle line so that a septum scroti is obtained, attached along the raphe line.

3. The external seminal fascia (fascia spermatica externa) is a continuation of the superficial fascia of the abdomen.

4. Fascia cremasterica is the continuation of fasciae intercruralis, which extends from the edges of the superficial inguinal ring; it covers m. cremaster, and therefore is called fascia cremasterica.

5. M. cremaster consists of bundles of striated muscle fibers, which are an extension of the transverse muscle of the abdomen (transversus abdominis). With the reduction of m. cremaster the testicle is pulled up.

6. The internal seminal fascia (fascia spermatica interna) is located immediately under m. cremaster. It is a continuation of fasciae transversalis, encompasses all the constituent parts of the spermatic cord and in the region of the testicle is attached to the outer surface of its serous cover.

7. Tunica vaginalis testis is formed from the vaginal process of the peritoneum (processus vaginalis) and forms a closed serous sac consisting of two plates – lamina parietalis and visceralis.

Blood supply, lymphatic drainage and innervation

The scrotum receives **arterial supply** from the anterior and posterior scrotal arteries. The anterior scrotal artery arises from the external pudendal artery, while the posterior is derived from the internal pudendal artery.

The scrotal veins follow the major arteries, draining into the external pudendal veins.

The lymph fluid drains to the nearby superficial inguinal nodes.

Cutaneous innervation to the scrotum is supplied via several nerves:

- Genital branch of genitofemoral nerve – derived from the femoral plexus and supplies the

anterolateral aspect of the scrotum.

- Anterior scrotal nerves – derived from the ilioinguinal nerve and supplies the anterior aspect of the scrotum.
- Posterior scrotal nerves – derived from the perineal nerve and supplies the posterior aspect of the scrotum.
- Perineal branches of posterior femoral cutaneous nerve – derived from the sacral plexus and supplies the inferior aspect of the scrotum.

2.5.2 Testicles

Testicles (testes) (Fig. 18). Testicles (testes) are two oval-shaped bodies, somewhat flattened laterally, located in the scrotum. The testicle length is equal to an average of 4 cm, the diameter is 3 cm, and the mass ranges from 15 to 25 g [10, 13].

The left testicle is usually dropped slightly lower than the right one. The spermatic cord (funiculus spermaticus) and epididymis approach the posterior margin of the testicle; the latter is located along the rear edge. Epididymis is a narrow, long formation, in which there is an upper, somewhat thickened part — the appendage head (caput epididymidis) and the lower, more pointed end — the tail (cauda epididymidis); the intermediate segment is the body (corpus epididymidis).

The testicle is surrounded by a dense fibrous coat of whitish coloration (tunica albuginea), lying directly on its parenchyma. At the posterior margin of the testicle, the fibrous tissue of the membrane protrudes shallowly inside the glandular tissue in the form of an incomplete vertical septum, or thickening (mediastinum testis); fibrous partitions (septula testis), which with their outer ends attach to the inner surface (tunicae albugineae) and thus divide the entire testicular parenchyma into lobules (lobuli testis), radially depart from it.

The number of lobules of the testicle reaches 250-300. The tops of the lobules are facing the testicular septum (mediastinum testis), and the bases to the tunica albuginea. The epididymis also has tunica albuginea, but more subtle.

The testicular parenchyma consists of the seminiferous tubules. There are twisted (tubuli seminiferi contorti) and straight (tubuli seminiferi recti) seminiferous tubules. In each lobule there are 2-3 tubules and more. Having a winding direction in the lobule itself (tubuli seminiferi contorti), approaching the testicular septum (mediastinum testis), and the convoluted tubules are connected to

each other and directly at the mediastinum narrow into short straight seminiferous tubules. Straight tubules open into the testicular network (rete testis), located in the mediastinum stratum. From the network of testicles, 12–15 outgoing tubules (ductuli efferentes testis) open, which are sent to the head of the epididymidis. Upon exiting the testicle, the outflowing tubules become winding and form a series of conical epididymis (lobulis coni epididymidis).

The place of formation of sperm - the main part of the sperm (sperma) - are only tubuli seminiferi contorti. Tubuli recti and canaliculi of the testicular network belong to the semen-bearing paths. The liquid component of the sperm is produced only in small quantities by the testes, since it is mainly a product of the excretion of the accessory glands of the reproductive apparatus, opening into the excretory tract.

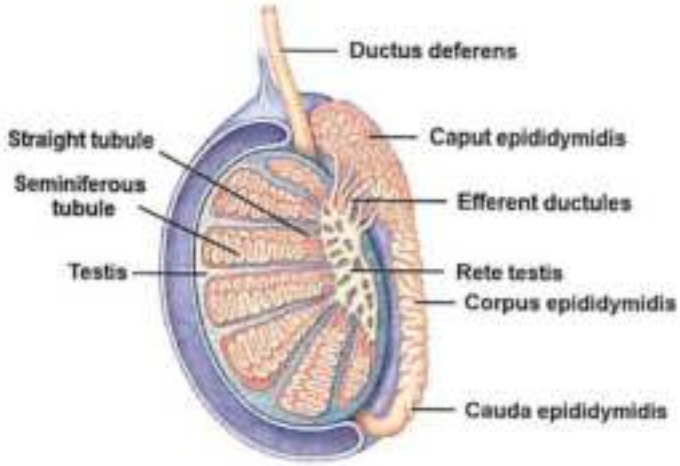

Fig. 18 - Anatomy of the testicle

(Illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcRSF1fWkHJuVDBvvXteQ877Q-8C4OLJJTYzbV1UNvvOGiZUbbJJ)

Ductuli efferentes open into a single canal of the appendage (ductus epididymidis), which, forming numerous curves, continues into the spermatic cord (ductus deferens). The deferent duct (ductus defferentes), lobules of epididymidis (lobuli epididymidis) and its initial section together form the epididymidis head.

Vas deferens is a direct extension of the epididymis canal and differs from the latter by a larger wall thickness.

Separated from the testicle vessels (a. and v. testiculares), the vas deferens upward and enters the spermatic cord.

As part of the spermatic cord, the ductus deferens rises vertically up to the superficial inguinal ring.

It has been found that it has been sent to the lumbar region of the inguinal canal. The bottom of the bladder and the bottom of the bladder It is noticeable that it will notice that it is expanding. The length of the ductus deferens is 40 - 45 cm. The average diameter is 2.5 mm, the width of its lumen is only 0.2 - 0.5 mm. The wall consists of three layers: the outer muscular wall, the tunica adventitia, then the middle muscular wall, the tunica muscularis, and the inner mucosa.

Spermatic cord (funiculus spermatacus) is a round strand 16-20 cm long, covered with an external seminal fascia and located between the inner inguinal ring and the upper pole of the testicle. The spermatic cord begins from the epididymis, and ends at the deep ring of the inguinal canal. The length of the spermatic cord in adults is 15–20 cm on average. It can be felt in the scrotum and in the superficial inguinal ring in the form of a rounded cord with a thickness of almost the little finger. The texture of the spermatic cord is soft, the surface is smooth. The spermatic cord consists of membranes within which the elements of the cord are located: the vas deferens, ductus deferens, the testicular artery, a. testicularis, vas deferens artery, a. ductus deferentis (from a. umbilicalis), pterygium venous plexus, plexus pampiniformis, testicular veins and veins of the vas deferens, lymphatic vessels, nerve plexus (testicular and vas deferens of the peritoneum, friable tissue.

The spermatic cord has scrotal and inguinal parts. The layers of both departments are the same, except that the inguinal region lacks the external spermaticus fascia, fascia spermatica externa, since it is formed by the superficial fascia of the abdomen, which is located outside the inguinal canal. In both parts, the inner lining immediately surrounding the elements of the spermatic cord is the inner spermatic fascia, fascia spermatica interna. As shown in the description of the inguinal canal and its contents, it is a protrusion of the transverse fascia of the abdomen. More superficially lies the muscle that suspends the testicle, m. cremaster [Riolan], with fascia cremasterica. Outside in the scrotal part of the spermatic cord is the external seed fascia, fascia spermatica externa.

Blood supply, lymphatic drainage and innervation

The arterial supply to both testes is primarily from the testicular arteries, which arise from the anterolateral aspect of the abdominal aorta just inferior to the renal arteries. They travel retroperitoneally, cross over the ureters and the inferior parts of the external iliac arteries to pass through the deep inguinal ring to enter the inguinal canal and become one of the components of the spermatic cord. The testicular artery enters the testis through the posterior midportion. The testicular artery or one of its branches anastomoses with the artery of the ductus deferens.

Venous drainage from the testis and epididymis form a network of 8-12 veins, called the pampiniform venous plexus, lying anterior to the ductus deferens and surrounding the testicular artery in the spermatic cord. The veins converge superiorly, forming a testicular vein, after passing through the deep inguinal ring. The right testicular vein enters the inferior vena cava, and the left testicular vein drains into the left renal vein.

Lymphatic drainage of the testis follows the testicular vessels (in the spermatic cord) to the right and left lumbar (caval/aortic) and preaortic lymph nodes at the second lumbar level.

Autonomic innervations of the testis arise as the testicular plexus of nerves on the testicular artery, which contains vagal parasympathetic and visceral afferent fibers and sympathetic fibers from the T7 segment of the spinal cord.

2.5.3 Prostate

The prostate gland (prostata) (Fig. 19) is an unpaired glandular muscular organ resembling a truncated cone. It allocates the top (apex), base (basis), front and rear surfaces (facies anterior et posterior). Its weight is about 23-25 grams; the vertical size is about 3 cm; the horizontal is 4 cm; the sagittal is about 2.5 cm. It eccentrically covers the initial part of the urethra and closely adheres to the bottom of the bladder with its base, and to the urogenital diaphragm at the apex. The posterior surface of the prostate gland is bordered by the wall of the rectum and is separated from it only by a thin plate of the pelvic fascia (septum rectovesicale). The urethra passes through the prostate gland from its base to the apex, located in the median plane, closer to its front surface [13].

The seminal vesicles are adjacent to the prostate gland at the back and top, and the spermatic ducts are located medially to them. The excretory duct of the seminal vesicle merges at an acute angle with the dilated part of the sperm duct. Formed after this ejaculating ducts (ductus ejaculatorius) penetrate through the posterior surface of the prostate gland, heading downwards, medially and anteriorly, opening in pars prostatica urethrae with two openings on the seed tubercle. A slit-like hole at the top of the seed tubercle leads to a small blind pocket located in the thickness of the prostate gland, which is called the prostate gland (utriculus prostaticus). The name indicates the origin of this formation from the fused lower ends of the ductus paramesonephricus, from which the woman develops the uterus and vagina.

Macroscopically, there are three lobes in the prostate gland: two lateral - right and left, separated by a groove (determined by palpation examination), and an average lobe (isthmus), which is located between the posterior surface

of the urethra, the bottom of the bladder and both deferent ducts.

The prostate parenchyma consists of alveoli, which, grouping, form 30-50 individual lobes surrounded by fibrous-muscular septa.

the interlobar partitions move away, gathering around the urethra.

All this muscle tissue is called the prostate muscle (substantia muscularis), which forms the internal involuntary sphincter of the bladder.

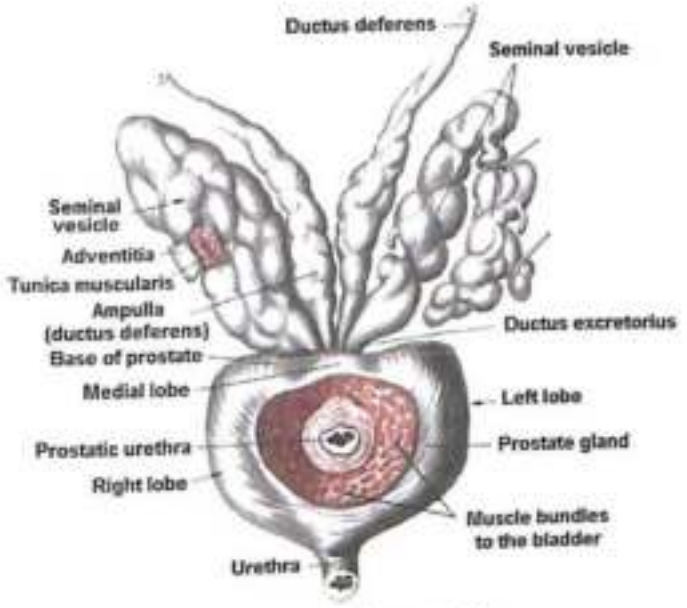

Fig. 19 - Anatomy of the prostate

(illustration from https://it.wikipedia.org/wiki/Prostata)

Each lobule passes into the duct (ductus prostaticus), which opens with pin holes in the prostatic urethra on the lateral surfaces of the seed tubercle. Since some ducts are combined, their total number is less than the number of lobules. The latter are concentrated mainly in the posterior and lateral parts of the gland, there are almost no anterior to the urethra [10].

Smooth muscular tissue is strongly developed here, from which

Outside, the prostate gland is covered with a capsule that is rich in elastic fibers and contains powerful bundles of smooth muscles that make up the annular prostate muscle. Above, it merges with the circular muscular layer of the bladder; below - with muscles forming an arbitrary sphincter of the membranous part of the urethra.

Blood supply, lymphatic drainage and innervation

The blood supply of the prostate gland is made from aa. vesicalis inferiors (the inferior vesical artery then branches into 2 main arterial branches to feed the prostate) and aa. rectalis mediae. They penetrate into it with numerous branches along the ejaculatory ducts, forming a rich network of capillaries.

The first arterial branch is the urethral artery that enters the prostatovesical junction posterolaterally and travels inward perpendicular to the urethra toward the bladder neck at approximately the 5 o'clock and 7 o'clock meridian.

The capsular artery is the second main branch of the prostate. It runs posterolateral to the prostate with the cavernous nerves. This artery enters the prostate at right angles to supply the glandular tissue.

A large number of **veins of the prostate gland**, anastomosing among themselves, form around it a plexus, which is part of the urogenital venous plexus, which is associated with the venous plexus of the rectum.

Lymphatic vessels begin in the parenchyma of the prostate gland and form around it, especially on the lower surface, a rich lymphatic network. From there, lymphatic drainage is carried out in the pre-bladder lymph nodes, in the lymphatic vessels passing near the ureters and deferent ducts along the side walls of the pelvis to the external and internal iliac lymph nodes.

The innervation of the prostate gland is carried out by sensory and postganglionic sympathetic and parasympathetic nerve fibers from the inferior hypogastric plexus (plexus hypogastricus inferior).

2.5.4 Seminal vesicles

Seminal vesicles (vesiculae seminales) (Fig. 19) lie laterally from the vas deferens, between the bottom of the bladder and the rectum. Each seminal vesicle has a length of up to 12 cm in expanded form, and a length of 5 cm in undressed. The lower pointed end of the seminal vesicle passes into a narrow excretory duct (ductus excretorius), which connects at an acute angle with the ductus deferens of the same side, forming together with it the ductus ejaculatorius. The latter is a thin tubule about 2 cm long, which, starting from the junction of the ductus deferens and ductus excretorius, passes through the thickness of the prostate gland and opens into the prostatic part of the urethra by a narrow opening at the base of the seminal tubercle.

The walls of the seminal vesicles consist of the same layers as the ductus deferens. Seminal vesicles are secretory organs that produce a liquid part of the sperm.

Blood supply, lymphatic drainage and innervation

Vessels and nerves: the ductus deferens receives arterial blood from a. ductus deferenis (a branch of iliaca interna), seminal vesicles - from aa.

vesicalis inferior, ductus deferentis, rectales.

Venous outflow occurs in v. deferentialis, which flows into v. iliaca interna.

Outflow of lymph occurs in the outer, internal iliac and sacral lymph nodes.

Ductus deferens and seminal vesicles are innervated by **plexus deferentialis**, formed by nerves from the plexus hypogastricus inferior.

2.5.5 Bulbourethral glands

Bulbourethral glands (glandulae bulbourethral) (Fig. 20) are two glands, each 0.5-0.7 cm in diameter, located in the thickness of the diaphragma urogenitale above the posterior end of the bulbus penis, posteriorly from the pars membranacea urethrae. The inferior duct of these

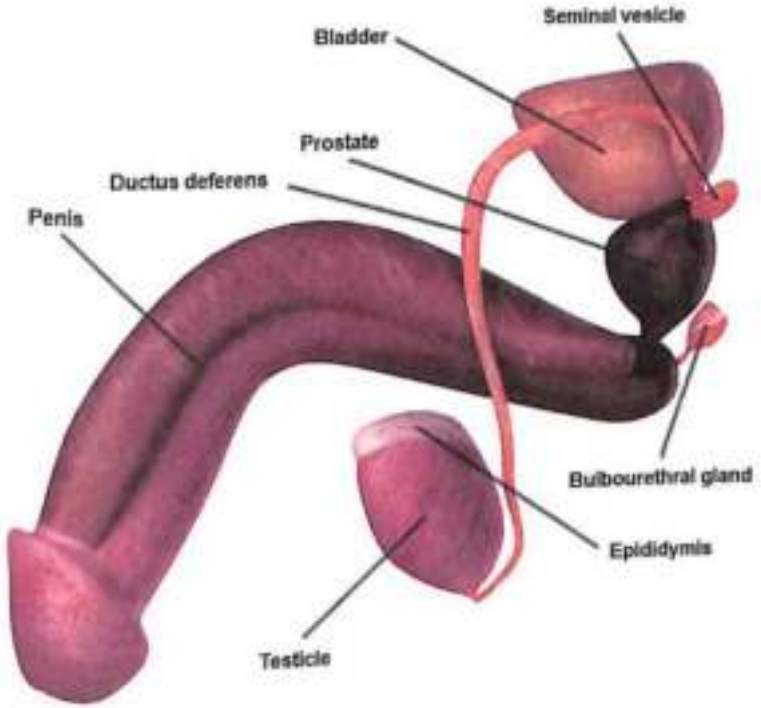

Fig. 20 - Anatomy of the bulbourethral gland

Illustration from http://www.knowyourbody.net/wp-content/uploads/2017/08/Cowpers-Gland.jpg

The blood supply of the prostate gland is made from aa. vesicalis inferiors (the inferior vesical artery then branches into 2 main arterial branches to feed the prostate) and aa. rectalis mediae. They penetrate into it with numerous branches along the ejaculatory ducts, forming a rich network of capillaries.

The first arterial branch is the urethral artery that enters the prostatovesical junction posterolaterally and travels inward perpendicular to the urethra toward the bladder neck at approximately the 5 o'clock and 7 o'clock meridian.

The capsular artery is the second main branch of the prostate. It runs posterolateral to the prostate with the cavernous nerves. This artery enters the prostate at right angles to supply the glandular tissue.

A large number of **veins of the prostate gland**, anastomosing among themselves, form around it a plexus, which is part of the urogenital venous plexus, which is associated with the venous plexus of the rectum.

Lymphatic vessels begin in the parenchyma of the prostate gland and form around it, especially on the lower surface, a rich lymphatic network. From there, lymphatic drainage is carried out in the pre-bladder lymph nodes, in the lymphatic vessels passing near the ureters and deferent ducts along the side walls of the pelvis to the external and internal iliac lymph nodes.

The innervation of the prostate gland is carried out by sensory and postganglionic sympathetic and parasympathetic nerve fibers from the inferior hypogastric plexus (plexus hypogastricus inferior).

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The walls of the seminal vesicles consist of the same layers as the ductus deferens. Seminal vesicles are secretory organs that produce a liquid part of the sperm.

Blood supply, lymphatic drainage and innervation

Vessels and nerves: the ductus deferens receives arterial blood from a. ductus deferenis (a branch of iliaca interna), seminal vesicles - from aa.

glands opens into the spongy part of the urethra in the bulbus area. The glands secrete a viscous fluid that protects the urethra from urinary tract irritation.

Blood supply, lymphatic drainage and innervation

Arteries to bulbourethral glands come from a. pudendae internae.

Venous outflow occurs in veins bulbus and diaphragmae urogenitale.

Lymphatic vessels go to the inn. lymphoidi iliaci interni.

The glands are innervated by **n. pudendus** and also from the plexus prostaticus vegetative plexus.

2.5.6 Penis

The penis (Fig. 21) refers to the external genital organs together with the scrotum. It consists of three bodies: the pair cavernous (corpus cavernosum penis) and the unpaired spongy (corpus spongiosum penis). The name of these bodies is due to the fact that they consist of numerous crossbars, fibrous-elastic cords with an admixture of unstressed muscle fibers, among the dense plexus of which there are gaps - caves lined with endothelium and filled with blood [10, 13].

The corpora cavernosa penis consists of two long cylindrical bodies with pointed ends, from which the posterior parts diverge and form the legs of the penis (crura penis), which are attached to the lower branches of the pubic bones. Corpus spongiosum penis, coated with albumin (tunica albuginea corporis spongiosi), lies under the cavernous bodies of the penis and penetrates the entire length of the urethra. It has a smaller diameter (1 cm) than the other two cavernous bodies, but unlike them it thickens at both ends, forming a head of the penis in front (glans penis) and a bulb (bulbus penis) in the back.

The back of the penis, attached to the pubic bone, is called the root (radix penis). Anterior to the penis ends head. The intermediate part between the head and the root is called the body (corpus penis). The upper surface of the body is wider than the lower and is called the back (dorsum penis). Corpus spongiosum penis is adjacent to the lower surface. At the head of the penis there is a vertical slit - the external opening of the urethra (ostium urethra externum); the head from the dorsal and lateral sides is somewhat above the level of the cavernous bodies, this edge of the head is called corona glandis, and the narrowing behind it is collum glandis.

The skin of the penis at the base of the head forms a loose fold, which is called the foreskin (preputium). On the underside of the head of the penis, the foreskin is connected to the skin of the head by a bridle (frenulum preputii). Around the corona glandis and on the

inner leaflet of the foreskin are located various sizes of sebaceous glands (glandulae preputiales).

The size of the penis depends on the amount of blood in the cells of the cavernous and spongy bodies.

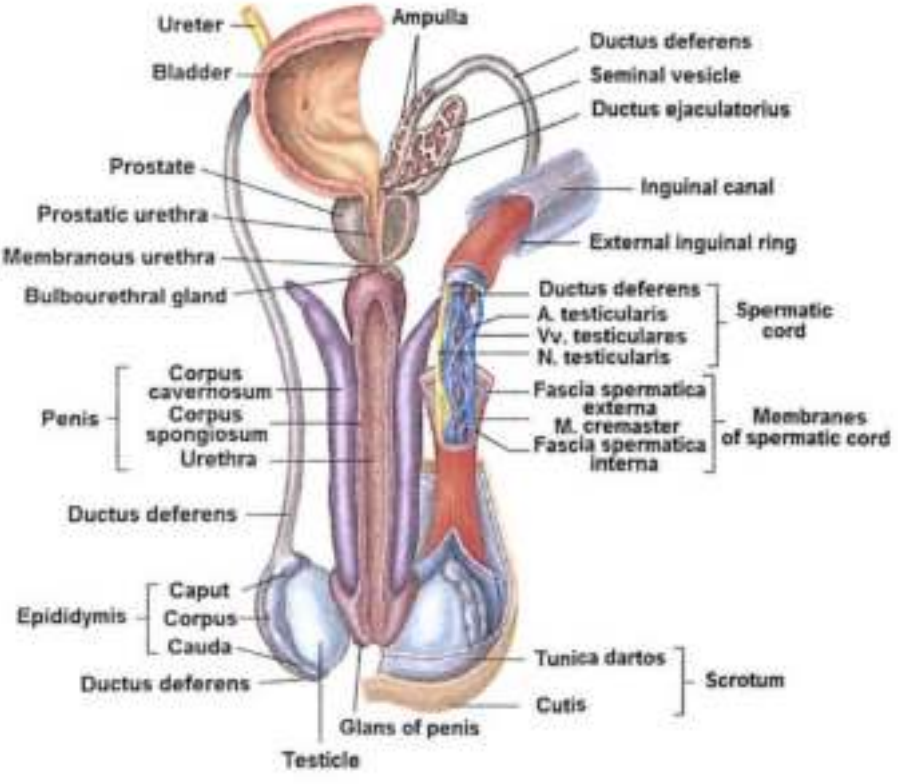

Fig. 21 - Anatomy of male genital organs

(illustration from https://lh3.googleusercontent.com/OBqJL2hmrRVscyTsYBDpHcdD0svc2tfF3ekG51EmJB-dbGBg/TvFUPS0B_EAAZ7o-bKy4=s107)

The secret of these glands is part of the preputial lubricant (smegma preputii), which collects in the space between the head and the foreskin - the cavity of the foreskin, opening in front of the hole, which passes the head when moving the foreskin backwards.

Blood supply, lymphatic drainage and innervations

Blood is brought to the penis through aa. profundae et dorsalis penis. Arterial branches, passing in connective tissue partitions, break up into thin curl arteries that open directly into the cavernous space. Blood veins

glands opens into the spongy part of the urethra in the bulbus area. The glands secrete a viscous fluid that protects the urethra from urinary tract irritation.

Blood supply, lymphatic drainage and innervation

Arteries to bulbourethral glands come from a. pudendae internae.

Venous outflow occurs in veins bulbus and diaphragmae urogenitale.

Lymphatic vessels go to the inn. lymphoidi iliaci interni.

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The skin of the penis at the base of the head forms a loose fold, which is called the foreskin (preputium). On the underside of the head of the penis, the foreskin is connected to the skin of the head by a bridle (frenulum preputii). Around the corona glandis and on the

(venae cavernosae) discharging from the cavernous bodies infuse into vv. profundae penis and in v. dorsalis penis. Due to the special arrangement of the blood vessels of the penis, the blood in the cavernous bodies can be retained, which leads to their compaction during erection.

The arteries of the penis are branches a. femoralis and a. pudenda interna. Venous outflow occurs at vv. dorsales penis superficialis et profundae in v. femoralis and in plexus venosus vesicalis.

Lymphatic drainage is carried out at the inn. lymphoidi inguinales and nodes of the pelvic cavity.

Afferent innervation is carried out by n. pudendus, efferent sympathetic - from plexus hypogastrics inferior, parasympathetic - nn. erigentes.

Function of male reproductive organs

Male reproductive system is a set of organs of the reproductive system (reproductive system) in men (male genital organs). It produces male sex cells, as well as male sex hormones, responsible for the formation and functioning of the body of the male type [13].

It has common elements with the urinary system, forming the male urogenital system. Male genital organs are the primary, that is, the first and main sexual characteristics of men, observed in each of them since the prenatal formation of these organs. Only during puberty under the action of activated sex hormones, the body acquires secondary sexual characteristics: body type and male hair growth, the predominance of muscle tissue over adipose tissue, a lower voice timbre compared to that of women.

Physiology of male genital organs. Physiology of intercourse

Sexual intercourse (synonym: coitus, intercourse, copulation) is a fragment of a complex picture of human sexual behavior. Despite the fact that sexual intercourse is a paired physiological process, changes in the body of a man and a woman differ significantly. Since, as a rule, sexual intercourse takes place in an intimate setting, the physiological changes of the body before, during and after sexual intercourse were described very speculatively. Nowadays, thanks in large part to research done by volunteers with the help of a special technique that captures changes in the body of men and women during intercourse, its physiology has become clear.

There are several stages of sexual intercourse, going into each other and united by the general concept of "sexual cycle":

- arousal;
- "plateau";
- orgasm;
- reverse development (detumescence).

Sexual intercourse is usually preceded by a period of mutual caresses. For the normal implementation of sexual intercourse in men, the participation of the following structural and functional components is necessary:

1) neurohumoral, due to the work of the central nervous and endocrine systems, which provide the power of sexual attraction and the excitability of the relevant parts of the central nervous system that regulate sexual behavior;

2) mental, due to the work of the cerebral cortex, ensuring the orientation of sexual desire and erection before the start of sexual intercourse;

3) erectional, mainly due to the work of the spinal centers, during which the penis is introduced into the vagina and frictions (movements of the penis into the vagina) occur;

4) ejaculation-orgasmic, also caused mainly by the work of the spinal centers, during which ejaculation occurs and an orgasm occurs.

At the stage of arousal in a man with sexual stimulation, there is an increase in blood flow to the genitals, while at the same time some difficulty in the outflow of blood through the veins.

This leads to a blood overflow of the cavernous bodies of the penis and an increase in its size. It is believed that the parasympathetic control of the lumen of the blood vessels is leading in the occurrence of erection.

The introduction of the penis, frictions in men lead to an increase in sexual arousal, increased heart rate and breathing, increased blood pressure, facial hyperemia. The maximum increase in blood pressure and heart rate in a man reaches during orgasm, which is experienced as a sensual sensation. In men, orgasm begins with the rhythmic contractions of the vas deferens, vas deferens and seminal vesicles. When this occurs, the release to the outside under high pressure of the ejaculate. In men, an orgasm lasts for a few seconds, after which a normal erection is quickly weakened and detumescence occurs - a decrease in the blood supply to the genitals. It is followed by a period of sexual refractoriness. Repeated erection is possible after some time.

A clear definition of the concepts of "norm", "normal" in the physiology of sexual intercourse is very difficult due to the extreme interweaving of biological, social, individual personality characteristics. It is believed that if sex life does not cause feelings of fatigue, discontent, if during the day the partners remain cheerful and vigorous, then it is obvious that their sex life is optimal.

Hormonal regulation of physiological functions

Male reproductive glands (testicles). The processes of spermatogenesis and the formation of male sex hormones - androgens - take place in them.

Spermatogenesis - the process of transformation of diploid male germ

cells into haploid, free and differentiated cells - spermatozoa.

There are four periods of spermatogenesis: 1) reproduction; 2) growth; 3) division and ripening; 4) formation, or spermiogenesis (spermioteliosis). In the first period, the diploid initial male sex cells (spermatogonia) are divided several times by mitosis (the number of divisions in each species is constant). In the second period, the germ cells (spermatocytes of the 1st order) increase in size, and their nucleus undergoes a long prophase, during which the conjugation of homologous chromosomes and crossing-over occur, accompanied by the exchange of sites between homologous chromosomes, and tetrad forms. In the third period, two divisions of maturation (meiosis) occur, the number of chromosomes is reduced or reduced by half (while in some tetrads in the first division homologous chromosomes diverge to the poles of the spindle, in the second - chromatids, then homologous chromosomes).

Thus, each spermatocyte of the 1st order gives 2 spermatocytes of the 2nd order, which after the second division form four haploid cells of the same size - spermatids. The latter do not divide, enter the fourth period of spermatogenesis, or spermatogenesis, and turn into spermatozoa: the spermatoid from the round becomes elongated, some structures (acrosome, side nucleus, flagellum, etc.) are newly formed, others disappear (ribosomes, endoplasmic reticulum and etc.) Most of the cytoplasm disappears from the cell. The elongated nucleus with condensed chromatin and acrosome (a derivative of the Golgi apparatus) is located at the apical pole of the cell and forms the head of the spermatozoon; the centriole usually lies at the basal pole of the nucleus, the flagellum originates from it; mitochondria surround the centriole or form the so-called incidental nucleus, located in the intermediate section of the spermatozoon. Mature sperm accumulate in the epididymis of the testis. Spermatogenesis continues in men to old age.

The duration of a complete spermatogenesis, consisting of four cycles, ranges from 64 to 75 days. But all spermatozoa do not mature at the same time: at any moment in the wall of the tubule hundreds and hundreds of cells can be found at different stages of spermatogenesis - initial, intermediate and final. One cycle of germinal epithelium is approximately 16 days.

Androgen formation occurs in the interstitial cells - gland cell (Leydig cells), localized in the interstitium between the seminiferous tubules and constituting approximately 20% of the total mass of the testicles. A small amount of male sex hormones is also produced in the reticular zone of the cortical substance of the adrenal glands.

Several steroid hormones belong to androgens, the most important of which is testosterone. The production of this hormone determines the adequate development of male primary and secondary sexual characteristics (masculinizing effect). Under the influence of testosterone during

puberty, the size of the penis and testicles increase, the male body hair appears, the tone of the voice changes. In addition, testosterone enhances protein synthesis (anabolic effect), which leads to the acceleration of growth processes, physical development, increase in muscle mass. Testosterone affects the formation of the bone skeleton - it accelerates the formation of the protein matrix of the bone, increases the deposition of calcium salts in it. As a result, the growth, thickness and strength of the bone increase. With the overproduction of testosterone, the metabolism is accelerated, the number of red blood cells increases in the blood.

The mechanism of action of testosterone is due to its penetration into the cell, transformation into a more active form (dihydrotestosterone) and further binding to the receptors of the nucleus and organelles, which leads to a change in the processes of protein synthesis and nucleic acids. Testosterone secretion is regulated by the luteinizing hormone of the adenohypophysis, whose production increases during puberty. With an increase in the blood testosterone by the mechanism of negative feedback, the production of luteinizing hormone is inhibited. The decrease in the production of both gona-dotropnyh hormones - follicle-stimulating and luteinizing - also occurs when spermatogenesis is accelerated.

In boys aged 10–11 years, the testicles usually lack active glandulocytes (Leydig cells), in which androgens are produced. However, testosterone secretion in these cells occurs during fetal development and remains in the child during the first weeks of life. This is due to the stimulating effect of chorionic gonadotropin, which is produced by the placenta.

Inadequate secretion of male sex hormones leads to the development of eunuchoidism, the main manifestations of which are delayed development of primary and secondary sexual characteristics, disproportion of the skeleton (disproportionately long limbs with relatively small body size), an increase in fat deposition in the chest, lower abdomen and hips. Often there is an increase in the mammary glands (gynecomastia). The lack of male sex hormones also leads to certain neuropsychic changes, in particular, a lack of attraction to the opposite sex and the loss of other typical psychophysiological features of a man.

The accessory sex glands are constantly experiencing the influence of andro genes, which contribute to their proper formation and normal functioning. Testosterone stimulates the formation of fructose in the seminal vesicles, citric acid and phosphatase in the prostate, cor-nitin in the epididymis, etc.

A decrease in the content of fructose, citric acid, acid phosphatase, cornitine in seminal fluid may indicate a decrease in the intrasecretory function of the testes. It was found that approximately 7–10 days after bilateral orrectomy, the male additional gonads in rodents atrophy to a minimum.

The normal level of testosterone in the plasma of an adult male is 12-35 nmol/l or 345-1010 ng/dl.

Anatomy of urogenital system

Urogenital apparatus includes the urinary (organa urinaria) and genital (organa genitalia) organs.

The kidneys are the paired organs, located in the retroperitoneal space, in the lumbar region, at the sides of the spine.

The kidney is divided into segments, which is due to the peculiarities of renal artery branching. There are following **segments**:

1. The upper segment (segmentum superius);
2. Upper front segment (segmentum superius anterius);
3. The lower segment (segmentum inferius);
4. Lower front segment (segmentum inferius anterius);
5. Posterior segment (segmentum posterius).

The kidney consists of a cortex (cortex renis) and a medulla (medulla renis) substance. The cortex is located on the periphery and between the pyramids (columnae renalis, c. Bertinii), the medulla is located in the center and is represented by pyramids (piramides renalis, Malpigii p.).

Function of kidneys:

1. Excretion of wastes;
2. Filtration, reabsorbing and secretion;
3. Water homeostasis;
4. Acid/base homeostasis;
5. Electrolyte homeostasis;
6. Blood pressure homeostasis;
7. Hormonal.

Ureters - paired tubular organs that provides urine from the renal pelvis to the bladder, is located in the retroperitoneal space. The ureter has three physiologic constrictions: the ureteropelvic junction, the crossing over the iliac vessels, and the ureterovesical junction.

The bladder (vesica urinaria, Greek - cystis) is an unpaired hollow muscular organ that serves to accumulate and excrete urine.

In men, the rectum, seminal vesicles and ampullae of the vas deferens adhere to the bladder behind; from above - the small intestine; the apex touches the prostate gland. At women behind to it contiguous cervix and a vagina; on top - the body and the bottom of the uterus; the apex of the bladder is located on the urogenital diaphragm.

Female urethra (urethra feminina) begins from the bladder with an internal opening (ostium urethrae internum) and is a tube 3-3.5 cm long, slightly curved by a bulge posteriorly and enveloping the lower margin of the pubic symphysis from below and behind. The female urethra pierces the pelvic diaphragm and the perineal membrane just posterior to the pubic symphysis.

Male urethra (urethra masculina) is a tube 16-22 cm long and 0.5-0.7 cm in diameter, extending from the bladder to the external opening of the urethra on the glans penis. Urethra serves not only for the excretion of urine, but also for passage of the sperm that enters the urethra through the ductus ejaculatorius.

Prostatic urethra (pars prostatica). The prostatic urethra is the portion of the urethra that traverses the prostate.

Membranous urethra (pars membranacea). The shortest and least distensible portion of the urethra is the membranous urethra. This region spans from the apex of the prostate to the bulb of the penis. It is invested in the external urethral sphincter muscle and the perineal membrane.

Spongy urethra (pars spongiosa). The spongy urethra is the region that spans the corpus spongiosum of the penis. It is divided into the pendulous urethra and the bulbous (or bulbar) urethra. The pendulous urethra is invested in the corpus spongiosum of the penis in the pendulous portion of the penis. The urethra is located concentrically within the corpus spongiosum.

The male genital organs (organa genitalia masculina) include the scrotum and testicles (testes) with their membranes, the vas deferens with seminal vesicles, the prostate gland, the bulbourethral glands, the penis and male urethra.

Scrotum is a separate protrusion of the anterior abdominal wall. It consists of two separate chambers, in which are located the testicles, epididymis and part of the spermatic cord.

The membranes of the testicle and the spermatic cord, counting from the outside, are as follows: skin (cutis), tunica dartos, external fascia spermatica (fascia spermatica externa), fascia cremasterica, m. cremaster, the internal seminal fascia (fascia spermatica interna), tunica vaginalis testis.

Testicles (testes) are paired, ovoid male reproductive organ that sits in the scrotum, separated from its mate by a scrotal septum. The testicle parenchyma consists of the seminiferous tubules. There are tortuous (tubuli seminiferi contorti) and direct (tubuli seminiferi recti) seminal tubules. In each lobule there are 2-3 tubules and more.

Epididymis is a narrow long formation in which the upper, somewhat thickened part is the head of the epididymis (caput epididymidis) and the lower, more pointed end - the tail (cauda epididymidis); the intermediate site constitutes the body (corpus epididymidis). Ductuli efferentes open into a single duct of the epididymis (ductus epididymidis), which, forming numerous bends, continues into the ductus deferens. Ductus defferentes, lobuli epididymidis and its initial section form the caput epididymidis.

Vas deferens are a direct extension of the epididymis canal and differ from the latter by a larger wall thickness. Separated from the testicle vessels (a. and v. testiculares), the vas deferens upward and enters the spermatic cord.

Spermatic cord (funiculus spermatacus) is a round strand 16-20 cm long, covered with an external seminal fascia and located between the inner inguinal ring and the upper pole of the testicle. Its composition includes the vas deferens, the ovarian artery, the artery of the seminiferous duct, the lazoid venous plexus, the lymphatic vessels of the testicle and epididymis, the nerves and the vaginal membrane of the peritoneum.

The prostate gland (prostata) is an unpaired glandular-muscular organ resembling a truncated cone in shape. It eccentrically covers the initial part of the urethra and closely belongs to its base to the bottom of the bladder, and the upper part to the urogenital diaphragm.

Seminal vesicles (vesiculae seminales) lie laterally from the vas deferens, between the bottom of the bladder and the rectum. Each seminal vesicle has a length of up to 12 cm in expanded form, and a length of 5 cm in undressed. The lower pointed end of the seminal vesicle passes into a narrow excretory duct (ductus excretorius), which connects at an acute angle with the ductus deferens of the same side, forming together with it the ductus ejaculatorius.

Bulbourethral glands (glandulae bulbourethral) are two glands, each 0.5-0.7 cm in diameter, located in the thickness of the diaphragma urogenitale above the posterior end of the bulbus penis, posteriorly from the pars membranacea urethrae.

The penis refers to the external genital organs together with the scrotum. It consists of three bodies: a paired cavernous (corpus cavernosum penis) and an unpaired spongiosum (corpus spongiosum penis).

Theme # 3: The main symptoms in urology: pain, changes in the act of micturition, quantitative and qualitative changes in urine, pathological discharge from the urethra and changes in sperm.

3.1 Pain

Pain arising from the genitourinary tract may be quite severe and is usually associated with:

1. **Obstruction:** (ureteric stone, urinary retention);

2. **Inflammation:** (pyelonephritis, prostatitis, epididymitis etc.). Inflammation of the mucosa of the bladder or urethra usually produces discomfort;

3. **Tumors of the urogenital tract** usually do not cause pain unless they produce obstruction or extend to adjacent nerves;

4. **Urological trauma.**

Dull aching pain in the lumbar region is observed in many kidney diseases: chronic pyelonephritis, urolithiasis, hydronephrosis, kidney tumors, etc. Pain in the lumbar region can also occur with vesicoureteral reflux.

The most characteristic type of pain in diseases of the upper urinary tract is **renal colic** (Fig. 22), which occurs when a sudden outflow of urine out of the ureter from the pelvis, which leads to an increase in pressure in the renal cavity. This is accompanied by compression of thin-walled veins of the kidney, ischemia of its parenchyma, dilatation of the fibrous capsule and edema of the parenchyma [20].

Renal colic occurs suddenly, has an intense character, is localized in the lumbar region and hypochondrium, and extends down the ureter, into the groin, external genitalia and the inner thigh. Renal colic can be accompanied by nausea, vomiting, frequent and painful urination (with the location of the calculus in the juxtavesical or intramural ureter).

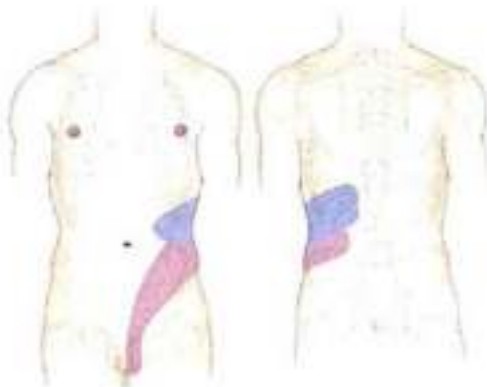

Fig. 22 - Renal colic: irradiation of pain

(illustration from https://i.pinimg.com/736x/8d/5b/1b/8d5b1b92ef98fe08f8e4fd3eb18a8592--kidney-stones-kidney-disease.jpg)

The main causes of renal colic are stones of the renal pelvis and ureter, blood clots and mucus, necrotic tissues, that is, pathological conditions that are accompanied by the acute onset obstruction of the ureter.

Pain in the lumbar region, arising at the time of urination, is a sign of vesicoureteral reflux, that is, reverse urine flow from the bladder to the ureter in the renal pelvis.

Pain in pathological conditions of the ureters is localized along their trajectory. The lesion of the ureter can be determined by the location of the pain. Thus, when the middle third of the ureter is involved in the pathological process, the pain radiates to the iliac region, with the lesion of the lower third to the scrotum in men and to the labia in women. However, more often ureteral diseases manifest painful sensations from the side of the corresponding kidney, which is caused by a violation of the passage of urine.

Pain in diseases of the bladder is localized in the suprapubic region. It can be permanent, not depending on the act of urination, or periodic, intensifying in connection with urination. The elucidation of the persistence of pain, their association with the act of urination, is a great importance for establishing the correct diagnosis. Pain in the bladder may be associated with overstretch of its wall with acute retention of urination, inflammation of the wall of the bladder or paravesical tissue, stones and invasive forms of malignant tumors.

Bladder stones are characterized by pain intensifying during movement, and with the act of urination there is an interruption, the laying of a urine stream. The pain often irradiates into the glans of penis. The pain in inflammatory diseases of the bladder is usually associated with an act of urination and it can occur before the beginning of urination, during or at the end of it.

Pain in the urethra is often associated with diseases of the prostate, bladder and even kidneys. Pain in diseases of urethra is localized along the body of penis, have a cutting character, intensifying with urination. The causes of these pains are acute and chronic inflammation, stones and tumors of the urethra.

Pain in diseases of the prostate gland is usually localized in the perineum, in the region of the sacrum or in the lower abdomen. Typical is their irradiation into the inguinal region, external genitalia and rectum. Acute prostatitis is characterized by intense pain. In severe cases, edema of the prostate gland can cause an acute delay in urination.

Pain in diseases of the external genital organs is localized in the corresponding half of the scrotum and irradiates along the spermatic cord to the waist region. Pain in the scrotum is usually a consequence of acute epididymitis, orchiepididymitis or torsion of the testis. These diseases are characterized by sharp pains that increase with movement. Mild aching pain in the scrotum without irradiation is most often associated with non-inflammatory diseases, such as varicocele and hydrocele.

Pain in the penis usually indicates its inflammation (cavernitis, balanoposthitis) or trauma. Persistent strong pain can be observed with a prolonged erection, not associated with sexual act, what is called priapism.

3.2 Changes in the act of micturition

Violations of urination, or dysuria, are a collective concept that includes various types of urination disorders. There are symptoms associated with irritation of the bladder, and symptoms caused by intravesical obstruction (hindered outflow from the bladder) [31]. The first include:

Pollakiuria - frequent urination in small portions. This symptom can occur both with urological (pyelonephritis, urolithiasis, acute and chronic cystitis, tuberculosis of the urinary system, benign prostatic hyperplasia, prostatitis, etc.), and with neurological (sugar or diabetes insipidus, pathological processes in neighboring with bladder organs and tissues) diseases.

Strangury - difficult painful urination in small portions, accompanied by frequent imperative urge to urinate. It occurs more often with stones of the bladder, with locally advanced forms of prostate and bladder cancer, with severe forms of acute cystitis.

Nocturia - by definition of the International Continence Society (ICS), the need to wake up at night to empty the bladder (two or more urination per night). Nycturia (in Russian-language sources) denotes the predominance of nocturnal diuresis over the daytime diuresis due to the release of fluid that has accumulated in the body during waking hours. If there is a lot of urine, then even with normal bladder capacity, nycturia can go into nocturia.

An imperative urge is a sudden strong urge to urinate, in which urine is sometimes impossible to hold.

Symptoms associated with intravesical obstruction include:

Ischuria - delay urination. Sharp acute and chronic retention of urination. The first is manifested by the impossibility of independent urination with strong urge to it, overflow of the bladder and severe pains in the lower abdomen. With chronic retention of urination, the patient urinates with a weakly weakened jet, while the so-called residual urine remains in the bladder. The amount of it can be from 50-100 ml to 1.5-2 liters, and in rare cases and more.

The most common cause of the development of ischuria is the intravesical obstruction that occurs with benign prostatic hyperplasia or cancer, bladder stones, strictures, tumors and urethral injuries.

Typical symptoms of intravesical obstruction are difficulty in the beginning of urination, the need for straining, a decrease in the pressure of the urine stream, a feeling of incomplete emptying of the bladder.

Terminal leakage - prolonged dropping of urine after the completion of the act of urination.

Intermittent excretion, pouring of the urine stream is a symptom observed in the presence of a calculus in the bladder.

Spraying of the urine stream often occurs with stricture of the urethra.

Urinary incontinence is an uncontrolled urinary incontinence by the patient, which occurs without the urge to urinate.

1. Stress urinary incontinence is a sudden involuntary discharge of urine due to physical stress, sneezing, coughing, fast walking or any other activity that causes an increase in intra-abdominal pressure. The pathogenesis of stress incontinence is based on the inadequacy of the sphincter apparatus of the bladder. In men, the most common cause of stress incontinence is damage to the sphincter as a result of surgical interventions on the prostate gland. In women, the main causes of this type of incontinence are the hypermobility of the urethra.

2. Urgent incontinence - incontinence, which occurs due to an irrepressible imperative urge to urinate. Urgent incontinence of urine is based on hyperactivity of the bladder (involuntary cuts of the detrusor during the filling phase). The main causes of bladder hyperactivity: 1) neurological pathology (violation of neurogenic regulation of the bladder function); 2) pathology of the urogenital system (cystitis, bladder stones, intravesical obstruction); 3) when it is impossible to determine the cause of hyperactivity is used the term "idiopathic hyperactivity of the bladder".

3. Mixed urinary incontinence is a combination of urgent and stress urinary incontinence in patients.

Enuresis - incontinence, which occurs during sleep. This type of urinary incontinence is common in children under 3 years of age, but is also detected in 15% of children aged 5 years and 1% at 15 years. Urological, neurological and psychiatric diseases in these patients, as a rule, are not detected.

Constant urinary incontinence - involuntary discharge of urine outside the sphincter mechanism through bladder defects. It occurs most often with vesicovaginal, urethrovaginal fistulas and ectopia of the ureteral orifice.

Urinary incontinence due to overflow (ischuria paradoxa) occurs as a result of prolonged delay and accumulation in the urinary bladder of a large amount of urine. This involuntary leakage of urine occurs when the intravesical pressure increases, which overcomes the sphincter resistance. Hypotension of detrusor is combined with hypotension of the sphincter. Incontinence is most often due to the severe form of the intravesical obstruction.

Undermining (dribbling) - involuntary loss of urine after the act of urination. In men, digging is caused by a delay in urine in the urethra distally of the internal sphincter, and in women - by the accumulation of urine in the urethral diverticulum or in the vagina.

3.3 Quantitative changes in urine

Daily diuresis is the volume of urine produced per day. It is near 1.5 liters in an adult. Changes in the amount of urine released include polyuria, oliguria, anuria and nycturia (in Russian-language sources) [31].

Polyuria - an increase in the amount of daily urine to 2-3 liters and more. With urological diseases, it is mainly associated with loss of kidneys concentration ability. It can be observed in chronic pyelonephritis, chronic renal failure and acute renal failure in the polyuric phase.

Oliguria - a daily diuresis less than 500 ml. Most often observed in the terminal stage of chronic renal failure and acute renal failure in the oliguric phase. It may not be associated with kidney disease, but is caused by a significant loss of fluid (increased sweating, bleeding, vomiting, diarrhea) or the presence of severe heart failure.

Anuria - complete cessation of urine or excretion of no more than 50 ml of urine per day. Types of anuria are arenal, prerenal, renal, and postrenal.

Arenal anuria occurs in the absence of kidneys. Such a condition can be congenital or caused by the removal of a single or only functioning kidney.

Prerenal (vascular) anuria can develop in shock states accompanied by massive blood loss, hypotension, with heart failure, vascular thrombosis of both or a single kidney.

The causes of **renal (parenchymal) anuria** are poisonings with nephrotoxic poisons, hemolysis with transfusion of incompatible blood, crash syndrome, etc.

Postrenal (obstructive) anuria develops as a result of stone obstruction or compression from the outside of either ureters or the ureter of a single kidney by a tumor.

Nycturia - the predominance of nocturnal diuresis over daytime. It can be observed in chronic pyelonephritis, chronic renal failure and heart failure.

3.4 Qualitative changes in urine

An important qualitative characteristic of urine is its relative density (specific gravity), which is normally 1020-1026. It can fluctuate within a fairly wide range within 24 hours, depending on the concentration of substances dissolved in the urine, especially urea, uric acid, creatinine etc.

Reduction of the relative density of urine below 1010 is called **hyposthenuria**. This condition is observed in diabetes insipidus, and more often occurs as a result of a decrease in the ability of the renal tubules to reabsorb water and is a sign of renal failure. When the renal function is impaired, hyposthenuria is

combined with isosthenuria, that is, the absence of fluctuations in the specific gravity of urine during the day. The combination of low and monotonous relative density of urine is called **hypoisosthenuria**.

Hypersthenuria is an increase in the relative density of urine of more than 1030. It may not be associated with kidney disease and can be observed as a variant of the norm with abundant perspiration in hot climates or a decrease in fluid intake. In renal failure hypersthenuria is associated with a sharp increase in the reabsorption of water in the renal tubules. An increase in the relative density of urine can also occur with neurological diseases, for example, with cardiovascular failure, diabetes mellitus with increased glucose content in the urine (glucosuria), and others.

The reaction (pH) of urine is normally on average from 4.5 to 8.0. It can vary within a day, depending on the nature of the fluid and food consumed. Vegetable products, milk, rye bread alkalinize; eating protein foods and fats increases the acidity of urine. Changes in the urine reaction can occur with a number of urological diseases, especially in the infection of the kidneys and urinary tract. A decrease in the pH of urine is observed with urate stones or tuberculosis of the urogenital system.

Transparency of urine

In a healthy person the freshly released urine is clear. Urine clouding is due to the presence in it of an increased number of epithelial cells of the urinary tract, bacteria, mucus, pus and salts. Microscopic examination of the urine sediment allows establishing the character of the salts.

The formation of a large number of calcium and magnesium salts of phosphoric acid in the urine is called phosphaturium, while urine acquires a murky whitish color and an alkaline reaction. This condition occurs with the eating milk products, alkaline mineral water, soda or as a consequence of the violation of mineral metabolism.

Oxaluria - the presence in the urine of a large number of calcium salts of oxalic acid - is the result of eating sorrel, spinach, coffee, cocoa, chocolate. It can also be observed in diabetes mellitus, jaundice, leukemia.

Uraturia - the content in the urine sediment of calcium salts of uric acid. Observed with excessive consumption of meat products and violation of purine metabolism (gout).

Leukocyturia - the detection of leukocytes in urine with its microscopic examination. It occurs with all inflammatory diseases of the organs of the urinary and excretory system and the prostate gland, except in cases where the focus of inflammation is delimited and does not communicate with the lumen of the urinary tract. The expressed leukocyturia (in the general analysis of urine leukocytes cover the entire field of vision) with a visually defined turbidity of urine is designated as pyuria, i.e. pus in the urine.

Bacteriuria - the presence of bacteria in the urine. Like leukocyturia,

bacteriuria accompanies inflammatory diseases of the urogenital system. Bacteriuria is detected by a bacterioscopic or bacteriological method. At the last after sowing urine determine the type and quantity of microorganisms. Depending on the number of bacteria found in 1 ml of urine, the bacteriuria is divided into true and false. True bacteriuria is considered when in 1 ml of urine, when it is sown on special media, more than 10^5 microbial bodies grow. False bacteriuria occurs when there are less than $0.5\text{-}10^5$ microbial bodies in 1 ml of urine. It is not regarded as a sign of a pathological process. Most often, inflammation of the kidneys and urinary tracts is sown with Gram-negative flora - intestinal and pseudomonas aeruginosa, various strains of the proteus, Klebsiella, less often - enterococcus, staphylococcus, etc.

Proteinuria (albuminuria) is the protein content in the urine. In a healthy person, the protein in the urine is absent or its content does not exceed 0.033 g / l. Daily excretion of protein with urine is 50 mg. Physiological proteinuria can occur during physical exertion, after consuming a large amount of protein. Pathological proteinuria usually occurs with kidney disease with nephron damage. Proteinuria is also divided into true (renal) and false (extra-renal). With true proteinuria, the protein penetrates from the blood into the urine through the pathologically altered membranes of the renal glomeruli, which occurs in nephrologic diseases such as glomerulonephritis, renal amyloidosis, nephrosclerosis, etc. True proteinuria can also be observed in poisonings, disorders of renal circulation, nephropathy of pregnant women. False proteinuria, as a rule, is a sign of urological diseases. It occurs when the leukocytes, red blood cells and urothelial cells that are in the urine disintegrate, which enter the urine, which has already passed the renal filter from the urinary tract.

Cylindruria is the formation in the urine of cylinders. True cylinders are "molds" of the renal tubules, consisting of protein (hyaline, granular, waxy, epithelial). False cylinders consist of salts, bacteria and mucus. True cylindruria is observed in nephrologic diseases (glomerulonephritis, amyloidosis of the kidneys) or prolonged use of nephrotoxic antibiotics. Hyaline cylinders are found in the urine after exercise or fever.

The color of the urine is normally straw-yellow. Its saturation varies and depends on the amount of pigments present in the urine (urochrome, urobilin, uroerithrin, etc.) and diuresis. In polyuria, urine is colorless or light yellow, and when its daily amount decreases, it becomes dark yellow.

Pale red color can impart urine to food products (beet, rhubarb) or drugs (amidopyrine, rifampicin).

Red color of urine of various degree of saturation: from pale pink to red-burgundy - is caused by the presence of blood (erythrocytes) - **hematuria** in it (Fig. 23). Depending

on the amount of blood in the urine is **microhematuria (erythrocyturia)** and **macrohematuria**. With microhematuria, the color of urine is visually unchanged, and the presence of blood in it is established by microscopic examination of the urine sediment. With macrohematuria, the blood content in the urine is considerable, and it acquires a different intensity of red color.

Staining of the urine stream varies from the location of the source of bleeding in the urinary tract. Depending on this, the following types of macrohematuria are:

Initial (initial) - only the first portion of urine is colored with blood, the rest of urine is of normal color. Observed with injuries and diseases of the urethra;

Terminal - the blood is visualized only in the last portion of urine, the initial portions of its usual color. Observed with diseases of the neck of the bladder, posterior urethra and prostate;

Total - urine is colored with blood throughout the act of urination. Most often it occurs in tumors of the kidneys of the ureters and bladder, hemorrhagic cystitis.

To determine the location of the pathological process that caused hematuria, a three-glassed sample is used. The patient urinates in three vessels. If the urine is dyed with blood only in the first, then we are talking about the initial hematuria, the presence of blood only in the third glass speaks of terminal hematuria. With total hematuria, all three portions of urine are colored with blood.

Hematuria can be observed in almost all diseases of the urinary tract. In most cases, the painless macrogematuria is caused by the oncological pathology of the urinary system. With the presence of blood in the urine, cystoscopy is shown, which an important study in establishing a topical diagnosis is. This study can reveal a bladder pathology that is a source of hematuria (tumor, stones, hemorrhagic cystitis), or the presence of blood from the mouth of one of the ureters.

Urethrorrhagia - the discharge of blood from the urethra outside the act of urination. It occurs only with trauma and diseases (tumors) of the urethra.

Hemoglobinuria - the appearance of hemoglobin in the urine. It occurs in hemoglobinemia caused by hemolysis due to poisoning with hemolysing poisons of both exogenous

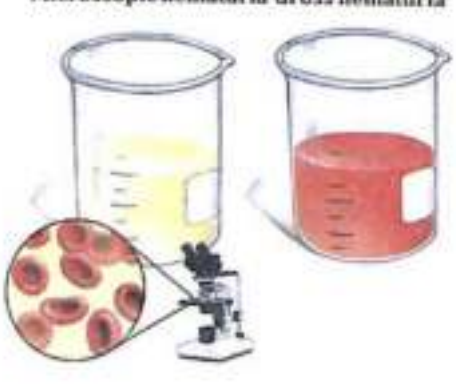

Fig. 23 - Hematuria

(Illustration from http://blog.cdtreatmentindia.com/wp-content/uploads/2016/06/Blood-in-Urine-Hematuria-Causes-Symptoms-Diagnosis-Complications-Treatment-in-India.jpg)

and endogenous origin or with transfusion of incompatible blood.

Myoglobinuria is the presence of myoglobin in the urine; while it is painted in a reddish-brown color. Myoglobinuria is observed in the syndrome of prolonged compression, crushing of the tissues and is associated with the entry into the urine of the pigment of the striated muscles. A serious complication of this condition is acute renal failure as a result of the pigmentation of the convoluted tubules of the kidneys.

Lipiduria is a presence of lipids in urine. The most common cause of this condition is the fracture of the tubular bones with the introduction of a large amount of lipids into the bloodstream, and then into the urine.

3.5 Pathological discharge from the urethra

Purulent or serous discharge from the external hole of the urethra, not associated with the act of urination, is a sign of inflammation of the urethra - urethritis. Purulent discharge is most pronounced with urethritis of gonorrheal etiology.

Prostatorrhea - the emission of prostatic secretions during straining associated with urination or defecation. At a microscopic examination spermatozoa are absent. It is a common symptom of chronic prostatitis.

Spermatorrhea - the emission of semen from the urethra without the sexual act, without erection, ejaculation and orgasm. It occurs in patients with chronic prostatitis, and may also be a symptom of organic damage to the central nervous system.

3.6 Changes in sperm

Aspermatism is the absence of the emission of semen during sexual intercourse. Spermatogenesis in this state, as a rule, is preserved [72].

There are true and false forms of aspermatism. With true aspermatism, the sexual act does not end with ejaculation and orgasm.

This is caused by congenital or acquired (cicatricial changes) by the obstruction of the excretory ducts of the prostate gland and the vas deferens. True aspermatism can also be associated with damage and organic diseases of the central nervous system. With false aspermatism, the sexual act ends with retrograde ejaculation and orgasm, that is, the ejaculate does not emerge outside the urethra, but is thrown back (retrograde) into the bladder. The causes of this condition can be congenital (ectopia of the

ejaculatory ducts) or acquired (stricture of the urethra, prostate gland surgery) of the disease.

Diagnosis of aspermia is based on the results of microscopic examination of the ejaculate and testicular biopsy.

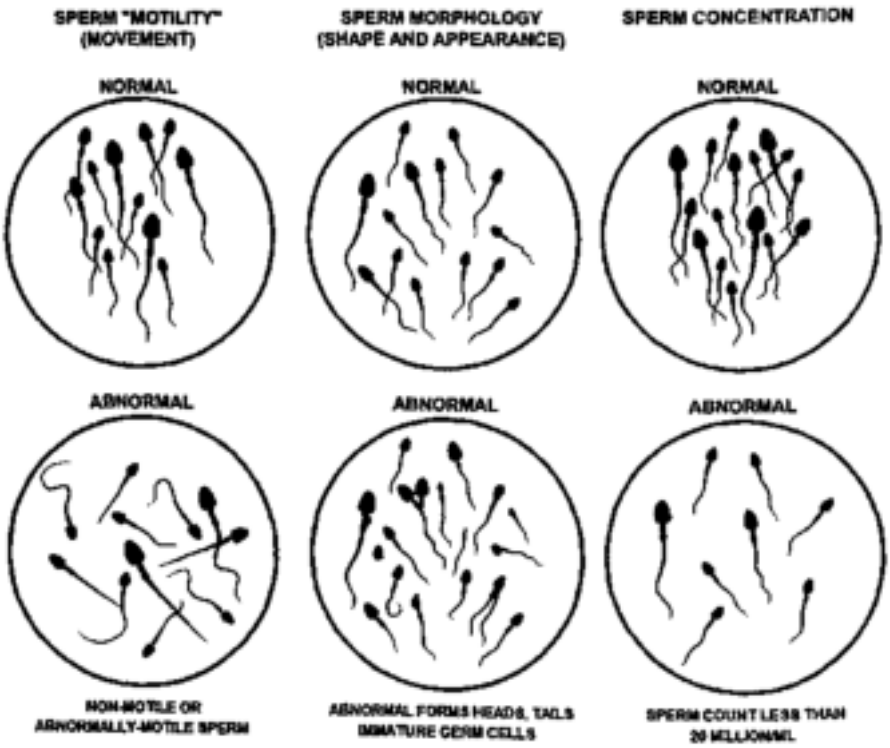

Fig. 24 – Normal and abnormal sperm

(Illustration from https://eda4.vectorstock.com/i/1000x1000/42/28/normal-and-abnormal-sperm-vector-6834228.jpg)

Aspermia - absence in the ejaculate of spermatozoa and cells of spermatogenesis with preserved spermatogenesis. Aspermia develops as a result of obstruction of the vas deferens due to malformations, inflammatory diseases of the genital organs, damage to them during operations on the organs of the scrotum or hernia repair.

Azoospermia - pathological condition in which spermatozoa are absent in the ejaculate. It occurs due to the defeat of the spermatogenic epithelium of the convoluted tubules of the testicle. The cause of azoospermia is most often the infectious diseases (infectious parotitis), poisoning with phosphorus, lead, arsenic,

hypovitaminosis A and E, testicular hypoplasia, varicocele.

Oligozoospermia - a decrease in the number of spermatozoa in the ejaculate (20 million or less in 1 ml) (Fig. 24). In male infertility, the most common is oligozoospermia.

The most frequent causes are abnormalities and damage to the testicles, hypovitaminosis, diabetes mellitus, alcoholism, poisoning with heavy metal, intoxication due to smoking and drugs, and others.

Asthenozoospermia - decrease in mobility up to 50% of spermatozoa present in the volume of seminal fluid.

Teratozoospermia is a condition in which more than 50% of pathological forms of spermatozoa are contained in semen.

Hemospermia - the presence of blood in the ejaculate. It is divided into the true (the blood enters the ejaculate in the testicles and the seminal pathways) and the false one (the blood is mixed in the ejaculate in the urethra). With true hemospermia, the color of the seminal fluid is uniform, brown, with a false in the seminal fluid there are veins of fresh blood. Hemospermia is often a symptom of inflammatory diseases of the genital organs, benign hyperplasia and prostate cancer.

The main symptoms in urology: pain, changes in the act of micturition, quantitative and qualitative changes in urine, pathological discharge from the urethra and changes in sperm.

Pain arising from the genitourinary tract may be quite severe and is usually associated with:

1. Obstruction: (ureteric stone, urinary retention);

2. Inflammation: (pyelonephritis, prostatitis, epididymitis etc.). Inflammation of the mucosa of the bladder or urethra usually produces discomfort;

3. Tumors of the urogenital tract usually do not cause pain unless they produce obstruction or extend to adjacent nerves;

4. Urological trauma.

Violations of urination, or dysuria, are a collective concept that includes various types of urination disorders.

The symptoms associated with **irritation of the bladder:**

Pollakiuria - frequent urination in small portions.

Strangury - difficult painful urination in small portions, accompanied by frequent imperative urge to urinate.

Nocturia - by definition of the International Continence Society (ICS), the need to wake up at night to empty the bladder (two or more urination per night).

An imperative urge is a sudden strong urge to urinate, in which urine is sometimes impossible to hold.

Symptoms associated with **intravesical obstruction** include:

Ischuria - delay urination. There are acute and chronic retention of urination.

Terminal leakage - prolonged dropping of urine after the completion of the act of urination.

Intermittent excretion, pouring of the urine stream is a symptom observed in the presence of a calculus in the bladder.

Spraying of the urine stream often occurs with stricture of the urethra.

Urinary incontinence is an uncontrolled urinary incontinence by the patient, which occurs without the urge to urinate.

1. **Stress urinary incontinence** is a sudden involuntary discharge of urine due to physical stress, sneezing, coughing, fast walking or any other activity that causes an increase in intra-abdominal pressure.

2. **Urgent incontinence** - incontinence, which occurs due to an irrepressible imperative urge to urinate.

3. **Mixed urinary incontinence** is a combination of urgent and stress urinary incontinence in patients.

Enuresis - incontinence, which occurs during sleep.

Constant urinary incontinence - involuntary discharge of urine outside the sphincter mechanism through bladder defects. It occurs most often with vesicovaginal, urethrovaginal fistulas and ectopia of the ureteral orifice.

Urinary incontinence due to overflow (ischuria paradoxa) occurs as a result of prolonged delay and accumulation in the urinary bladder of a large amount of urine.

Undermining (dribbling) - involuntary loss of urine after the act of urination. In men, digging is caused by a delay in urine in the urethra distally of the internal sphincter, and in women - by the accumulation of urine in the urethral diverticulum or in the vagina.

Quantitative changes in urine are:

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Oliguria - a daily diuresis less than 500 ml.

Anuria - complete cessation of urine or excretion of no more than 50 ml of urine per day. Types of anuria are arenal, prerenal, renal, postrenal.

Arenal anuria occurs in the absence of kidneys. Such a condition can be congenital or caused by the removal of a single or only functioning kidney.

Prerenal (vascular) anuria can develop in shock states accompanied by massive blood loss, hypotension, with heart failure, vascular thrombosis of both or a single kidney.

The causes of **renal (parenchymal) anuria** are poisonings with nephrotoxic poisons, hemolysis with transfusion of incompatible blood, crash syndrome, etc.

Postrenal (obstructive) anuria develops as a result of stone obstruction or compression from the outside of both ureters or the ureter of a single kidney by a tumor.

Nycturia - the predominance of nocturnal diuresis over daytime. It can be observed in chronic pyelonephritis, chronic renal failure and heart failure.

Qualitative changes in urine are:

Reduction of the relative density of urine below 1010 is called **hyposthenuria.** The combination of low and monotonous relative density of urine is called **hypoisosthenuria**.

Hypersthenuria is an increase in the relative density of urine of more than 1030.

Oxaluria - the presence in the urine of a large number of calcium salts of oxalic acid

Uraturia - the content in the urine sediment of calcium salts of uric acid.

Leukocyturia - the detection of leukocytes in urine with its microscopic examination.

Bacteriuria - the presence of bacteria in the urine.

Proteinuria (albuminuria) is the protein content in the urine.

Cylindruria is the formation in the urine of cylinders.

Red color of urine of various degree of saturation: from pale pink to red-burgundy - is caused by the presence of blood (erythrocytes) - **hematuria**. Depending

on the amount of blood in the urine is **microhematuria (erythrocyturia)** and **macrohematuria**. The following types of macrohematuria are:

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Myoglobinuria is the presence of myoglobin in the urine; while it is painted in a reddish-brown color.

Lipiduria is a presence of lipids in urine.

Pathological discharge from the urethra are:

Prostatorrhea - the emission of prostatic secretions during straining associated with urination or defecation.

Spermatorrhea - the emission of semen from the urethra without the sexual act, without erection, ejaculation and orgasm.

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Changes in sperm are:

Aspermatism is the absence of the emission of semen during sexual intercourse.

Aspermia - absence in the ejaculate of spermatozoa and cells of spermatogenesis with preserved spermatogenesis.

Azoospermia - pathological condition in which spermatozoa are absent in the ejaculate.

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Teratozoospermia is a condition in which more than 50% of pathological forms of spermatozoa are contained in semen.

Hemospermia - the presence of blood in the ejaculate.

Theme # 4: Clinical methods of examination: anamnesis, physical examination and palpation. Laboratory, ultrasound and X-ray methods of examination.

4.1 Anamnesis

History taking and clinical examination include the initial approach to the patient and collection of the database information which represent the most important steps in reaching the diagnosis. Laboratory data, radiology films, and reports giving a certain diagnosis, should be considered in the proper time, without overlooking the initial steps of basic clinical urology [9].

Age, gender, race, and ethnicity are important in the overall history of the client with suspected renal or urinary dysfunction. A sudden onset of hypertension in clients older than 50 years of age suggests possible kidney disease.

It is necessary to find out the time of the onset of the disease, to study the features of its development (Tab. 1). Some urological diseases, for example urolithiasis, are asymptomatic for a long time, and then manifest (renal colic) suddenly. So, for a certain time, the only clinical manifestation of urinary tract tumors can be the appearance of blood in the urine, which patients can associate with the intake of food products, etc.

It is necessary to gather information about all previous methods of treatment and the nature of the operations performed, it is advisable to get acquainted with the available medical documents. In the case of a patient taking any medications (especially antibacterial drugs), it is necessary to find out the nature and duration of previous therapy.

Tab. 1 - Details of the current symptoms

Details of the current symptoms (OLD CARTS):
Onset: date it began, sudden or gradual, over how long?
Location and radiation: ask the patient to point to the site with one finger and whether the pain moves anywhere else?
Duration
Characters: nature of the symptom
Aggravating factors: What makes the symptom worse?
Relieving factors: What makes the symptom better?
Timing and frequency: improving or deteriorating with time
Severity

4.2. Physical examination

When examining the lumbar region you should evaluate its symmetry, the presence of traces of damage, swelling, and hyperemia.

The inflammatory process in the kidney and/or perinephric fat causes a noticeable scoliosis on the affected

side, which is explained by the involvement in the process m. psoas.

While examining the anterior abdominal wall, you can reveal swelling above the pubis (Fig. 25).

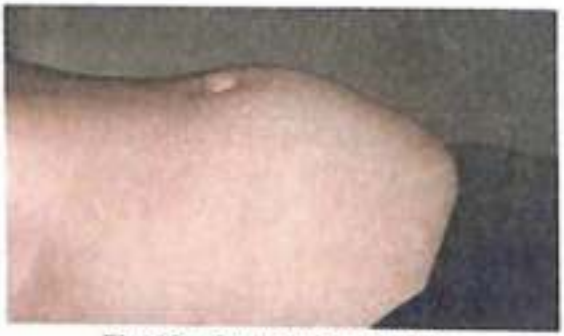

Fig. 25 - Overflowing bladder

(Illustration from https://www.treatment-online.com.ua/images/5_renal_and_urinary_system/5_1_renal_and_urinary_system/5_1_17.jpg)

This swelling is associated with an overflowing bladder caused by an acute urinary retention [35].

While examining the penis pay attention to the presence of rashes and condylomas. Expose the prepuce; inspect the glans penis, the inner surface of the prepuce, the external opening of the urethra, which is normally located on the tip of the glans penis.

With hypospadias (dystopia of the external hole of the urethra), the urethra opens on the ventral surface of the penis, in the scrotum or on the perineum. There is a complete or partial absence of the anterior wall of the urethra.

Phimosis is a condition in which the foreskin of the penis cannot be pulled back past the glans. A balloon-like swelling under the foreskin may occur with urination. In teenagers and adults, it may result in pain during an erection, but is otherwise not painful. Those affected are at greater risk of inflammation of the glans, known as balanitis, and other complications.

Inspection of the scrotum is carried out in the upright position of the patient. It is necessary to pay attention on the condition of the skin and symmetry of both halves of the scrotum. The increase is observed with fluid accumulation between the testicles, tumors of the scrotum, generalized edema (with heart function failure).

With a pronounced varicocele, the enlarged veins of the spermatic cord can be visually determined. Hyperemia of the skin can be a sign of acute inflammatory diseases of the scrotal organs.

4.3 Palpation

The kidneys cannot be palpated normally even in a slim person (Fig. 26). You need to use both hands to feel the kidneys. With the left hand on the back of the patient under the 12th rib pushing upwards and the right hand

pushing down just below the costal margin. Ask the patient to take a deep breath to help descend the kidney as you attempt to trap it between your two hands. The examiner is required to somewhat firmly push his/her hands together as the patient inhales air with a deep breath. The enlarged kidney may be felt as you try to capture it between your two hands in conjunction with the commencement of inspiration.

Fig. 26 - Palpation of the kidney
Illustration from https://lechimepochki.ru/wp-content/uploads/2017/06/3-22.jpg

On inspiration one may feel the lower pole of the kidney moving down between the hands in response to this the examiner can ballot or push the kidney forwards and backwards between the hands. An easily palpable and/or tender kidney is abnormal.

If you are able to palpate the kidneys try to describe its texture and size. It is usually tender in hydronephrosis or when acutely infected in pyelonephritis. Another method for assessing kidney tenderness is to percuss over them. The kidney is palpable if it is displaced (dystopia, nephroptosis) or enlarged.

An obligatory method of general clinical examination is the determination of symptom of effleurage. For this, in the position of the patient standing or sitting with the edge of the palm, light tapping is performed in the costal-lumbar corner. The observed pain may be due to inflammation or stretching of the capsule of the kidney. The symptom is positive in many inflammatory and non-inflammatory diseases of the kidneys and paranephric fiber.

The urinary bladder is palpated in the form of a globular formation of an elastic consistency. Detect the bladder with a physical examination is possible provided that it contains at least 150 ml of urine. A bimanual digital examination is also used: in women, through the vagina, in men, through the rectum.

On palpation of the penis evaluate the consistency of the corpus cavernosum. The seals in the albumen of the cavernous bodies, often combined with complaints of curvature of the penis and weakening of erection, are referred to as Peyronie's disease (fibroplastic induction of the penis).

On palpation of the urethra assess the condition and consistency of the urethra, paraurethral tissues. In chronic urethritis or strictures of the urethra, it is possible to probe its consolidation, and in urolithiasis, stones stuck in the anterior urethra.

Palpation of the scrotum (Fig. 27) is performed in the following sequence: testicles, appendages,

spermatic cord, the area of the external inguinal ring.

On palpation, you should pay attention to the presence of both testicles, assess their symmetry, size and consistency (normally tight-elastic). The left testicle is usually located below the right. The epididymis is located on its back surface. It distinguishes the head, body and tail.

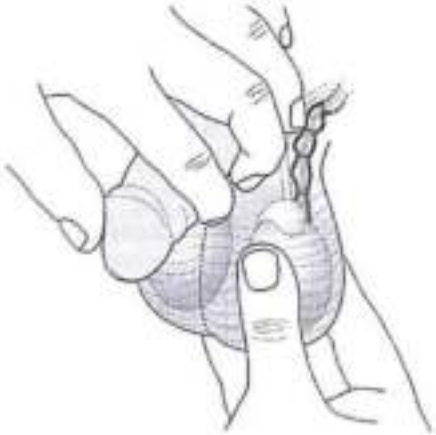

Fig. 27 - Palpation of the scrotum
(illustration from https://vprostatit.ru/wp-content/uploads/2017/10/pochemu-u-muzhchin-oshhushhayutsya-boli-v-levom-yaichke_moskovka.jpg)

The increase in the scrotum and the presence of additional formations during palpation requires a differential diagnosis of diseases of the scrotum organs by the method of diaphanoscopy. To do this, in a dark room the light source is fed from the posterior surface of the scrotum. Translucent content of the testicular membranes speaks in favor of hydrocele - fluid accumulation between the leaves of the vaginal testis. The absence of translucency indicates a testicular neoplasm, accumulation of blood between the sheets of the above shell or in the scrotum tissues.

Spermatocele - a cystic formation in the area of the epididymis - is palpated in the form of an elastic globular formation. Palpable thickening of the spermatic cord and the presence in the scrotum of multiple convoluted veins of the system of the pterygium-like plexus is characteristic of varicocele. Half of the scrotum, which is varicocele, is omitted. The study should be made in the position of the patient standing and lying down. The presence of the patient's right-sided varicocele or varicocele from any side that does not disappear in a horizontal position (Valsalva maneuver), especially in adulthood, may indicate a neoplasm of the kidney.

Palpation of the external inguinal ring can detect inguinal and femoral hernias. Using the index finger, they estimate the size of the external opening of the inguinal canal, after which they ask the patient to cough: the presence of a hernia is indicated by a positive symptom of a cough shock (an increase in intra-abdominal pressure occurs with cough). With cryptorchidism (congenital absence of one or both testicles in the scrotum) in the area of the inguinal ligament it is often possible to palpate an ectopic testicle.

Assessment of the prostate gland condition involves conducting a digital transrectal examination (Fig. 28). Examination is carried out in the position of the patient on the side or in

the knee-elbow position. To exclude diseases of the rectum should be palpated not only the prostate gland, but also the inner surface of the rectum.

The most common cause of an increase in the prostate gland is benign prostatic hyperplasia (adenoma) of the prostate, in which the increase in size

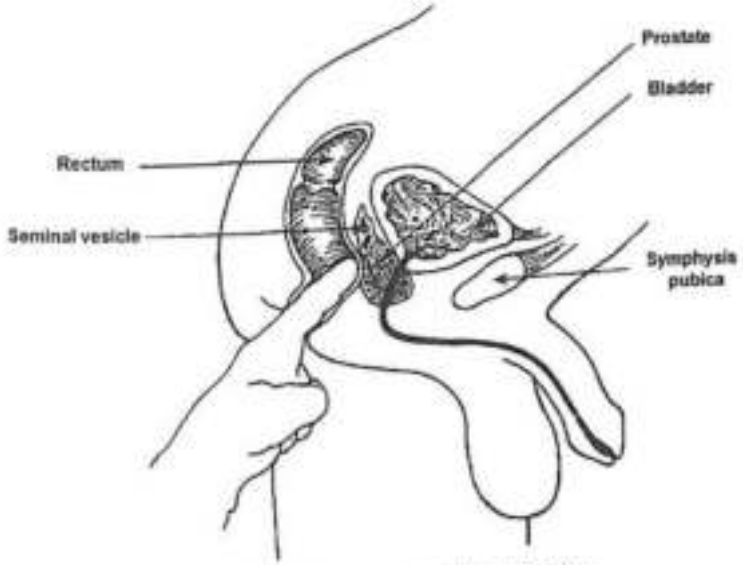

Fig. 28 - Digital rectal examination

Illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcSwHUa8h23uJBtpLFhevYIbkKxXF-vudLV32FvpL3svEOKrm_Ij

The index finger of the right hand, introduced into the rectum, determine the size of the prostate. Normal prostate gland has a size of 2.5-4.5 cm in the transverse direction and 2.5-3.5 cm - in the longitudinal, elastic consistency. In the middle of the gland is determined by the groove, dividing it into symmetrical lobes.

In the study of the prostate, the bias of the rectal mucosa, the presence or absence in the prostate gland of dense nodes, foci of fluctuation, infiltrates in the surrounding tissues is also assessed.

of the gland is determined, the smoothness of the median interlobar groove, followed by its disappearance. In prostate cancer is determined by one or more dense sites mainly in its peripheral parts.

With acute prostatitis, the gland is enlarged, sharply painful. With an abscess of the prostate, there may be foci of fluctuation.

In chronic inflammatory process, the prostate gland is slightly enlarged in size, has an uneven consistency.

Seminal vesicles during rectal examination can be palpated quite rarely (when they are inflamed or increased as a result of obstruction of the excretory ducts). Palpation assess their size, boundaries, tenderness and texture.

Percussion and auscultation. Kidney percussion in healthy people are not determined due to the characteristics of their topographical location. Only with their significant increase can you get a blunt sound when percussion over the region XI-XII of the thoracic and II-III lumbar vertebrae on both sides of the spine. Auscultation of the renal vessels makes it possible to identify systolic murmur in the projection of the renal arteries, due to their stenosis. Percussion with a filled bladder allows you to determine the dullness above the pubis, which helps in establishing the boundaries of the organ.

4.4 Laboratory methods

Blood test. Complete blood count in inflammatory diseases of the genitourinary organs is accompanied by leukocytosis with a shift of the leukocyte formula to the left, an increase in the erythrocyte sedimentation rate (ESR). In malignant tumors, a significant increase in ESR, development of anemia can be observed [25].

Biochemical blood tests include an assessment of the total nitrogen-excreting renal function: creatinine, urea, and uric acid values (these values increase in renal failure); states of homeostasis (electrolytes - Na, K, Cl, C02). It is obligatory to determine indicators of liver function - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes. Increased serum glucose may indicate the presence of diabetes mellitus.

Blood test for prostate specific antigen (PSA). In men over 45 years old and in cases of suspected prostate cancer, it is imperative to determine the level of PSA in the blood serum - a special glycoprotein produced by the prostate secretory epithelium and ensuring dilution of the ejaculate. Its main amount is in the ducts of the prostate gland, whereas in the serum in the absence of diseases of the prostate gland its concentration is low. The generally accepted rate of PSA in serum is from 0 to 4 ng / ml.

The definition of PSA is an essential component of screening for prostate cancer. Patients with elevated PSA are subject to further examination. A multifocal prostate biopsy is used to verify the diagnosis.

PSA is an organ-specific, but not tumor-specific marker and may increase for a number of other reasons: benign prostatic hyperplasia, acute and chronic prostatitis, after various instrumental examinations (catheterization, cystoscopy, biopsy), during acute and chronic urinary retention, after ejaculation, driving cycling, massage the prostate gland; digital rectal examination.

Analysis of urine (Fig. 29). Urinalysis plays a major role in recognizing diseases of the kidneys, urinary tract and genital organs.

Laboratory Test	Reference Standard/Range
Urinalysis	
Color	Yellow
Specific gravity	1.005-1.030
pH	5.0-8.0
Blood	Negative
Protein	Negative
Glucose	Negative
Leukocyte esterase	Negative
Nitrite	Negative
Urine microscopy	
RBCs	0-5/hpf
White blood cells	0-5/hpf
Casts	None
Dysmorphic RBCs	None
Urinary protein:creatinine ratio*	<150 mg/g

Fig. 29 – Urinalysis test

(Illustration from https://jamanetwork.com/data/Journals/JAMA/936505/joi170089f1.png)

Urinalysis includes determining its color, transparency, odor, reaction, relative density, presence and degree of urinary glucose and protein in the urine, counting blood cells, epithelial cells of the urinary tract, cylinders, salts and bacteria. For the study, fresh urine should be taken, since prolonged standing of the urine is accompanied by a change in its original composition (due to the destruction of the formed elements, the proliferation of microbes, changes in pH) and, consequently, leads to unreliability of the results of the analysis.

For the analysis is taken the average portion of urine. After the toilet of the external genital organs, the woman pushes the labia lips apart and collects a medium portion of urine into a container. If there are doubts about the purity of collected urine from women, it should be collected by catheterization of the bladder. Men need to move the foreskin and hold the toilet head of the penis. The patient begins to urinate into the toilet, and then substitutes a sterile container.

Urine study by Stamey-Mears. The generally accepted standard in the topical diagnosis of inflammatory diseases of the lower urinary tract in men is considered to be batch microscopic examination of urine. For microscopic examination and seeding four samples are taken. The first is the first 5-10 ml of urine mixed with the contents of the urethra. The second sample is a medium portion of urine. The third is the secret of the prostate gland, which is obtained after a transrectal massage of the organ. The fourth sample is a mixture of cystic urine and prostate secretion. Bacteriologically, the first urine sample characterizes the microflora of the urethra, the second - the bladder, and the secret of the prostate gland (the third sample) and the fourth urine sample - the microflora of the prostate gland. Thus, this study allows to localize the pathological process (urethritis, prostatitis, cystitis, etc.) and choose the optimal treatment tactics in each particular case [25].

The amount of urine. In a healthy person, the daily amount of urine depends on a number of factors (physical activity, amount of fluids taken, etc.) and averages 1500 ml.

The color of urine depends on the concentration of pigments in it (mainly urochrome). Normally, the urine is clear, straw yellow in color. Discoloration of urine may be due to the nature of nutrition, drugs, existing diseases. The color intensity of urine decreases with its abundant discharge (up to transparent) and, accordingly, increases with oliguria.

The relative density of urine during the day may vary and depends on the amount of fluid consumed and diuresis. Normally, daily variations in the relative density of urine are in the range from 1020 to 1026.

Low urine density, determined by repeated studies, may indicate a decrease in the concentration ability of the kidneys (in patients with chronic pyelonephritis and chronic renal failure). High urine density is observed in nephrotic syndrome, in patients with diabetes mellitus.

To assess the concentration function of the kidneys used **Zimnitsky sample**. To do this, urine is collected during the day every 3 hours. In each portion determine the relative density of urine. While maintaining the ability of the kidneys to osmotic dilution and concentration, there is a significant fluctuation in urine volume and relative density in individual portions. Low relative density with minor fluctuations is regarded as hypoisostenuria, which is characteristic of the late stage of chronic renal failure.

The urine pH is normally weakly acidic and ranges from 4.5 to 8.0. The reaction of urine is due to the content of free hydrogen ions in it. Alkaline reaction can be observed when urine is contaminated, bacteria multiply in it.

Smell of urine. Normal urine has a weak peculiar odor, when it stays for a long time, it smells of ammonia. In diabetic patients, urine may acquire the smell of rotten apples (acetonuria).

4.5 Ultrasound examination

Ultrasound examination (ultrasound, sonography) is the most widely used method of visualization in medical practice, which is due to its significant advantages: the absence of radiation load, non-invasiveness, mobility and accessibility [14, 15].

The method does not require the use of contrasting substances, and its effectiveness does not depend on the functional state of the kidneys, which is of particular importance in urological practice.

Currently, in practical medicine, ultrasound scanners operating in real time are used with image construction in the gray scale. In the operation of the instruments the physical phenomenon of echolocation is realized. The reflected ultrasound energy is captured by a scanning sensor and converted into electrical energy, which indirectly forms a visual image on the screen of

the ultrasound device in a palette of gray shades in both two- and three-dimensional images.

With the passage of an ultrasonic wave through a homogeneous liquid medium, the reflected energy is minimal, so an image in black is formed on the screen, which is called an anechoic structure. In the case when the fluid is contained in a closed cavity (cyst), the wall farthest from the ultrasound source is visualized better, and immediately behind it the effect of dorsal amplification is formed, which is an important sign of the fluid nature of the formation being studied. High hydrophilicity of tissues (zones of inflammatory edema, tumor tissue) also leads to the formation of an image in shades of black or dark gray, which is associated with low energy of the reflected ultrasound. This structure is called hypoechogenic.

Unlike liquid structures, hypoechoic formations do not have the effect of dorsal amplification. With an increase in the impedance of the structure under study, the power of the reflected ultrasound wave increases, this is accompanied by the formation on the screen of a structure of more and more light shades of gray, called hyperechoic. The more significant the echo density (impedance) is in the investigated volume, the brighter shades the image formed on the screen is characterized. The largest reflected energy is formed by the interaction of an ultrasonic wave and structures containing calcium (stone, bone) or air (gas bubbles in the intestine).

The best visualization of the internal organs is possible with a minimum content of gases in the intestine, for which ultrasound is performed on an empty stomach or using special techniques that lead to a reduction in flatulence. Locating the pelvic organs with transabdominal access is possible only when the bladder is tightly filled, which in this case plays the role of an acoustic window that conducts an ultrasonic wave from the surface of the patient's body to the object under study.

Currently, ultrasonic scanners use sensors of three modifications with various forms of the locating surface: linear, convex and sector - with a location frequency from 2 to 14 MHz. The higher the frequency of the location, the higher the resolution the sensor has and the larger the scale of the resulting image. At the same time, high-resolution sensors are suitable for the study of surface structures. In urological practice, these are the external genital organs, since the power of an ultrasonic wave decreases significantly with increasing frequency.

The task of the doctor during ultrasound diagnostics is to obtain a clear image of the object of study. For this purpose, various sonographic accesses and special modified sensors are used. Scanning through the skin is called transcutaneous. Transcutaneous ultrasound scanning of the abdominal organs and the small pelvis is traditionally called transadbominal sonography.

In addition to transcutaneous research, endocorporal scanning methods are often used, in which the sensor is placed in the human body through physiological holes. The most widely used are transvaginal and transrectal sensors, which are used to study the organs of the small pelvis. When performing transvaginal ultrasound imaging, the bladder, internal genital organs, mid- and lower-ampoule colon, Douglas space, partly urethra and distal ureters are available. In transrectal ultrasound, the internal genital organs are visualized regardless of the sex of the patient being examined, the bladder, the urethra throughout its length, the vesicoureteral segments and the pelvic ureters.

Transurethral access is not widespread due to the significant list of contraindications.

Nowadays, ultrasound scanners equipped with miniature high-resolution sensors and mounted in the proximal end of the flexible ureteroscope are increasingly used. This method, called endoluminal sonography, allows you to conduct a study of all parts of the urinary tract, which brings valuable diagnostic information for diseases of the ureter, the renal pelvis-pelvis system.

Ultrasound of vessels of various organs is possible due to the Doppler effect, which is based on the registration of small moving particles. In clinical practice, this method was used in 1956 by Satomuru for ultrasound of the heart. Currently, several ultrasound techniques are used to study the vascular system, which are based on the use of the Doppler effect - color Doppler mapping, energy Doppler. These techniques give an idea of the vascular architectonics of the object being examined. Spectral analysis allows to estimate the distribution of the Doppler frequency shift, to determine the quantitative velocity characteristics of the vascular blood flow. The combination of seroscal ultrasound image, color Doppler mapping and spectral analysis is called triplex scanning.

Doppler techniques in practical urology are used to solve a wide range of diagnostic issues. The most common color Doppler mapping technique. The definition of chaotic vascular structures in the tissue bulk formation of the kidney in most cases indicates its malignant character. If an asymmetric increase in the blood supply to the pathological hypoechoic areas in the prostate is detected, the probability of its malignant lesion increases significantly.

Spectral analysis of blood flow is used in the differential diagnosis of renovascular hypertension. The study of speed indicators at various levels of the renal vessels: from the main renal artery to the arcuate arteries - allows you to determine the cause of arterial hypertension. Spectral Doppler analysis is used in the differential diagnosis of erectile dysfunction. This technique is carried out using a pharmacological test. Methodical sequence includes the determination of speed indicators of blood flow in the cavernous arteries and dorsal vein of the penis in a state of rest. Later, after intracavernosal administration of the drug (papaverine,

caverdest, etc.), the penile blood flow is re-measured with indices determined. Comparison of the obtained results allows not only to establish the diagnosis of vasogenic erectile dysfunction, but also to differentiate the most interested vascular link - arterial, venous. The use of tabulated drugs that cause a state of tumescence is also described.

In accordance with the diagnostic tasks, the types of ultrasound are divided into screening, initial and expert. Screening studies aimed at identifying the preclinical stages of diseases are related to preventive medicine and are carried out by healthy people who are at risk for any disease. An initial (primary) ultrasound scan is performed on patients who seek medical help in connection with the occurrence of certain complaints. Its purpose is to establish the cause, the anatomical substrate of the existing clinical picture. The diagnostic task of an expert ultrasound is not only confirming the diagnosis, but to a greater extent establishing the extent and stage of the process, involving other organs and systems in the pathological process.

Ultrasound examination of kidneys. The main access when locating the kidneys is the skull-side arrangement of the sensor in the mid-axillary line. This projection gives an image of the kidney, comparable to the image during X-ray examination. When scanning along the long axis of an organ, the kidney has the appearance of an oval formation with clear, even contours. Multiposition scanning with sequential movement of the scanning plane allows obtaining information about all parts of the organ in which the parenchyma and the centrally located echo complex are differentiated. The cortical layer has a uniform, somewhat elevated echogenicity compared with the medulla. The medulla, or pyramids, on the anatomical preparation of the kidney have the appearance of triangular structures, the base facing the contour of the kidney and the apex of the abdominal system. Normally, the part of the pyramid that is visible during ultrasound is about a third of the thickness of the parenchyma [12, 14].

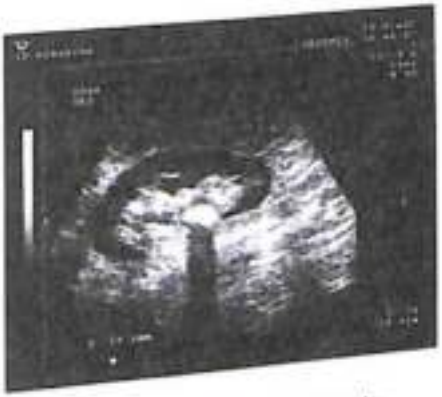

Fig. 30 - Stone in the renal cavity
(Illustration from https://lh3.googleusercontent.com/y4hL-G2xCUcL1q4d6ZO21TNjQ358aZrj1h45vO287gbu1XxUmh8QXFAX5LqDwHES-8MyV1s=s99)

The centrally located echo complex is characterized by significant echo density compared with other parts of the kidney. Such anatomical structures as elements of the abdominal system, vascular formations, lymphatic drainage system, and adipose tissue take part in the formation of the central

sine image. In healthy people in the absence of water load, the elements of the abdominal system, as a rule, do not differentiate; it is possible to visualize individual cups up to 5 mm. Under water load conditions, the pelvis is sometimes visualized, as a rule; it has the shape of a triangle with a size of no more than 15 mm.

The nature of the focal pathology of the kidney is determined by the sonographic picture of the revealed changes - from anechoic formation with dorsal amplification to hypere-echogenous education, which gives an acoustic shadow. An anechoic fluid formation in the projection of the kidney by its origin can be a cyst or an extension of the cups and pelvis - hydronephrosis.

Focal formation of low density without dorsal amplification in the projection of the kidney may indicate a local increase in tissue hydrophilicity. Such changes may be due to either inflammatory changes (the formation of a carbuncle of the kidney), or the presence of tumor tissue.

The pattern of echo-dense formation without dorsal amplification is characteristic of the presence of a highly reflective tissue structure, such as fat (lipoma), fibrous tissue (fibroma) or a mixed structure (angiomyoplasty). Echo-dense structure with the formation of acoustic shadow indicates the presence of calcium in the identified formation. Localization of such education in the abdominal system of the kidney or urinary tract speaks of the available stone (Fig. 30).

Ultrasound of the bladder (Fig. 31). Ultrasound of the bladder is possible only if it is adequately filled with urine, when the folding of the mucous layer decreases. Bladder visualization is possible transabdominal, transrectal and transvaginal access.

In urological practice, a combination of transabdominal and transrectal access is preferred. The first allows you to judge the state of the bladder as a whole. Transrectal access provides valuable information about the lower parts of the ureters, urethra, genitals.

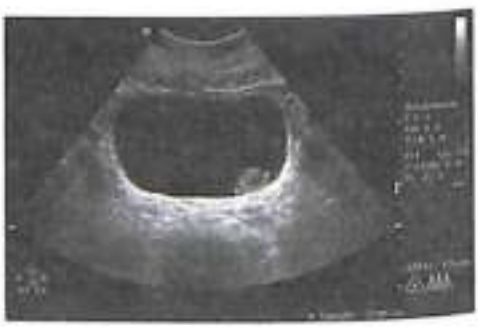

Fig. 31 - Ultrasound of the bladder

(Illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcQHgBPw24dIJkP50bEVwc67dBrgvKq9827jT5EXgr6EzGeOT59)

With ultrasound, the bladder wall has a three-layer structure. The middle hypoechoic layer is represented by the middle layer of the detrusor, the inner hyperechoic layer is a single image of the inner layer of the detrusor and the urothelial lining, the outer hyperechoic layer is the image of the outer layer of the detrusor and adventitia.

With adequate filling of the bladder distinguish its anatomical divisions - the bottom, the top and side walls. The bladder neck has the appearance of a shallow funnel. Urine in the bladder is a fully anechoic environment, without suspension. Sometimes it is possible to observe the flow of urine bolus from the mouth of the ureter, which is associated with the occurrence of turbulent flow.

With transrectal scanning, the lower segment of the bladder is better visualized. The cystic ureteral segment is a structure consisting of the yuxtaseical, intramural parts of the ureter and the bladder zone near the mouth. The mouth of the ureter is defined in the form of a slit-like formation, somewhat elevated above the inner surface of the bladder. With the passage of a bolus of urine, the mouth rises, opens, and the stream of urine enters the cavity of the bladder. According to transrectal ultrasound, motor function of the vesicoureteral segment can be assessed. The frequency of contractions of the ureter is normally 4-6 per minute. With the contraction of the ureter, its walls are completely closed, while the diameter of the juxtavesical part does not exceed 3.5 mm. The wall of the ureter itself is located in the form of an echo-dense homogeneous structure about 1.0 mm wide. At the time of passage of the urine bolus, the ureter expands and reaches 3-4 mm.

Ultrasound of the prostate (Fig. 32). Ultrasound of the prostate gland. Visualization of the prostate gland is possible with both transabdominal and transrectal access. The prostate gland in the transverse scan is an oval-shaped formation; when scanned in the sagittal scan, it has the shape of a triangle with a wide base and a pointed apical end.

The peripheral zone is the dominant prostate in the volume and is located in the form of a homogeneous, echo-dense tissue in the posterolateral part of the prostate from the base to the apex. The central and peripheral zones have less echo density, which allows to differentiate these parts of the prostate. The transitional zone is located posterior to the urethra and covers the prostatic portion of the ejaculatory ducts. The total image of these sections of the prostate is normally about 30% of the volume of the gland [15].

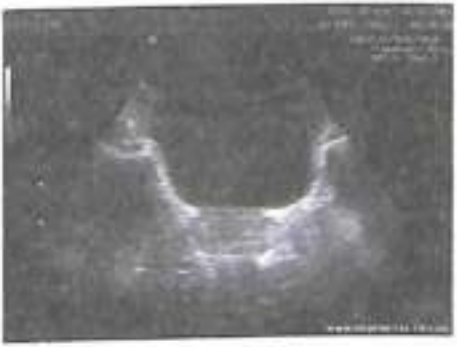

Fig. 32 - Ultrasound of the prostate
(illustration from http://cc-cph.com/wp-content/uploads/2016/02/HAHHOV_00001.jpg)

Visualization of the vascular architectonics of the prostate gland is carried out using Doppler ultrasound. An asymmetrical increase in the blood supply to the hypoechoic sites in the prostate greatly increases the likelihood of its malignant lesion.

Ultrasound of the scrotum (Fig. 33). When ultrasound of the scrotum organs use high-resolution sensors, from 5 to 12 MHz, which allows a good view of small structures and structures. Normally, the testicle is defined as a hyperechoic oval-shaped formation with clear, even contours.

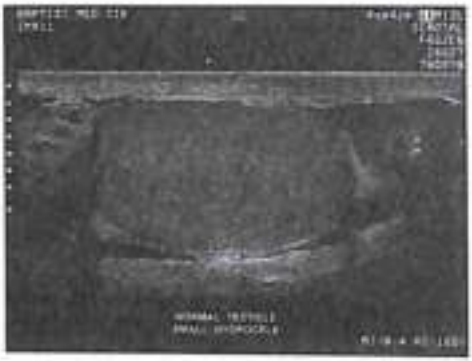

Fig. 33 - Ultrasound of the testicle
(Illustration from https://diagnostic-med.ru/files/source/diagnostic/uzi%20moshonki/uzi799.jpg)

The structure of the testicle is characterized as a homogeneous hyperechoic tissue. In the central parts of it is determined by the linear structure of high density, oriented along the longitudinal organ, which corresponds to the image of the mediastinum of the testicle. In the cranial parts of the testicle, the head of the appendage is well visualized, having a shape close to triangular.

The caudal part of the testicle adjoins the appendage tail, repeating the shape of the testicle. The body of the appendage is rendered indistinctly. In its echogenicity, the epididymis is close to the echogenicity of the testicle itself, it is homogeneous and has clear contours.

Intershell liquid is anechoic, transparent, normally determined as a minimum interlayer from 0.3 to 0.7 cm, mainly in the projection of the head and tail of the epididymidis.

4.6 X-ray examination

In the diagnosis of diseases of the kidneys and urinary tract x-ray methods play a key role.

They are widely used in clinical practice, however, some of them due to the introduction of more informative diagnostic methods have now lost their importance (X-ray tomography, pneumorin, presacral pneumoretroperitoneum).

The quality of X-ray examination largely depends on the proper preparation of the patient. To do this, on the eve of the procedure, products that promote gas formation (carbohydrates, vegetables, dairy products) are excluded from the patient's diet, and a cleansing enema is performed. If the enema is not possible, prescribe laxatives (castor oil, Fortrans), as well as drugs that reduce gas formation (activated carbon, simethicone). In order to avoid the

accumulation of "hungry" gases in the morning, a light breakfast is recommended before the test (for example, tea with a small amount of white bread).

Overview photo. X-ray examination of the urological patient should always begin with an overview picture of the kidneys and urinary tract (Fig. 34).

An overview of the urinary tract should cover the location of all organs of the urinary system. An X-ray film of 30 x 40 cm is usually used.

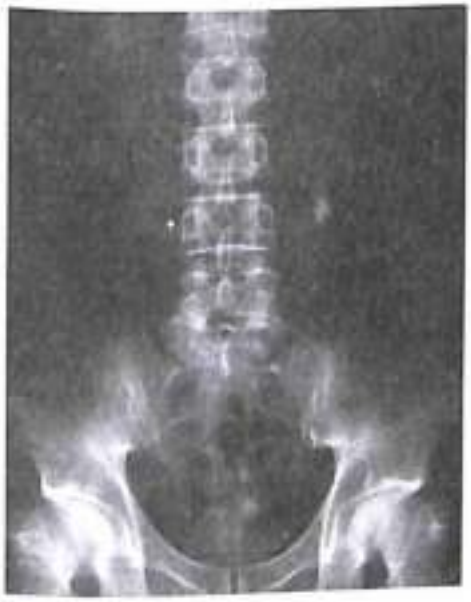

Fig. 34 – Overview X-ray photo of urinary system
(illustration from https://i.pinimg.com/originals/59/eb/b3/59ceb350d81a2bfbcbeac80eadd2b00.jpg)

When interpreting radiographs, first of all, they study the state of the bone skeleton: the lower thoracic and lumbar vertebrae, ribs and pelvic bones. Evaluate the contours of m. psoas, the disappearance or change of which may indicate a pathological process in the retroperitoneal space. The lack of visibility of objects in the retroperitoneal space may be due to flatulence, that is, accumulation of intestinal gases.

With good preparation of the patient in the overview picture you can see the shadow of the kidneys, which are located: to the right - from the upper edge of the I lumbar vertebra to the body of the III lumbar vertebra, to the left - from the body of the XII thoracic to the body of the II lumbar vertebra. Normally, their contours are smooth, and the shadows are homogeneous. Changes in size, shape, location, and contours make it possible to suspect an abnormality or kidney disease. Ureters on the review radiograph are not visible.

The bladder with tight filling with concentrated urine can be defined as a rounded shadow in the projection of the pelvic ring.

Stones of the kidneys and urinary tract are visualized in the overview image in the form of radiopaque shadows. Their localization, size, shape, quantity, density are evaluated. Simulate concrements in the urinary tract can aneurysmal wall calcified vessels dilated, ath-rosklerоticheskie plaque, gallstones, fecal stones, calcified tuberculosis caverns fibromatous and lymph nodes as well

as flebolity - governmental calcified deposits having a rounded shape and in the center of illumination.

Excretory urography is one of the leading research methods in urology, based on the ability of the kidneys to emit a radiopaque substance. This method allows evaluating the functional and anatomical state of the kidneys, pelvis, ureters and bladder.

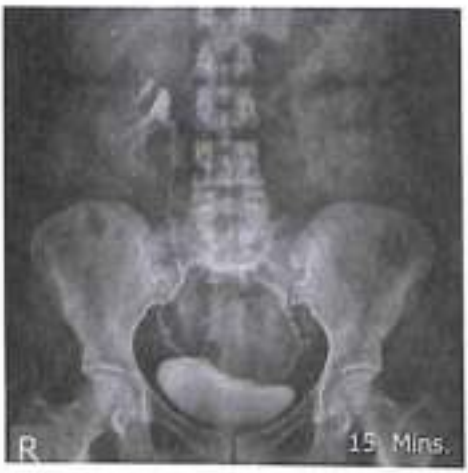

Fig. 35 – Photo of the third phase (15 min) of intravenous urography
(illustration from https://images.radiopaedia.org/images/19862374/5b3e9588c5fe82b68637919aa95087_jumbo.jpeg)

A prerequisite for performing excretory urography is adequate renal function. For the study used X-ray-herbal preparations containing iodine (urografin, urotrast, etc.). There are also modern drugs with low osmolarity (omnipack). Calculation of the dose of a contrast agent is made taking into account body weight, age and condition of the patient, the presence of concomitant diseases. With satisfactory renal function, 20 ml of a contrast agent is usually administered intravenously. If necessary, the study is carried out with 40 or 60 ml of contrast.

After intravenous administration of a radiopaque substance, after 1 minute, an image of a functioning renal parenchyma is detected on a radiograph (image of the nephrogram). After 3 min, the contrast is determined in the urinary tract (pyelogram phase). Usually, several pictures are taken at the 7th, 15th (Fig. 35), 25th, and 40th minute, allowing assessing the condition of the upper urinary tract. In the absence of discharge of a contrasting substance, delayed images are taken by the kidney, which can be performed in 1-2 hours. When the bladder is filled with contrast, an image of it is obtained (descending cystogram).

When interpreting the urograms, attention is paid to the size, shape, position of the kidneys, the timeliness of excretion of the contrast agent, the anatomical structure of the renal pelvis system, the presence of filling defects and obstacles to the passage of urine. The saturation of the shadow of the contrast agent in the urinary tract, the time it appears in the ureters and bladder should be evaluated. In this case, the shadow of the calculus that was previously visible in the overview picture may be absent.

On the excretory urogram, the shadow of the X-ray positive stone disappears due to its layering on the radiopaque substance. It appears in

later photographs as the outflow of contrast and impregnation of calculus. X-ray negative stone creates a defect filling contrasting substance.

In the absence of contrasting shadows on the radiograph, a congenital absence of a kidney, a block of a kidney with a stone in renal colic, hydronephrotic transformation and other diseases accompanied by inhibition of renal function can be assumed.

Undesirable reactions and complications in the case of intravenous administration of X-ray contrast preparations are more often observed with the use of hypo-molar X-ray contrast agents, more rarely with low osmolar substances. To prevent such complications, you should carefully determine the allergological history and, in order to check the body's sensitivity to iodine, inject 1-2 ml of a contrast agent intravenously, and then, without removing the needle from the vein, with a satisfactory condition of the patient, after 2-3 minutes interval the entire volume of the drug.

The introduction of a contrast agent should be made slowly (within 2 minutes) in the presence of a doctor. If side effects occur, 10-20 ml of 30% sodium thiosulfate solution should be immediately slowly introduced into the vein. Minor side effects can be nausea, vomiting, dizziness. Allergic reactions to contrasting substances (urticaria, bronchospasm, anaphylactic shock), which develop in about 5% of cases, are much more dangerous. If it is necessary to conduct excretory urography in patients with allergic reactions to hyperosmolar contrast agents, only low-osmolar substances are used and premedication is performed with glucocorticoids and antihistamine preparations.

Contraindications to excretory urography are shock, collapse, severe liver and kidney disease with severe azotemia, hyperthyroidism, diabetes, hypertension in the stage of decompensation and pregnancy.

Retrograde (ascending) ureteropyelography. This study is based on filling the ureter, pelvis and cups with a radiopaque substance by retrograde injection through a catheter previously inserted into the ureter. For this purpose, using liquid contrast agents (urografin, omnipack). Gaseous contrasts (oxygen, air) are currently used extremely rarely.

At present, the indications for conducting this study have narrowed considerably due to the advent of more informative and less invasive diagnostic methods, such as sonography, computed tomography (CT) and magnetic resonance imaging (MRI).

Retrograde ureteropyelography is used in cases when excretory urography does not give a clear image of the upper urinary tract or is impracticable due to severe azotemia, allergic reactions to a contrast agent. To conduct this study resorted to the narrowing of the ureters of various origins, tuberculosis, tumors of the upper urinary tract, X-ray negative stones, anomalies of the urinary

system, as well as the need to visualize the stump of the ureter of a remote kidney. For the detection of X-ray negative stones, solutions of a low concentration contrast agent or pneumopyelography are used.

Retrograde ureteropyelography is contraindicated in cases of massive hematuria, an active inflammatory process in the urogenital organs, and inability to perform cystoscopy.

Retrograde ureteropyelography begins with cystoscopy, after which a catheter is inserted into the mouth of the corresponding ureter to a height of 20-25 cm (or, if necessary, into the pelvis). Then take a review of the urinary tract to control the location of the catheter. Slowly inject a radiopaque substance (usually not more than 3-5 ml) and take pictures. In order to avoid infectious complications, retrograde urethyelography should not be performed simultaneously from both sides.

Complications of retrograde uteropielography are the development of pyelorenal reflux, accompanied by fever, chills, pain in the lumbar region; exacerbation of pyelonephritis; perforation of the ureter.

Antegrade (downward) pyelo-ureterography is a research method based on the visualization of the upper urinary tract by introducing a contrast agent into the renal pelvis using percutaneous puncture or nephrostomy drainage.

Antegrade percutaneous pyelo-ureterography is indicated for patients with obstruction of ureters of various origins (stricture, stone, tumor, etc.), when other diagnostic methods do not allow to establish the correct diagnosis. The study helps to determine the nature and level of obstruction of the ureters.

Antegrade pyelourethrography is used to assess the condition of the upper urinary tract in patients with nephrostomy in the postoperative period, especially after plastic surgery on the pelvis and ureter.

Contraindications to the performance of antegrade percutaneous pyelhoretehography are: infections of the skin and soft tissues in the lumbar region, as well as conditions involving a violation of blood clotting.

Cystography is a method of X-ray examination of the bladder by pre-filling it with a contrast agent. Cystography may be descending (during excretory urography) and ascending (retrograde), which, in turn, is divided into static and during urination (Fig. 36).

Descending cystography is a standard X-ray examination of the bladder during excretory urography. Purposefully, it is used to obtain information about the state of the bladder when it is impossible to catheterize due to obstruction of the urethra. In normal kidney function, a distinct shadow of the bladder appears 30-40 minutes after the injection of a contrast agent into the bloodstream. If the contrast is insufficient, produce later shots, after 60-90 minutes.

Retrograde cystography is a method of X-ray identification of the bladder by introducing into its cavity a

liquid or gaseous (pneumocystogram) contrast media along a catheter installed along the urethra. The study is made in the position of the patient on the back with the hips retracted and bent at the hip joints. Using a catheter, 200-250 ml of a contrast agent is injected into the bladder, followed by an X-ray.

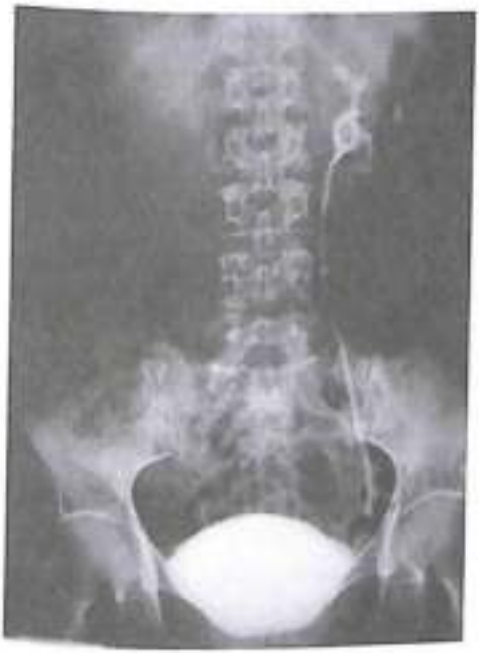

Fig. 36 – Cystogram

(illustration from https://www.researchgate.net/publication/816354?figure/fig2/AS:489913150906369@1493815809021/Retrograde-cystography-in-a-patient-who-received-an-internal-ureteral-stent-6-weeks.png)

A normal bladder, with sufficient filling, has a rounded (mainly in men) or oval (in women) shape and clear even contours. The lower edge of its shadow is located at the level of the upper border of the symphysis, and the upper edge is at the level of the III-IV sacral vertebrae. In children, the bladder is located above the symphysis than in adults.

Cystography is the main method for diagnosing penetrating ruptures of the bladder, allowing determining the flux of a radiopaque substance outside the organ. It can also be used to diagnose cystocele, bladder fistula, tumors and bladder stones. In patients with benign prostatic hyperplasia on the cystogram, the resulting rounded filling defect along the lower contour of the bladder can be clearly determined. Bladder diverticula are detected on the cystogram in the form of bag-shaped protrusions of its wall.

Contraindications for retrograde cystography are acute inflammatory diseases of the lower urinary tract, prostate gland and scrotum organs. In patients with traumatic damage to the bladder, the integrity of the urethra is pre-ascertained by urethrography.

Most of the previously proposed modifications of cystography due to the advent of more informative research methods have now lost their meaning. The test of time was withstood only by a mock cystography — radiography performed during the release of the bladder from a contrast agent, that is, at the time of urination. Mick cystography is widely used in pediatric urology to identify vesicoureteral reflux. Also, this study is resorted to, if necessary, to visualize the posterior urethra (antegrade urethrography) in patients with strictures and urethral valves, ectopia of the ureter orifice into the urethra.

Urethrography is an x-ray method for studying the urethra by pre-contrasting it. There are downward (antegrade, mycotic) and ascending (retrograde) urethrography.

Antegrade urethrography is performed at the time of urination after pre-filling the bladder with a radiopaque substance. This produces a good image of the prostatic and membranous urethra, so this study is used primarily to diagnose diseases of these parts of the urethra.

Retrograde urethrography is performed much more frequently. It is usually made in an oblique position of the patient on the back: a rotated pelvis forms an angle of 45 ° with the horizontal plane of the table, one leg is bent at the hip and knee joints and pressed to the body, the second is stretched. In this position, the urethra is projected on the soft tissue of the thigh. The penis is pulled parallel to the bent hip. Contrast material is slowly injected with a rubber-tipped syringe (to avoid urethrovenous reflux), it is inserted into the urethra. In the process of introducing contrast make an X-ray.

Urethrography is the main method for diagnosing lesions and strictures of the urethra. A characteristic X-ray sign of a penetrating rupture of the urethra is the spread of the contrast agent beyond its limits and the absence of its admission to the overlying urethra and bladder. Indications for it are also anomalies, neoplasms, debris and fistulas of the urethra. Urethrography is contraindicated in acute inflammation of the lower urinary tract and genital organs.

Computed tomography (CT). This is one of the most informative diagnostic methods. Unlike conventional X-ray CT, it allows to obtain a snapshot of the transverse (axial) cut of the human body with a layer-by-layer step of 1-10 mm (Fig. 37).

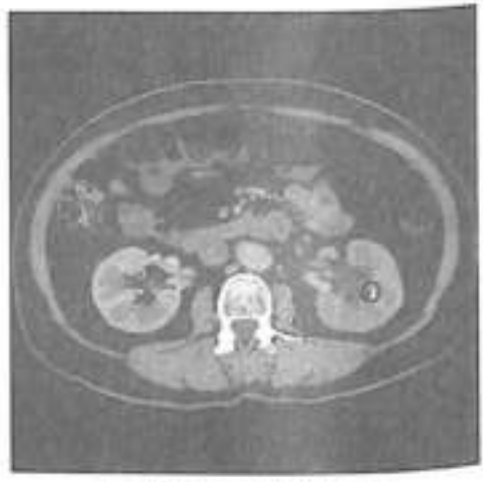

Fig. 37 – CT of the kidneys
(illustration from http://uLeydsc.ru/wp-content/uploads/2017/08/kt-scan-11-1.jpg)

The method is based on the measurement and computer processing of the difference in the attenuation of X-rays by different tissues in density. Using a movable x-ray tube moving around an object at an angle of 360°, an axial, layer-by-layer millimeter-scan scanning of the patient's body is performed. In addition to conventional CT, there is a spiral CT and a more advanced multispiral CT.

To improve the differentiation of organs from each other, various amplification techniques are used using oral or intravenous contrasting.

With helical scanning, two actions are simultaneously performed: rotation of the radiation source — an X-ray tube and continuous movement of the table with the patient along the longitudinal axis. The best image quality is provided by multispiral CT. The advantage of multislice research is a greater number of perceiving detectors, which makes it possible to obtain a better picture with the possibility of a three-dimensional image of the studied organ with a lower radiation load on the patient. In addition, this method allows obtaining multiplanar, three-dimensional and virtual endoscopic images of the urinary tract.

CT scan is one of the leading methods for diagnosing urological diseases; due to its higher informativeness and safety compared to other radiological methods, it has become the most widespread throughout the world.

Multispiral CT with intravenous contrast enhancement and three-dimensional image reconstruction is currently one of the most advanced imaging techniques in modern urology. The indications for the implementation of this research method have recently expanded considerably. This is the differential diagnosis of cysts, tumors of the kidneys and adrenal glands; assessment of the state of the vascular bed, regional and distant metastases in tumors of the genitourinary system; tuberculous lesion; kidney injury; volumetric formations and purulent processes of the retroperitoneal space; retroperitoneal fibrosis; urolithiasis disease; diseases of the bladder (tumors, diverticula, stones, etc.) and prostate gland.

Positron emission tomography (PET) is a radionuclide tomographic method.

It is based on the ability to track the distribution of biologically active compounds labeled with positron-emitting radioisotopes with the help of special detection equipment (PET scanner). The most widely used method in oncourology. PET provides valuable information in patients with suspected cancer of the kidney, bladder, prostate, testicular tumor.

The most informative are positron emission tomographs, combined with computed tomographs, which allow to simultaneously study anatomical (CT) and functional (PET) data.

4.7 Other methods

Magnetic resonance imaging (MRI). Magnetic resonance imaging is a tomographic method for studying internal organs and tissues using the phenomenon of nuclear magnetic resonance.

The method of magnetic nuclear resonance allows us to study the human

body based on the saturation of its tissues with hydrogen and the features of their magnetic properties associated with being surrounded by different atoms and molecules.

The essence of the phenomenon lies in the fact that the nuclei of hydrogen atoms, being in a constant magnetic field, are capable of absorbing energy, and, upon the termination of the magnetic field, emit it in the form of a radio signal (resonant energy release). The obtained information is digitally processed and presented on the computer screen in the form of anatomical sections of the studied area.

MRI allows obtaining images in three mutually perpendicular projections - transverse (axial), frontal (coronal) and sagittal, as well as in oblique (oblique) projections.

Indications for MRI in urology are:

- tumors, cysts of the kidneys and neoplasms of the retroperitoneal space;
- specific and non-specific kidney disease;
- visualization of the urinary tract without the use of contrast agents;
- abnormalities and pathologies of kidney vessels;
- Ormond disease;
- urolithiasis;
- bladder tumors (advantages over CT - in a more accurate assessment of the degree of tumor invasion into the bladder wall);
- condition of regional lymph nodes;
- prostate cancer with determination of the stage and extent of the tumor process.

The advantages of MRI compared with other methods of radiation diagnostics include safety (absence of ionizing radiation), the ability to visualize tomograms in any planes, a clear image of anatomical structures due to the natural contrasting of tissues.

Contraindications for MRI: the presence in the patient's body of various metal structures (joint prostheses, pacemakers), claustrophobia and relative contraindication - pregnancy in the early (up to 3 months) terms.

MRI is the most informative, safe and promising research method. It significantly improved the detection of urological diseases, replacing a number of radiological methods, accompanied by radiation exposure.

Radionuclide scans. Over the past decades, radioisotope, or radionuclide, research methods that allow quantifying the state of blood circulation in the organ under study, as well as to study the state of tissue metabolism in it, have been widely included in urology. Radionuclide diagnostics is based on the introduction into the body of short-lived radioactive isotopes and the control of their

distribution and excretion. To assess metabolic disorders, a radiopharmaceutical is used, consisting of a vector molecule directly involved in tissue metabolism and a radioactive label linked to it.

Radionuclide studies are divided into two groups: dynamic and static. Dynamic studies are conducted to study the dynamics of distribution and accumulation of the radiopharmaceutical in a particular organ. They consist of a series of frames that are recorded from the time of intravenous injection of the radiopharmaceutical for some time. Then, using computer programs, data are processed and the radiopharmaceutical distribution curves are plotted. Static studies are used to determine the spatial distribution of the radiopharmaceutical in the tissues of the body.

These methods allow you to get information about the nature of the pathological process, the degree of its prevalence, the presence of focal lesions and formations (tumors, cysts, kidney infarction). The obtained data can be used for differential diagnosis between various diseases, but, as a rule, they state the presence and localization of disorders, without specifying their etiology.

There are no contraindications to radioisotope studies; there are only limitations for conducting in vivo studies associated with radiation exposure, which are governed by the recommendations of the Ministry of Health.

The following dynamic studies are most common in urological practice: indirect radioisotope renoangiography, radioisotope renography, renal scintigraphy.

Indirect radioisotope renoangiography allows evaluating glomerular filtration, tubular secretion, urodynamics, and state of the parenchyma, blood supply and topography of the organ. The principle of the method is based on the study of the passage of the labeled compound through the vascular system of the kidneys. The technique of the study consists in the intravenous administration of technetium 99 (^{99m}Tc) or ^{131}I-albumin and continuous recording of radioactivity over the kidneys for 30-60 seconds. The resulting study is called an indirect radioisotope renal angiogram and consists of two sections: the ascending (arterial) and descending (venous). The first one reflects the process of filling the arterial bed with the preparation, the second one - removing the drug through the venous collectors after the intrarenal circulation along the capillary bed.

Radioisotope renography is a functional research method that graphically depicts the process of secreting a radioactive substance and its isolation from the abdominal system of the kidneys. The registration of a radioactive signal in the lumbar region above the kidneys is done with a radio circulograph. Either a tubulotropic drug is used - hippuran, labeled with ^{131}I or ^{123}I, or a glomerulotropic compound - complex ^{99m}Tc- or ^{113m}In-DTPA (diethyltriaminopentoacetic acid). The

kidneys secrete 80% of hippuran as a result of its secretion in the proximal tubules and only 20% by glomerular filtration. The resulting graph in normal kidney function has ascending (secretory) and descending (excretory) areas. In computer processing of curves (radioisotope renograms), it is possible to quantify the rate of canalicular secretion, the time it takes for the isotope to pass through the parenchyma of the kidney and the rate of its excretion, and also calculate the renal clearance. Renograms of the right and left kidneys are considered symmetrical if the difference between the curves for individual indicators does not exceed 20%.

Renal scintigraphy. With this method of research, a radiopharmaceutical consisting of a vector molecule and a radioactive marker is administered to the patient. The vector molecule is absorbed by the renal parenchyma. The radioactive label serves as a "transmitter": emits gamma rays, which are recorded by a gamma camera. This reproduces the image of the various stages of the passage of labeled isotopes through the kidneys.

Normally, the image of the renal parenchyma appears by the 3-5th minute after the introduction of labeled hippuran, then the contrast decreases, and the radiopharmaceutical fills the cup-pelvis system, the bladder is contrasted by the 10-15th minute. The main indication for this study is the need to study the functional activity of various parts of the renal parenchyma.

The presence of an avascular "silent" focus suggests a kidney cyst, a zone of infarction of the kidney tissue. Kidney tumors are characterized by a sharp increase and decrease in the accumulation of the radiopharmaceutical. In patients with chronic renal failure of various genesis, isotope diagnostics makes it possible to obtain important information about the number of functioning renal parenchyma, to determine the prognosis of the disease and treatment tactics. Radionuclide studies can be used in transplantation to assess the status of a transplanted kidney. Using scintigraphy, it is possible to make a differential diagnosis of testicular torsion and acute epididymitis, to identify the testicle in a patient with cryptorchidism.

Radioisotope diagnosis in oncourology is particularly important, as it allows diagnosing metastatic lesions of other organs and tissues. The following diagnostic methods can be used for this purpose: indirect lymphoscintigraphy, indirect radioisotope inferior venocavography, radioisotope osteoscintigraphy, PET.

Most often in medical practice, radionuclide scintigraphy of the bones of the skeleton is used, which makes it possible to identify osteoblastic metastases, which is manifested by hyperfixation of the radiopharmaceutical in the affected areas. However, it should be borne in mind that the pathological accumulation of the radiopharmaceutical can also be noted with the consequences of bone fractures and marked periostitis.

Radioisotope research in nephrosclerosis determines the most affected areas of the kidney and its size. With anomalies of the relationship and location of the kidneys, it can reveal a horseshoe-shaped, L-shaped or dystopic kidney. In the differential diagnosis of the nature of the volume of the formation of radioisotope research allows us to determine the avascular sites characteristic of cysts and ischemic lesions (infarction) of the kidney or hypervascular areas, indicating the presence of a tumor. It is informative when assessing the safety of renal tissue in cases of hydronephrosis, suspected renovascular hypertension, thrombosis of the renal vein.

Registration of a radioisotope drug after its intravenous administration and accumulation over the bladder area is called radioisotope cystography, and its combination with radioisotope examination of the kidneys is called radioisotope renocystography.

With this study, it is possible to identify vesicoureteral reflux, when the graphic registration of radioactivity decreases over the bladder area during urination and simultaneously rises above the kidneys.

By registering radioactivity over the bladder after urinating, it is possible to determine the presence and amount of residual urine in it.

Clinical, laboratory and instrumental methods of examination

History taking and clinical examination include the initial approach to the patient and collection of the database information which represent the most important steps in reaching the diagnosis. Laboratory data, radiology films, and reports giving a certain diagnosis, should be considered in the proper time, without overlooking the initial steps of basic clinical urology.

Physical examination.

Palpation.

Laboratory methods:

Blood tests can be used to diagnose and monitor a variety of urologic conditions. In many cases, the results of blood work can help doctors determine if further lab tests or treatments are necessary. Blood testing is a routine procedure.

Blood urea nitrogen (BUN) test. This test, which is used to evaluate kidney function, diagnose kidney problems, and monitor dialysis results, involves measuring the level of nitrogen in the urea of the blood.

Creatinine test. Creatinine (Cr) forms when a substance found in muscle tissue breaks down.

Prostate-specific antigen (PSA) test. This test may be used in men to screen for prostate cancer (beginning at the age of 50 or at age 40 if at higher risk) and to monitor prostate cancer treatment.

Calcium test. This test, which measures the level of calcium in the blood, can be used to screen patients for kidney disease.

Phosphate (phosphorus) test, which measure phosphate levels in the blood, are used to diagnose kidney problems and monitor dialysis.

Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG) tests. These tests are used to help diagnose testicular cancer.

Urinalysis.

Instrumental methods:

Ultrasound examination. Ultrasound examination (ultrasound, sonography) is the most widely used method of visualization in medical practice, which is due to its significant advantages: the absence of radiation load, non-invasiveness, mobility and accessibility. The method does not require the use of contrast agents, and its effectiveness does not depend on the functional state of the kidneys, which is of particular importance in urological practice.

X-ray examination:

Overview photo. X-ray examination of a urological patient should always begin with an overview of the kidneys and urinary tract. The urinary tract survey should cover the area of the location of all organs of the urinary system.

Intravenous pyelography (IVP) is one of the leading methods of research in urology, based on the ability of the kidneys to excrete radiopaque substances.

Voiding cystourethrography (VCUG). A VCUG is an X-ray image of the bladder and urethra taken while the bladder is full and during urination, also called voiding.

Computed tomography (CT). Computerized tomography scans use a combination of X-rays and computer technology to create three-dimensional (3-D) images.

Other methods:

Magnetic resonance imaging (MRI) is a test that takes pictures of the body's internal organs and soft tissues without using X-rays. MRI machines use radio waves

and magnets to produce detailed pictures of the body's internal organs and soft tissues.

Magnetic resonance angiogram (MRA). An MRA is a type of MRI that provides the most detailed view of kidney arteries—the blood vessels that supply blood to the kidneys.

Radionuclide scans. A radionuclide scan is an imaging technique that relies on the detection of small amounts of radiation after injection of radioactive chemicals.

Theme # 5: Clinical manifestation, diagnostic, treatment and prevention of urolithiasis.

5.1 Urolithiasis: theories, etiology and pathogenesis, types of stones, risk factors

Urolithiasis is a metabolic disease that manifested in the formation of kidney stones and other organs of urinary system.

Urolithiasis continues to occupy an important place in the daily practice of the urologist and general practitioners. The basis for the development of urolithiasis are disorders of metabolic processes in the body, often occurring against the background of morphofunctional changes in the patient's urinary system, hereditary predisposition and diseases of the endocrine system.

On average, the risk of urolithiasis is within 5-10%. The frequency of urolithiasis is higher among men than among women (ratio of about 3: 1), most often occurs at the age of 40-50 years. Progressive and repetitive stone formation is a common problem for all types of stones.

In many countries, urolithiasis accounts for up to 40% of all urological diseases. In urological hospitals, more than a third of patients undergo urolithiasis treatment.

Many scientists predict that the incidence of urolithiasis will continue to grow due to the changing nature of food, social conditions of life and the increasing influence of adverse environmental factors that have a direct effect on the human body.

The medical and social significance of urolithiasis is due to the fact that 2/3 of patients develop at working age (from 20 to 50 years) and result in disability of every fifth patient.

Stones in most cases arise and form in the kidney cups, but may be located in the pelvis, ureter, bladder and urethra. More often, stones are formed in one of the kidneys, but in almost a third of patients, stone formation is bilateral.

The shape of stones can be very different, size - from 1 mm to giant - more than 10 cm, weight - up to 1000 g.

Theories of urolithiatis:

- Nucleation theory;
- Stone matrix theory;
- Inhibitor of crystallization theory.

Most investigators acknowledge that these 3 theories describe the 3 basic factors influencing urinary stone formation. It is likely that more than one factor operates in causing stone disease. A generalized model of stone formation combining these 3 basic theories has been proposed.

Etiology and pathogenesis. Urolithiasis is a polyetiological disease, and the causes of stone formation and growth vary from one patient to another.

A large amount of data has been collected on the etiology and pathogenesis of urolithiasis, but so far this problem cannot be considered finally resolved. Being supersaturated with saline, urine, due to the presence of buffer systems, remains without free crystals from the moment of its formation in the distal tubules of the nephron until elimination from the body. The formation of crystals in the urine occurs when the buffer systems are damaged or when the primary nucleus occurs, which, as a rule, is combined with stagnation in the urinary tract.

There are various factors that affect the formation of kidney stones. Enzymopathies (tubulopathies) have certain significance in the etiology of urolithiasis - impaired metabolic processes in the proximal and distal tubules.

Numerous factors contribute to the formation of stone against the background of tubulopathy, which are divided into exogenous and endogenous.

Exogenous pathogenetic factors include climatic and geochemical conditions, dietary habits. Thus, the high temperature and humidity of the air, the composition of drinking water and the saturation of its mineral salts affect the formation of stone due to the restriction of water consumption, but especially because of the increased sweating and dehydration of the body, which increases the concentration of salts in the urine and promotes their crystallization.

Of great importance in the occurrence of kidney stone formation is the nature of nutrition, as vegetable and dairy foods contribute to alkalization of urine, and meat - its oxidation. Among the factors contributing to stone formation, it should be noted an excess in the food of canned food, salt, freeze-dried and reconstituted products, lack of vitamins A & C, as well as an excess of vitamin D.

Endogenous pathogenetic factors of stone formation include impaired outflow of urine from the kidney, slowing of the renal hemocyclic circulation, the presence of a chronic inflammatory process in the kidney.

Changes in the urinary tract, predisposing to the appearance of calculi, are divided as follows:

- congenital malformations that create urine stasis;
- obturation of the urinary tract;
- inflammatory and parasitic diseases of the urinary tract;
- foreign bodies;
- kidney injury.

Contribute to the formation of kidney stones and diseases that require prolonged bed rest, such as fractures of the spine and extremities, diseases of the nervous system, etc.

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- Stone matrix theory;
- Inhibitor of crystallization theory.

Most investigators acknowledge that these 3 theories describe the 3 basic factors influencing urinary stone formation. It is likely that more than one factor operates in causing stone disease. A generalized model of stone formation combining these 3 basic theories has been proposed.

Etiology and pathogenesis. Urolithiasis is a polyetiological disease, and the causes of stone formation and growth vary from one patient to another.

A large amount of data has been collected on the etiology and pathogenesis of urolithiasis, but so far this problem cannot be considered finally resolved. Being supersaturated with saline, urine, due to the presence of buffer systems, remains without free crystals from the moment of its formation in the distal tubules of the nephron until elimination from the body. The formation of crystals in the urine occurs when the buffer systems are damaged or when the primary nucleus occurs, which, as a rule, is combined with stagnation in the urinary tract.

There are various factors that affect the formation of kidney stones. Enzymopathies (tubulopathies) have certain significance in the etiology of urolithiasis - impaired metabolic processes in the proximal and distal tubules.

Numerous factors contribute to the formation of stone against the background of tubulopathy, which are divided into exogenous and endogenous.

Exogenous pathogenetic factors include climatic and geochemical conditions, dietary habits. Thus, the high temperature and humidity of the air, the composition of drinking water and the saturation of its mineral salts affect the formation of stone due to the restriction of water consumption, but especially because of the increased sweating and dehydration of the body, which increases the concentration of salts in the urine and promotes their crystallization.

Of great importance in the occurrence of kidney stone formation is the nature of nutrition, as vegetable and dairy foods contribute to alkalization of urine, and meat - its oxidation. Among the factors contributing to stone formation, it should be noted an excess in the food of canned food, salt, freeze-dried and reconstituted products, lack of vitamins A & C, as well as an excess of vitamin D.

Endogenous pathogenetic factors of stone formation include impaired outflow of urine from the kidney, slowing of the renal hemocyclic circulation, the presence of a chronic inflammatory process in the kidney.

Changes in the urinary tract, predisposing to the appearance of calculi, are divided as follows:

- congenital malformations that create urine stasis;
- obturation of the urinary tract;
- inflammatory and parasitic diseases of the urinary tract;
- foreign bodies;
- kidney injury.

Contribute to the formation of kidney stones and diseases that require prolonged bed rest, such as fractures of the spine and extremities, diseases of the nervous system, etc.

Hyperfunction of the parathyroid glands — primary and secondary hyperparathyroidism — takes a special place among the endogenous factors contributing to the development of nephrolithiasis. In these diseases, a toxic effect on the epithelium of the proximal convoluted tubule occurs, which leads to its pronounced dystrophy. Dystrophy of the epithelium of the renal tubules is accompanied by an increase in the blood and urine levels of neutral mucopolysaccharides, which can form into polysaccharide cylinders; each of them can become the core of a calculus.

The process of stone formation is explained by the theory of the matrix of protein composition, the basis of which can be fibrin. When the kidney penetrates into the abdominal system, fibrinogen is transformed into insoluble fibrin due to low fibrinolytic activity of the urine, and salts are subsequently deposited on it [18].

Types of stones. Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects; or adverse drug effects (drug stones) (Tab. 2). Risc factors of urolithiasis described in Tab. 3.

Tab. 2 - Types of stones

Types of stones	
Non-infection stones	Calcium oxalate
	Calcium phosphate
	Uric acid
Infection stones	Magnesium ammonium phosphate
	Carbonate apatite
	Ammonium urate
Genetic causes	Cystine
	Xanthine
	2,8-dihydroxyadenine
Drug stones	

Tab. 3 - Risk factors of urolithiasis

Risk factors	
General factors	Early onset of urolithiasis (especially children and teenagers)
	Familial stone formation
	Brushite-containing stones
	Uric acid and urate-containing stones
	Infection stones
	Solitary kidney (the kidney itself does not

	particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation	Hyperparathyroidism
	Metabolic syndrome
	Nephrocalcinosis
	Polycystic kidney disease (PKD)
	Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery
	Sarcoidosis
	Spinal cord injury, neurogenic bladder
Genetically determined stone formation	Cystinuria (type A, B and AB)
	Primary hyperoxaluria (PH)
	Renal tubular acidosis (RTA) type I
	2,8-Dihydroxyadeninuria
	Xanthinuria
	Lesch-Nyhan syndrome
	Cystic fibrosis
Drugs associated with stone formation	
Anatomical abnormalities associated with stone formation	Medullary sponge kidney (tubular ectasia)
	Ureteropelvic junction (UPJ) obstruction
	Calyceal diverticulum, calyceal cyst
	Ureteral stricture
	Vesico-uretero-renal reflux
	Horseshoe kidney
	Ureterocele

5.2 Clinical manifistation

Clinical manifestations of urolithiasis are very numerous. Usually, the formation and growth of kidney stones are asymptomatic, but as the urinary tract increases with stone, the degree of urodynamics of the upper urinary tract is disturbed, and the trauma of the urothelium of the cups, pelvis and ureter joins, pyelonephritis and chronic renal insufficiency, the symptoms of the disease become vivid.

The classic symptoms of urolithiasis are pain, which often has the character of renal colic, post-pain total gross hematuria, pollakiuria, and the discharge of calculi. These symptoms, with the exception of the latter, can be observed in many

urological diseases, therefore, in the diagnosis of urolithiasis, it is important to evaluate the entire symptom complex.

Pain. Pain is the most common symptom of urolithiasis. The severity and nature of pain are determined by the location, mobility, size and shape of the stone. In the presence of a fixed stone that does not cause a violation of the outflow of urine from the kidney, there may be no pain at all ("silent stones"). Dull pain during urolithiasis can be constant, but more often it is intermittent in nature and appears or increases with movement, physical exertion, body shaking when jumping, and running. Dull back pain noted more than 80% of patients with urolithiasis.

Constant aching pains without attacks of renal colic are more often observed with large stones located in the pelvis or cups, when there is no pronounced violation of urine outflow from the kidney. Often, such patients do not seek medical care for a long time, so the disease progresses, there are many of its complications.

Often the first manifestation of urolithiasis is an attack of acute pain in the lumbar region in the form of renal colic, which is the most characteristic symptom that causes the patient to seek medical help at any time of the day.

The cause of renal colic is a sudden disturbance of urine outflow from the kidney, caused by spasm of the urinary tract as a result of the passage of stone or urinary salt crystals, which cause irritation of sensory nerve endings located in the submucosal layer of the pelvis or ureter. At the same time, there is a sharp increase in the intralocal pressure with stretching of the pelvis and cups, and then the fibrous capsule of the kidney due to edema of the renal tissue and an increase in this organ [21].

Irritation of the interoceptors of the cups and the fibrous capsule of the kidney leads to a spastic reduction of the smooth muscles of the urinary tract, which further increases the pressure inside the pelvis. At the same time, a reflex vascular spasm of the kidney occurs, which, in turn, further intensifies the pain due to irritation of the baroreceptors. All these irritations are transmitted to the spinal cord, and then to the cerebral cortex, where the pain center is stimulated.

Renal colic is characterized by severe cramping pain in the lumbar region, which appears in the form of a sudden attack. As a rule, pain radiates to the groin, external genitals, the inner surface of the thigh.

Due to irritation of the solar plexus, nausea, vomiting, intestinal paresis, unilateral tension of the lumbar muscles and muscles of the anterior abdominal wall are usually noted.

During an attack of renal colic, the patient is restless, tossing about, taking different positions. An attack of renal colic can be accompanied by oliguria, sometimes even anuria, stunning chills, bradycardia, and other symptoms. With the localization of the stone in the intramural ureter often occurs dysuria.

Renal colic occurs most often with urolithiasis. Almost 70% of patients with an attack of renal colic have different forms of urolithiasis, in the remaining patients other urological diseases are detected that contribute to a sudden disturbance of urine outflow from the kidneys (nephroptosis, kidney tuberculosis, etc.).

Hematuria. There is an admixture of blood in the urine (90%), but it cannot be considered a constant symptom of urolithiasis. The cause of hematuria can be damage by calculus of the mucous membrane of the pelvis or the cup. In addition, one of the causes of gross hematuria in urolithiasis is the rupture of the thin-walled veins of the fornikal plexuses, caused by the rapid recovery of the outflow of urine after a sudden increase in the intralocal pressure.

Gross hematuria often occurs immediately after stopping an attack of renal colic; therefore, it is characterized as total and post-pain, unlike pre-pain, which is observed in a tumor of the kidney. Microscopic hematuria with up to 20-25 unchanged red blood cells in the field of view most often appears in patients with nephrolithiasis after exercise or after tapping on the lumbar region.

In patients with low ureteral stones, especially in the juxestic and intramural regions, pollakiuria, nocturia, dysuria may appear due to reflex effects, and even acute urinary retention may occur during renal colic. Severe dysuria sometimes leads to misdiagnosis. Often, patients with stones of the lower ureter for a long time are treated with diagnoses of cystitis, prostatitis, BPH and other diseases.

Dysuria with bladder stones is caused by irritation of the mucous membrane or secondary cystitis. Leukocyturia is almost a constant symptom of kidney disease, although it is more correct to consider it as a symptom of a complication of this disease, namely, calculous pyelonephritis [22].

Hematuria and leukocyturia may be absent if you examine the urine taken at the time of renal colic, i.e., when calculating ureter calculus when urine enters the bladder from a healthy kidney.

The separation of the stone. Pathognomonic and most reliable sign of urolithiasis - the discharge of stones or sand with urine. Most often, the stones disappear on their own soon after an attack of renal colic, but occasionally (no more than in 20% of patients), painless discharge may occur.

Usually, stones of small sizes, up to 1 cm in diameter, are diverted with urine. The discharge of a stone depends not only on its size and shape, but also on the state of urodynamics of the urinary tract.

When the stone moves along the ureter, it can linger in the juxtaseical or intramural department, then, due to reflex influences, dysuria or even acute urinary retention can occur in patients.

5.3 Diagnostics

Basic analysis should include:

- Stick testing of urine for red cells (suggestive of urolithiasis), white cells and nitrites (both suggestive of infection) and pH (pH above 7 suggests urea-splitting organisms such as Proteus spp. whilst a pH below 5 suggests uric acid stones);
- Blood for FBC, CRP, renal function, electrolytes, calcium, phosphate and urate, creatinine;
- Prothrombin time and international normalised ratio if intervention is planned;
- Non-enhanced CT (Fig. 38) scanning is now the imaging modality of choice and has

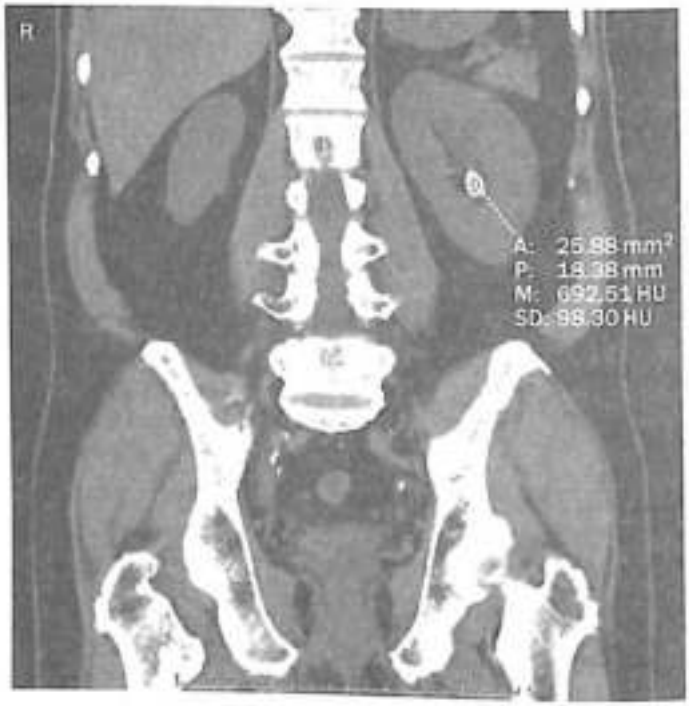

Fig. 38 - Computed tomography of urinary system
(Illustration from https://lh3.googleusercontent.com/t-5ykh24mKEUxFbwB-FSnl-qfIcHTXHeTeS-IbHVCNASovdLaysnf2jQnvUOi_wmTvdCA=s119)

- Midstream specimen of urine for microscopy (pyuria suggests infection), culture and sensitivities;

replaced intravenous pyelogram (IVP);

- Ultrasound scanning may be helpful to differentiate radio-opaque from radiolucent stones

and in detecting evidence of obstruction;

- Plain X-rays of the kidney, ureter and bladder (KUB) are useful in watching the passage of radio-opaque stones (around 75% of stones are of calcium and so will be radio-opaque).
- The European Association of Urology's guidelines on urolithiasis recommend stone analysis for:
- All first-time stone formers;
- All patients with recurrent stones who are on pharmacological preventing therapy;
- Patients who have had early recurrence after complete stone clearance;
- Late recurrence after a long stone-free period (stone composition may change).

Encourage the patient to try to catch the stone for analysis [23].

Differential diagnosis. This depends upon the position of the pain and the presence or absence of pyrexia and includes:

- Biliary colic;
- Dissection of an aortic aneurism: beware the patient who presents with features of renal colic for the first time over the age of 60. This may be dissection of aortic aneurysm leading to ruptured aortic aneurysm;
- Pyelonephritis: very high temperature. Pain is unlikely to radiate to the groin;
- Acute pancreatitis;
- Acute appendicitis;
- Perforated peptic ulcer;
- Epididymo-orchitis or torsion of the testis: very tender testis.

5.4 Treatment

Treatment of urolithiasis is complex and is aimed at the elimination of pain, the restoration of impaired urine outflow, the destruction and/or removal of the stone, the correction of urodynamic disorders, the prevention of inflammatory complications, preventive and metaphylactic measures [73]. Given the variety of clinical forms of the urolithiasis, for each patient the treatment plan is made individually. Spontaneous removal of stones can occur in 80% of cases, if the size of the stone is not more than 4 mm in diameter. At large sizes, the probability of an independent deviation of the stone decreases. The probability of ureteral stones departing depending on the localization for the upper third of the ureter is 25%, the average - 45%, with stones of the lower third of the ureter - 70%. The complex of therapeutic measures aimed at the expulsion of the stone includes: active treatment, exercise therapy (walking, running, jumping), increased diuresis (diuretics, heavy drink or intravenous fluids), analgesics, spasmolytic drugs, alpha-blockers (silodosin, tamsulosin,

alfuzosin, doxazazine), plant uroseptics, antibacterial therapy, physiotherapy (amplipulse, ultrasound stimulation, local vibration therapy, etc.).

Dynamic observation and stone-throwing therapy are indicated for stone sizes of no more than 5 mm without disturbing the urodynamics with the pain syndrome that has been coped. In all other cases the stone is subject to destruction and/or disposal. To this end, remote lithotripsy, contact ureterolithorpsy and ureterolithoextraction, percutaneous nephroureterolytotripsy, laparoscopic and extremely rarely open operations are currently used.

Remote shock wave lithotripsy is shown and is most effective for kidney stones of a size up to 2.0 cm and ureter stones up to 1.0 cm. The density of the calculus is also of definite importance. In some cases, it is possible to crush larger stones, but with mandatory pre-drainage of the kidney stent

Endoscopic contact lithotripsy is carried out by bringing to the stone under the supervision of the vision of the energy source and destroying it as a result of direct (contact) exposure. Depending on the type of energy generated, contact lithotripters can be pneumatic, electrohydraulic, ultrasonic, laser and electrokinetic. Distinguish between contact ureterolitotripsy and nephrolithotripsy.

Percutaneous contact nephro- and ureterolithotripsy consists in the puncture of the cup-pulmonary system of the kidney through the skin of the lumbar region. After that the created channel is expanded to the appropriate size and an endoscope is installed on it in the cavity system. Under the control of vision, contact crushing of the stone is carried out with the removal of its fragments. By this method, stones of any size, including coral ones, can be destroyed in one or two sessions.

Currently, due to the high effectiveness of the above-mentioned methods of treatment, laparoscopic and, especially, open organ-saving operations with kidney and ureteral stones (nephro-, pyelo-, ureterolithotomy) are extremely rare. Nephrectomy is performed with renal scarring of the kidney with a lack of its function or calculous pionephrosis.

Bladder stones are predominantly found in older men and children and are the result of infravesical obstruction [23].

Etiology and pathogenesis. Stones can migrate from the upper urinary tract or form directly in the bladder. In either case, they are secondary, with the only difference being that in the first they are secondary to the place of formation, and in the second to the primary obstructive disease (benign hyperplasia, prostate cancer, urethral stricture, neurogenic dysfunction of the urinary bladder, etc.), as a result of which, due to stagnation of urine in the bladder, they are formed. Stones can form on foreign bodies that are long-term in the bladder, primarily on ligatures of non-absorbable material

(ligature stones). Stone formation in women is observed in diseases of the bladder neck due to radiation cystitis, in vesicovaginal fistulas.

The main symptoms of bladder stones are pain in the suprapubic area, dysuria, and hematuria. Pain in the projection of the bladder at rest decreases or disappears. Characterized by the appearance and / or strengthening it during movement, walking, shaking ride with irradiation to the urethra and genitals. Accompanying urination disorders (pollakiuria, stranguria, terminal hematuria) also depend on motor activity, therefore dysuric phenomena are characteristic of the bladder stone during the daytime. A reliable sign of a bladder stone is the symptom of interruption of a stream of urine, which disappears when the patient assumes a horizontal position. Sometimes patients can urinate only in the prone position. The penetration of a stone into the bladder neck or its entry into the urethra leads to an acute urinary retention. Hematuria occurs as a result of damage to the bladder mucosa and / or the development of the inflammatory process.

Diagnosis is based on characteristic complaints and anamnesis data. Patients are diagnosed with nephrolithiasis with stones, bladder obstruction (hyperplasia, prostate cancer, anomalies, strictures of the urethra, etc.) preceding operations on nearby organs, radiation therapy. Examination of male patients should end with rectal palpation of the prostate gland, which makes it possible to suspect its disease, and in women - with a vaginal examination to detect radiation injuries and vaginal urinary fistulas.

In the analysis of urine red blood cells and white blood cells are detected. Salt crystals can be episodic and often depend on the nature of the food and the urine pH. Bacteriological urine culture allows to identify its microflora and determine the titer of bacteriuria, which is important when conducting antibacterial treatment.

Ultrasound allows you to identify hyperechogenic education with acoustic shadow, their number and size.

On the survey radiograph can detect X-ray positive stones in the projection of the bladder.

CT provides an opportunity to identify both X-ray positive and X-ray negative bladder stones. Modern and most informative methods for examining patients are spiral and multispiral CT with the possibility of three-dimensional image reconstruction.

Urethrocystoscopy allows you to determine the capacity of the bladder and the condition of its mucous membrane, detail the shape, color, size and number of stones, as well as identify associated diseases (prostatic hyperplasia, urethral stricture, diverticulum, tumor, etc.).

Treatment is prompt. Two methods are used: stone-breaking (cystolithotripsy) and stone-cutting (cystolithotomy).

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Treatment is prompt. Two methods are used: stone-breaking (cystolithotripsy) and stone-cutting (cystolithotomy).

Stone breaking is an operation of choice and is performed by means of remote lithotripsy or endoscopic contact destruction of stones. In the latter case, contact lithotripters with different types of energy (electrohydraulic, ultrasonic, pneumatic and laser) and mechanical lithotripter are used. It consists of two branches, which, after being introduced into the bladder, open up, a stone is clamped between them under visual control, and then the branches are compressed, causing the stone to collapse.

Cystolithotomy is currently rarely used and, as a rule, when performing open operations on the prostate gland [18].

The prognosis depends on the severity of the disease, which led to infravesical obstruction followed by stone formation. With the elimination of the underlying disease, the prognosis is favorable; otherwise recurrent stone formation is possible.

Stones of the urethra are observed only in men. They can either form directly in the urethra if there are constrictions, valves or diverticula, or enter the urethra from the overlying urinary tract. Patients complain of pain in the area of the urethra, difficulty, painful urination and a thin jet of urine with spray. Full obstruction of the urethra with a stone is manifested by an acute delay in urination.

The stones of the anterior urethra are easily detected by palpation of the urethra, and the posterior one by finger rectal examination. Characterized by leukocyturia, hematuria. The final diagnosis is established on the basis of ultrasound, radiography of the pelvic region, urethral examination by bougies or metal catheters (characterized by a sense of contact of the metal with the stone) and urethroscopy.

Treatment of stones of the urethra consists in their endoscopic removal. Stones of the scaphoid fossa are removed with forceps or forceps. The narrowed outer orifice of the urethra is dilated with conical bougies or dissected.

Initial management can either be done as an inpatient or on an urgent outpatient basis, usually depending on how easily the pain can be controlled.

Indications for hospital admission:

- Fever;
- Solitary kidney;
- Known non-functioning kidney;
- Inadequate pain relief or persistent pain;
- Inability to take adequate fluids due to nausea and vomiting;
- Anuria;
- Pregnancy;
- Poor social support;
- Inability to arrange urgent outpatient department follow-up;
- People over the age of 60 years should be admitted if there are concerns on clinical condition or diagnostic certainty (a leaking aortic

aneurysm may present with identical symptoms).

Complications:

- Complete blockage of the urinary flow from a kidney decreases glomerular filtration rate (GFR) and, if it persists for more than 48 hours, may cause irreversible renal damage;
- If ureteric stones cause symptoms after four weeks, there is a 20% risk of complications, including deterioration of renal function, sepsis and ureteric stricture;
- Infection can be life-threatening;
- Persisting obstruction predisposes to pyelonephritis.

Prognosis:

- Most symptomatic renal stones are small (less than 5 mm in diameter) and pass spontaneously;
- Stones less than 5 mm in diameter pass spontaneously in up to 80% of people;
- Stones between 5 mm and 10 mm in diameter pass spontaneously in about 50% of people;
- Stones larger than 1 cm in diameter usually require intervention (urgent intervention is required if complete obstruction or infection is present);
- Two thirds of stones that pass spontaneously will do so within four weeks of onset of symptoms;
- A stone that has not passed within 1-2 months is unlikely to pass spontaneously.

The following features predispose to recurrent stone formation:

- First attack before 25 years of age;
- Single functioning kidney;
- A disease that predisposes to stone formation;
- Abnormalities of the renal tract.

5.5 Prevention

Recurrence of renal stones is common and therefore patients who have had a renal stone should be advised to adapt and adopt several lifestyle measures which will help to prevent or delay recurrence:

- Increase fluid intake to maintain urine output at 2-3 litres per day;
- Reduce salt intake;
- Reduce the amount of meat and animal protein eaten;

- Reduce oxalate intake (foods rich in oxalate include chocolate, rhubarb, nuts) and urate-rich foods (eg, offal and certain fish);
- Drink regular cranberry juice: increases citrate excretion and reduces oxalate and phosphate excretion;
- Maintain calcium intake at normal levels (lowering intake increases excretion of calcium oxalate);
- Depending on the composition of the stone, medication to prevent further stone formation is sometimes given - eg, thiazide diuretics (for calcium stones), allopurinol (for uric acid stones) and calcium citrate (for oxalate stones) [22].

Urolothiasis

Urolithiasis is a metabolic disease that, due to a violation of the physico-chemical balance of urine under the influence of endogenous and exogenous factors, is manifested by the formation of stones in the urinary tract.

Theories of urolithiatis:

1. Nucleation theory;

2. Stone matrix theory;

3. Inhibitor of crystallization theory.

Clinical manifestation. Many stones are asymptomatic and discovered during investigations for other conditions. The classical features of renal colic are sudden severe pain. It is usually caused by stones in the kidney, renal pelvis or ureter, causing dilatation, stretching and spasm of the ureter.

Diagnostic:

1. Stick testing of urine;

2. Midstream specimen of urine for microscopy, culture and sensitivities;

3. Blood for FBC, CRP, renal function, electrolytes, calcium, phosphate and urate, creatinine;

4. Prothrombin time and international normalised ratio if intervention is planned;

5. Non-enhanced CT scanning is now the imaging modality of choice and has replaced intravenous pyelogram (IVP);

6. Ultrasound scanning may be helpful to differentiate radio-opaque from radiolucent stones and in detecting evidence of obstruction;

7. Plain X-rays of the kidney, ureter and bladder (KUB) are useful in watching the passage of radio-opaque stones (around 75% of stones are of calcium and so will be radio-opaque).

Treatment. Treatment of urolithiasis is complex and is aimed at the elimination of pain, the restoration of impaired urine outflow, the destruction and/or removal of the stone, the correction of urodynamic disorders, the prevention of inflammatory complications, preventive and metaphylactic measures. Spontaneous removal of stones can occur in 80% of cases, if the size of the stone is not more than 4 mm in diameter.

The complex of therapeutic measures aimed at the expulsion of the stone includes: active treatment, exercise therapy (walking, running, jumping), increased diuresis (diuretics, heavy drink or intravenous fluids), analgesics, spasmolytic drugs, alpha-blockers (silodosin, tamsulosin, alfuzosin, doxazazine), plant uroseptics, antibacterial therapy, physiotherapy (amplipulse, ultrasound stimulation, local vibration therapy, etc.).

Remote lithotripsy, contact ureterolithorpsy and ureterolithoextraction, percutaneous nephroureterolytotripsy, laparoscopic and extremely rarely open operations are currently used.

Indications for hospital admission:

1. Fever;

2. Solitary kidney;

3. Known non-functioning kidney;

4. Inadequate pain relief or persistent pain;

5. Inability to take adequate fluids due to nausea and vomiting;

6. Anuria;

7. Pregnancy;

8. Poor social support;

9. Inability to arrange urgent outpatient department follow-up;

10. People over the age of 60 years should be admitted if there are concerns on clinical condition or diagnostic certainty (a leaking aortic aneurysm may present with identical symptoms).

Theme # 6: Urological infections: actuality, classification, clinical manifestation, diagnostic tools and treatment of acute pyelonephritis, cystitis, urethritis, bacterial prostatitis, epididymitis and orchitis.

6.1 Actuality

Urinary tract infections are the most common infectious diseases that require significant financial expenditures. Nosocomial UTIs are the largest reservoir of antibiotic-resistant microorganisms in medical institutions.

According to epidemiological data, most often UTI develops in women: almost 50% of women undergo UTI at least once in a lifetime. In men, the incidence of UTI is much less and amounts to 5–8 cases per 10,000 people. In elderly and senile patients, UTIs occupy the second place in the frequency of occurrence and account for approximately 25% of all infectious diseases. Bacteriuria develops in up to 25% of patients who require a urinary catheter for one week or more with a daily risk of 5-7%.

The recent Global Prevalence Infection in Urology (GPIU) studies have shown that 10-12% of patients hospitalised in urological wards have a healthcare-associated infection (HAI). The strains retrieved from these patients are even more resistant [29].

6.2 Classification of urological infections and risk factors

The guidelines of European Association of Urology (2015) give a short summary of a tentative improved system of classification (Tab. 4) of urinary tract infection based on:

- anatomical level of infection;
- grade of severity of infection;
- underlying risk factors;
- microbiological findings.

The symptoms focus on the anatomical level of infection, defined as:

- Urethra: urethritis;
- Urinary bladder: cystitis;
- Kidney: pyelonephritis;
- Prostate gland: prostatitis;
- Testicle (epididymis): orchitis (epididymitis);
- Bloodstream: sepsis.

Risk groups for urinary tract infections:

- female. Women suffer from such infections 5 times more often than men. This is due to the physiological peculiarity.
- the body of a woman is a short and wide urethra,
- connection with which the infection more easily penetrates the urinary tract;
- elderly people;

- patients with urinary characteristics
- systems (for example, an enlarged prostate gland can make it harder
- urine outflow from the bladder));
- patients with renal pathology (for example, urolithiasis
- disease where stones are an additional risk factor for
- development of infections);
- resuscitation and intensive care patients
- (use of urethral catheters);
- persons suffering from diabetes.

Factors predisposing to the occurrence of urinary tract infections are:

- hypothermia (most of the problems of this nature
- occurs in the cool season);
- the presence of a respiratory infection in a patient (frequent
- activation of urological infections during the cold season);
- reduced immunity;
- violations of the outflow of urine of a different nature.

Tab. 4 - Criteria for the diagnosis of urinary tract infection, as modified according to IDSA/European Society of Clinical Microbiology and Infectious Diseases guidelines

Category	Description	Clinical features	Laboratory investigations
1	**Asymptomatic bacteriuria**	No urinary symptoms	>10 WBC/mm^3 >10^5 cfu/mL in 2 consecutive MSU cultures >24 h apart
2	**Acute uncomplicated urinary tract infection in women** **Acute uncomplicated cystitis in women**	Dysuria, urgency, frequency, suprapubic pain, no urinary symptomsin 4 weeks before this episode	>10 WBC/mm^3 >10^3 cfu/mL

3	**Acute uncomplicated pyelonephritis**	Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urological abnormalities	>10 WBC/mm^3 >10^4 cfu/mL
4	**Complicated urinary tract infection**	Any combination of symptoms from categories 1 and 2 above; 1 or more factors associated with a complicated urinary tract infection	>10 WBC/mm^3 >10^5 cfu/mL in women >10^4 cfu/mL in men or in straight catheter urine in women
5	**Recurrent urinary tract infection (antimicrobial prophylaxis)**	At least 3 episodes of uncomplicated infection documented by culture in past 12 months; women only; no structural/functional abnormalities	<10^3 cfu/mL

6.3 Acute pyelonephritis and cystitis and in adults

Epidemiology, aetiology and pathophysiology. Almost half of all women will experience at least one episode of UTI during their lifetime. Nearly 1 in 3 women will have had at least one episode of UTI by the age of 24 years.

Only a small number of 15-50 year-old men suffer from acute uncomplicated cystitis. As reviewed, UTI (cystitis and pyelonephritis) occurs more frequently in patients with diabetes mellitus, which may represent an independent risk factor. It is, however, difficult to determine the impact of renal insufficiency on the epidemiology of UTI because of the wide variety of underlying diseases.

The spectrum of aetiological agents is similar in uncomplicated upper and lower UTIs, with E. coli the causative pathogen in 70-95% of cases and Staphylococcus saprophyticus in 5-10%. Occasionally, other Enterobacteriaceae, such as Proteus mirabilis and Klebsiella sp., are isolated.

Symptoms and signs of UTI in the adult are as follows:

- Dysuria;
- Urinary urgency and frequency;
- A sensation of bladder fullness or lower abdominal discomfort;
- Suprapubic tenderness;
- Flank pain and costovertebral angle tenderness (may be present in cystitis but suggest upper UTI);
- Bloody urine;
- Fevers, chills, and malaise (may be noted in patients with cystitis, but more frequently associated with upper UTI).

6.3.1 Acute pyelonephritis in adults (uncomplicated, complicated)

Pyelonephritis is a nonspecific infectious-inflammatory process, characterized by simultaneous or sequential lesions of the renal lobes and the renal parenchyma (mainly interstitial tissue).

Infectious agents are Gram-negative bacteria of the intestinal group Escherichia coli, Proteus mirabilis, Enterococcus species, Enterobacter. Less commonly found are Klebsiella, Staphylococcus, and Candida albicans.

If pyelonephritis is a nosocomial infection, Escherichia coli, Klebsiella, Proteus, Staphylococcus aureus, Candida are most commonly found as pathogens. Staphylococcus aureus is usually found in purulent kidney lesions due to hematogenous spread of the infection.

Clinical diagnosis. Acute pyelonephritis is suggested by local symptoms (acute pain in the lumbar region on the affected side or dull pain, aching in nature, may be slight or reach high intensity, take paroxysmal character (for example, during obstruction) and general symptoms that characterized by the development of intoxication syndrome (fever up to 38-40°C; chills; general weakness; arthralgia, myalgia; loss of appetite; nausea, sometimes vomiting). [29, 30]

Chronic pyelonephritis. Outside the exacerbation, this form of pyelonephritis is of little or asymptomatic. In the period of exacerbation, general and local clinical manifestations are possible, similar to those in acute pyelonephritis, but less intense. Lumbar pain is the most common complaint of patients.

The severity of pain varies from a feeling of heaviness and discomfort to severe pain during a relapse of infection. The asymmetry of pain is characteristic. Sometimes with pyelonephritis, an atypical localization of pain is noted - in the sacrum or coccyx. Attacks of renal colic indicate occlusion of the ureter with stone, blood clot or pus, as well as tissue debris in necrotizing papillitis.

Pollakiuria (frequent urination) and stranguria (pain during urination) are usually noted. In the stage of renal dysfunction, permanent pollakiuria and

nocturia reflect a decrease in the concentration ability of the kidneys.

Elderly and senile patients often develop an atypical clinical picture, either with an erased clinic or with pronounced common manifestations and a lack of local symptoms.

Factors that suggest a potential complicated urinary tract infection described in Tab. 6.

Tab. 5 – Clinical manifestation of acute pyelonephritis

Clinical diagnosis	
History	Lower urinary tract symptoms (e.g., frequency, urgency, dysuria)
	Upper urinary tract symptoms (e.g., flank pain)
	Constitutional symptoms (e.g., fever, chills, malaise)
	Gastrointestinal symptoms (e.g., nausea, vomiting, anorexia, abdominal pain)
Physical examination	Fever (temperature > 38.0°C), tachycardia, hypotension
	Costovertebral angle tenderness
	Possible abdominal or suprapubic tenderness
Laboratory tests	Urinalysis showing positive leukocyte esterase test, microscopic pyuria or hematuria, or white blood cell casts
	Peripheral blood smear showing leukocytosis, with or without left shift
	Positive blood culture in 15 to 30 percent of cases
	Urine culture growing $\geq 10^5$ colony-forming units per mL of urine

Tab. 6 - Factors that suggest a potential complicated urinary tract infection

The presence of an indwelling catheter, stent or split (urethral, ureteral, renal) or the use of intermittent bladder catheterization
Post-void residual urine of >100 mL
An obstructive uropathy of any aetiology (upper and lower urinary tracts), e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumor
Vesicoureteric reflux or other functional abnormalities
Urinary tract modifications/deviation, such as ileal loop or pouch
Chemical or radiation injuries of the uroepithelium
Peri- and postoperative urinary tract infection, including renal transplantation

Diagnostic Testing

Examination of patients with pyelonephritis includes the collection of complaints, anamnesis, physical examination, and then proceed to special diagnostic methods.

In laboratory studies, blood tests show pronounced leukocytosis (up to 30-40 thousand) with a significant neutrophilic shift of the leukocyte formula to the left to the young forms, an increase in the ESR to 40-80 mm/h. However, a clear dependence of changes in peripheral blood on the severity of clinical manifestations is not always observed: in severe cases of the disease, as well as in weakened patients, the leukocytosis can be moderate, insignificant or absent, leukopenia is sometimes noted.

The characteristic signs of acute pyelonephritis in the study of urine sediment are proteinuria, leukocyturia, and significant (true) bacteria-uria, especially if they are detected simultaneously. False proteinuria in the inflammatory process in the kidney is caused by decay when blood cells form in the urine and in most cases do not exceed 1.0 g/l (from traces to 0.033-1.0 g/l). It is represented predominantly by albumin, less frequently by gamma globulins. Leukocyturia (pyuria) is the most characteristic sign of pyelonephritis. It often reaches significant severity (leukocytes cover the entire field of view or are found in clusters) and may be absent only when the inflammatory process is localized only in the cortical substance of the kidney or during obstruction of the ureter. In pyelonephritis, erythrocyturia can be observed (microhematuria), less often - gross hematuria (with necrosis of the renal papillae, calculous pyelonephritis). Severe disease is accompanied by cylindruria (granular and waxy cylinders). Bacteriuria is found in most cases, however, like leukocyturia, it is intermittent in nature, and therefore repeated urine tests for microflora are important. To confirm pyelonephritis, only the presence of true bacteriuria, meaning the presence of at least 50-100 thousand microbial bodies in 1 ml of urine, is important. [26]

Sowing urine and determining the sensitivity of microorganisms to antibiotics are made before, during, and after treatment of the patient. With uncomplicated acute pyelonephritis, control urine culture is performed on the 4th day and 10 days after the end of antibiotic therapy, with complicated pyelonephritis, respectively, on the 5-7th day and after 4-6 weeks. Such bacteriological examination is necessary to identify resistant forms of microorganisms and to correct antibiotic therapy during treatment, as well as to determine the recurrence of infection after the course of therapy.

An increase in serum creatinine and urea is a sign of renal failure. Serum creatinine and urea levels should be determined before conducting studies with intravenous administration of radiopaque drugs. Increased blood levels of urea, creatinine as a result of impaired renal function is possible in severe purulent pyelonephritis with severe intoxication or a bilateral process. In these cases, liver damage and the development of

hepatorenal syndrome with impaired protein-forming, detoxification, pigment (with the presence of jaundice), prothrombinobases and its other functions are often observed.

Ultrasound of the kidney has high accuracy in identifying the size of the kidney, the heterogeneity of its structure, the deformation of the renal pelvis system, the presence of pyonephrosis and the state of the renal fatty tissue. Reducing the mobility of the kidney in combination with its increase is the most important ultrasound sign of acute pyelonephritis, and the expansion of the renal pelvis system is in favor of the obstructive (secondary) nature of the disease. [26, 27]

Excretory urography allows you to establish the cause and level of obstruction of the urinary tract. In the first 3-4 days acute pyelonephritis may not be accompanied by leukocyturia. In such cases, diagnosis of primary pyelonephritis is particularly difficult, since there are no signs of impaired outflow of urine from the kidney. In such patients, excretory urography with imaging on inspiration and expiration on a single film has a great diagnostic value: it allows you to identify a restriction of mobility of the kidney on the affected side.

CT is the most modern and informative diagnostic method for the study of purulent-inflammatory diseases of the kidneys. CT allows to determine the cause and level of possible obstruction of the ureter, to detect foci of destruction of the renal parenchyma.

The diagnostic value of this method is due to the high resolution and the ability to clearly differentiate normal tissue from the diseased. The results of CT facilitate the surgeon the choice of optimal access for open or percutaneous interventions, in particular when the carbuncle of the kidney or peri-nephral abscess.

Treatment (Tab. 7, 8)

Tab. 7 – Recommended initial empirical oral antimicrobial therapy in mild and moderate acute uncomplicated pyelonephritis

Oral therapy in mild and moderate uncomplicated pyelonephritis		
Antibiotics	Daily dose	Duration of therapy
Ciprofloxacin	500-750 mg twice a day	7-10 days

Levofloxacin	500 mg once daily	7-10 days
Levofloxacin	750 mg once daily	5 days
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)		
Cefpodoxime proxetil	200 mg twice a day	10 days
Ceftibuten	400 mg once daily	10 days
Only if the pathogen is known susceptible (not for initial empirical therapy)		
Trimethoprim-sulphamethoxazole	160/800 mg twice a day	14 days
Co-amoxiclav (not studied as monotherapy for acute uncomplicated pyelonephritis and mainly for Gram-positive pathogens)	0.5/0.125 g three times a day	14 days
Fluoroquinolones are contraindicated during pregnancy		

Acute pyelonephritis requires treatment in a hospital. When revealing the obstructive nature of the disease, first of all it is necessary to ensure an adequate outflow of urine from the affected kidney. Restore patency of the ureter can be by catheterization or stenting. If it is not possible to hold the ureter catheter above the site of its obstruction, percutaneous puncture nephrostomy should be performed.

Further treatment consists in the appointment of antibacterial and symptomatic therapy, compliance with bed rest, the use of non-steroidal anti-inflammatory drugs and the use of large amounts of fluid. [17]

Empirical antibacterial therapy should include parenteral administration of broad-spectrum drugs that primarily affect the Gram-negative flora (fluoroquinolones,

cephalosporins, aminoglycosides). Further correction of treatment taking into account the results of urine culture and determining the sensitivity of the pathogen to antibiotics is performed. The course of treatment for acute uncomplicated pyelonephritis is 7-14 days.

One of the important components of treatment is therapy, aimed at increasing immunity and improving the general condition of the body. Among the immunomodulators used Wobenzim®, Lavomax®, preparations Echinacea (immunal, etc.).

Complex treatment of both acute and chronic pyelonephritis includes the appointment of phytourseptics, which have a diuretic, antibacterial, anti-inflammatory, astringent and tonic effect (cranberry leaves, bearberry, kidney tea, birch buds, juniper berries, etc.).

As a rule, acute pyelonephritis with a timely begun treatment proceeds favorably. After 3-5 days, the temperature decreases, the manifestations of intoxication and pain in the lumbar region decrease, the blood picture improves. Within 7-10 days, bacteriuria and leukocyturia are practically eliminated. Absolute recovery occurs 3-4 weeks later.

Tab. 8 – Recommended initial empirical parenteral antimicrobial therapy in severe acute uncomplicated pyelonephritis

Initial parenteral therapy in severe uncomplicated pyelonephritis After improvement, the patient can be switched to an oral regimen using one of the agents (if active against the infecting organism) to complete the 1-2-week course of therapy. Therefore, only daily dose and no duration of therapy are indicated.	
Antibiotics	**Daily dose**
Ciprofloxacin	400 mg twice a day
Levofloxacin	250-500 mg once daily
Levofloxacin	750 mg once daily

Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)	
Cefpodoxime proxetil	2 g three times a day
Ceftriaxone	1-2 g once daily
Ceftazidime	1-2 g three times a day
Cefepime	1-2 g twice a day
Co-amoxiclav	1.5 g three times a day
Piperacillin/tazobactam	2.5-4.5 g three times a day
Gentamicin	5 mg/kg once daily
Amikacin*	15 mg/kg once daily
Ertapenem	1 g once daily
Imipinem/cilastatin	0.5/0.5 g three times a day
Meropenem	1 g three times a day
Doripenem	0.5 g three times a day
Fluoroquinolones are contraindicated during pregnancy	

6.3.2 Acute episode of cystitis (lower UTI) in adults (uncomplicated, complicated)

Cystitis is an infectious-inflammatory disease of the wall of the bladder with a predominant lesion of its mucous membrane.

Epidemiology. Women are sick more often than men, in a ratio of 3: 1, which is due to:

- anatomical and physiological features of the urogenital system of women (short and wide urethra, proximity of the genital tract and rectum);
- gynecological diseases;
- changes in the hormonal background during pregnancy, with the intake of hormonal contraceptives, in the post-menopausal period (microcirculation disorders leading to weakening of local immunity, atrophy of the vaginal mucosa, and reduction in mucus formation).

Clinical diagnosis. The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those women who have no other risk factors for complicated UTIs. In elderly women genitourinary symptoms are not necessarily related to UTI. [24]

The rapid onset of the disease with characteristic symptoms can immediately be suspected acute cystitis. In clinical and biochemical blood tests, pathological changes are usually not observed.

The urine is turbid, with a smell. In the study, its reaction is more often alkaline, a large number of leukocytes and bacteria are always detected, red blood cells, epithelium, cylinders can be present, false proteinuria is noted, that is, caused by the disintegration of a large number of blood elements.

Bacterioscopy allows you to visually (using a microscope) to determine the presence of an infectious agent. More informative is the culture of urine with the definition of bacterial culture and a test for sensitivity to antibiotics. The disadvantage of this method is the duration of its implementation, therefore, with a clinically confirmed diagnosis of cystitis, antibiotic therapy is initiated with broad-spectrum drugs, without waiting for the results of the sowing.

It is important to note that in acute cystitis, invasive diagnostic methods are contraindicated, primarily cystoscopy. [26, 27]

Treatment

Therapeutic tactics for acute cystitis is to prescribe antibacterial therapy, rest, plenty of drink are recommended, sharp and extractive dishes are excluded from the diet. Painful sensations can be suppressed

by the appointment of non-steroidal anti-inflammatory drugs that have anti-inflammatory and analgesic action.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available (Tab. 9). These regimens are recommended for women, but not for men. Most ESBL-producing E. coli are still susceptible to fosfomycin. However, in Spain a parallel increase in community use of fosfomycin and resistance to fosfomycin in ESBL-producing E. coli has been observed.

Tab. 9 – Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy women

Antibiotics	Daily dose	Duration of therapy	Comments
First choice			
Fosfomycin trometamol	3 g single dose	1 day	
Nitrofurantoin macrocrystal	100 mg twice a day	5 days	
Pivmecillinam	400 mg three times a day	3 days	
Alternatives			
Ciprofloxacin	250 mg twice a day	3 days	Not during pregnancy
Levofloxacin	250 mg once daily	3 days	Not during pregnancy
Ofloxacin	200 mg twice a day	3 days	Not during pregnancy

Cephalosporin (e.g. cefadroxil)	500 mg twice a day	3 days	Or comparable
If local resistance pattern is known (E. coli resistance <20%)			
Trimethoprim	200 mg twice a day	5 days	Not in the first trimester of pregnancy
Trimethoprim-sulphamethoxazole	160/800 mg twice a day	3 days	Only in the second trimester of pregnancy

Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for E. coli of < 20%. Despite still lower resistance rates in some areas, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection of resistance.

Aminopenicillins are no more suitable for empirical therapy because of the worldwide high E. coli resistance. Aminopenicillins in combination with a betalactamase inhibitor such as ampicillin/sulbactam or amoxicillin/slavulanic acid and oral cephalosporins are in general not so effective as short-term therapy and are not recommended for empirical therapy because of ecological collateral damage, but can be used in selected cases.

6.4 Urethritis

Urethritis is an inflammation of the urethra.

Aetiology, epidemiology and pathogenesis. The vast majority of urethritis is transmitted sexually. The incubation period can range from several hours to several months. A significant role in the pathogenesis of urethritis is played by the state of the macroorganism. Contributing local factors are hypo- and epispadias, narrowing of the urethra.

There are nonspecific and specific (gonococcal) urethritis. Gonococcal urethritis is caused by microorganisms Neisseria gonorrhoeae (gram-negative intracellular diplococci).

Urethritis can be primary and secondary. In primary urethritis, the

inflammatory process begins directly from the mucous membrane of the urethra. In a secondary infection, the infection enters the urethra from an inflammatory focus that exists in another organ (bladder, prostate, vagina, etc.). [17]

Trichomonas urethritis is caused by Trichomonas vaginalis. The duration of the incubation period of trichomonas urethritis is 10-12 days. The disease is characterized by the appearance of itching, burning in the area of the external opening of the urethra. In the first portion of urine with shaking, many small vesicles are found, which is associated with mucus formation. However, the same picture can be observed in the initial phase of allergic urethritis. Then there are secretions, first mucous, then mucopurulent. They can be abundant, have a yellowish color and do not differ from the discharge in acute gonorrheal urethritis. Without treatment, after 3-4 weeks, acute events subside, and the urethritis becomes torpid. One of the complications can be inflammation of the excretory ducts of the prostate gland.

Mycoplasma and chlamydial urethritis are sexually transmitted and can cause infertility. Pathogens differ from bacteria in the plasticity of the outer membrane. Hence, polymorphism and the possibility of passing through bacterial filters. These urethritis are characterized by the complete absence of any specificity, therefore, the search for mycoplasmas and chlamydia should be carried out for all long-flowing torpid and chronic urethritis. In patients with chlamydial urethritis, extragenital manifestations of the disease may occur (conjunctivitis, arthritis, lesions of internal organs and skin) - the so-called Reiter syndrome.

Viral urethritis is more commonly caused by the herpes virus. The duration of the incubation period varies widely. The onset of herpetic urethritis is accompanied by a burning sensation, a feeling of discomfort in the urethra. Groups of strained hemispherical small bubbles appear on the skin, and after opening them, painful erosion remains. An important feature of the course of herpetic urethritis is its persistent recurrence. The disease can last many years, escalating without apparent periodicity.

Fungal (mycotic) urethritis develops as a result of lesion of the mucous membrane of the urethra by yeast fungi and is relatively rare. Most often it is a complication of long-term antibiotic therapy, less often - it is transmitted from a sexual partner suffering from candidiotic vulvovaginitis. Clinical manifestations are very scarce.

Complications of urethritis are prostatitis, orchiepididymitis, cystitis, and in the long-term period - narrowing of the urethra.

Diagnostics

A Gram stain of a urethral discharge or a urethral smear that shows more than five leukocytes per high power field (× 1,000) and eventually, gonococci located intracellularly as Gram-negative 127 ystematiza, indicate pyogenic urethritis. The Gram stain is a rapid

diagnostic test for evaluating urethritis. Laboratories should use validated nucleic acid amplification tests (NAATs) to detect chlamydia and 128ystemati which are better than any of the other tests available for the diagnosis of chlamydial and gonococcal infections with respect to overall sensitivity, specificity, and ease of specimen transport. N. gonorrhoeae and chlamydia cultures are mainly to evaluate treatment failures and monitor developing resistance to current treatment.

In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. If an amplification system is used for identifying the pathogens, the first voiding urine specimen can be taken instead of a urethral smear. Trichomonas sp. Can usually be identified microscopically.

Treatment

The main method of treatment of urethritis is antibacterial therapy, based on the sensitivity of the identified pathogens to the drugs used. Depending on the form and severity of the disease, antibiotics of various groups are used: semisynthetic penicillins, tetracyclines, cephalosporins of the 2nd and 3rd generations.

With bacterial urethritis, various variants of streptococci, staphylococci, Escherichia coli, enterococci and other microorganisms that can exist in the genitourinary system of healthy men and women are found. The recommended treatment regimens include the use of antibacterial drugs (doxycycline 100 mg twice a day for 7 days or azithromycin 1000 mg once). As an alternative, macrolides (erythromycin, clarithromycin, roxithromycin) or fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) are prescribed. Treatment of gonorrheic urethritis consists in the appointment of cefexime once per os in a dose of 400 mg or ceftriaxone in a dose of 250 mg once. The drugs of the second line are fluoroquinolones. They are used in the resistance of the pathogen to cephalosporins.

In the treatment of trichomoniasis, metronidazole (inside 2 g once) or tinidazole (inside 2 g once) is used.

Therapy of mycoplasmic and chlamydial urethritis consists in the administration of azithromycin and doxycycline, and as alternative drugs – roxithromycin and clarithromycin.

At the primary clinical episode of herpetic urethritis, antiviral drugs (acyclovir – 200 mg, famcielovir – 500 mg) are used. With frequent (more than 6 times a year) relapses, suppressive therapy should be started.

Treatment of fungal urethritis consists in the abolition of antibacterial drugs and the appointment of antifungal agents.

Local treatment of chronic urethritis includes instillations in the urethra of 0.25-0.5% silver nitrate solution, 1-3% protargol solution or 0.5% dioxygen solution.

6.5 Bacterial prostatitis

Acute bacterial prostatitis is rare and does not exceed 2-3% of all inflammatory processes in the prostate gland. The clinical picture of the disease is characterized by a rapid onset and consists of severe pain in the perineum, lower abdomen, sacrum, malaise, and fever, often with chills, frequent painful and difficult urination. The patient is pale, there is tachycardia, and there may be nausea. With transrectal palpation, the prostate gland is enlarged, tense, sharply painful, in the presence of an abscess, fluctuation is determined. Sometimes the pain is so strong that patients do not allow to fully conduct this study. [6]

Chronic prostatitis is much more common and occurs in 10-35% of men of reproductive age. Patients complain mainly of pain in the lower abdomen, perineum. Their irradiation is possible in the anus, scrotum, sacrum, inguinal region. Sometimes patients have a burning sensation in the perineum and urethra. As a rule, there is a clear correlation of pain with sexual contacts: their strengthening during sexual abstinence and relief, until they disappear after coitus. When defecation may occur unpleasant or painful sensations in the pelvic area, associated with the pressure of feces on the inflamed gland.

Patients complain of frequent, painful urination, urge, feeling of incomplete emptying of the bladder, less often - difficulty urinating, weak urine flow.

Changes in the state of the erogenous zones of the small pelvis can lead to an increase in their excitability or, conversely, to inhibition of sensitivity, which may be accompanied by disorders of sexual function.

The course of chronic prostatitis may be accompanied by the release of a small amount of unclear liquid from the urethra in the morning. Sometimes there is a clear connection with the discharge of the process of defecation. The prostate is caused by hyperproduction of prostatic secretion and dysfunction of the locking mechanisms of the distal tubules and the seed tubercle.

A large part of patients with a detailed history taking noted an increase in mental and physical fatigue, depression, and psychiatric phenomena.

It is recommended that European urologists use the classification suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis with confirmed or suspected infection is distinguished from chronic pelvic pain syndrome (CPPS) (Tab. 10).

Diagnostics

Diagnosis is based on the examination of the patient's complaints, careful collection of anamnesis, laboratory and special methods of

examining the state of the prostate gland.

One of the most reliable and informative diagnostic methods is the digital rectal examination of the prostate gland. In chronic prostatitis, it is more often of normal size, asymmetrical, soft-elastic or testovato consistency, heterogeneous, with areas of cicatricial contractions, moderately painful during palpation. After the massage, the iron becomes softer, sometimes even flabby, which indicates a normal evacuation of the contents into the lumen of the urethra.

After inspection, you must obtain the secret of the prostate for microscopic and bacteriological examination. The detection of leukocytes in it, a decrease in the number of lecithin grains indicate an inflammatory process. As a rule, there is an inverse relationship between the number of leukocytes and lecithin grains (which is influenced by the degree of activity of the inflammatory process). The prostate secretion may also contain epithelial cells.

The prismatic epithelium is shed from the prostate gland, and the secretory - from its acini. Identification of pathogenic microorganisms in the course of bacteriological culture studies indicates the bacterial (infectious) nature of the disease. Prostate gland material can also be obtained from a Stamey-Mears test.

Ultrasound of the prostate gland is the third most important after digital examination and microscopy of the resulting secret. It is conducted through the anterior abdominal wall and rectal probe. The most informative is transrectal ultrasound. Sonography can reveal asymmetry, changes in the size of the gland, the presence of nodes, formations, inclusions, cavities, calcinates, and diffuse changes in the parenchyma.

Differential diagnosis. Chronic prostatitis should be primarily differentiated from tumor diseases and prostate tuberculosis, as well as inflammation of adjacent organs (vesiculitis, cystitis, paraproctitis). In most cases, laboratory data (tumor markers, bacterioscopic and bacteriological research of prostate secretion on Mycobacterium tuberculosis), ultrasound, CT and MRI, skeletal scintigraphy and prostate biopsy allow you to establish the correct diagnosis.

Tab. 10 - Classification system of prostatitis by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Category	Pain	Bacteria	WBCs	NIDDK (Current)	Description	Meares/Stamey (Old)
I	+	+	+	Acute	**Acute prostatitis** is a	Acute bacterial

				prostatitis	bacterial infection of the prostate gland that requires urgent medical treatment	prostatitis
II	±	+	+	Chronic bacterial prostatitis	**Chronic bacterial prostatitis** is a relatively rare condition that usually presents as intermittent urin ary tract infections	Chronic bacterial prostatitis
IIIa	+	-	+	Inflammator y CP/CPPS	**Chronic prostatitis/chro nic pelvic pain syndrome**, accounting for 90%-95% of prostatitis diagnoses, formerly known as chronic nonbacterial prostatitis	Nonbacterial prostatitis
IIIb	+	-	-	Noninflam-matory CP/CPPS		Prostatodinia
IV	-	-	+	Asymptomat ic inflammator y prostatitis	**Asymptomatic inflammatory prostatitis** patic nts have no history of genitourinary pain complaints, but leukocytosis is noted, usually during evaluation for	(none)

					other conditions. Between 6-19% of men have pus cells in their semen but no symptom	

Treatment

Etiotropic antibiotic therapy includes broad-spectrum antibiotics, allowing to eliminate the entire spectrum of microorganisms found in the secret of the prostate gland.

Acute prostatitis requires emergency hospitalization with parenteral administration of antibacterial drugs, anti-inflammatory, detoxification, restorative therapy.

In chronic prostatitis, long-term multi-course complex treatment is necessary, as a rule, in out-patient conditions.

The duration of antibiotic therapy for acute prostatitis is 2-4 weeks, and for chronic - 4-6 weeks. Fluoroquinolones (levofloxacin, ciprofloxacin - 500 mg orally 1-2 times a day, lomefloxacin, moxifloxacin, ofloxacin - 400 mg orally 1-2 times a day) are drugs of choice Doxycycline and trimethoprim are considered second-line drugs, and cefotaxime, ceftriaxone and amikacin are reserved as second-line drugs.

Non-steroidal anti-inflammatory drugs (diclofenac sodium - orally 50 mg 2 times a day after meals for 20 days) can eliminate pain. Bioregulatory peptides: prostate extract (vi-taprost, prostatilen) is used for 30 days in the form of suppositories for the night. Alpha-1-adrenergic blockers in patients with chronic prostatitis are prescribed for marked disorders of urination. In 20-70% of patients with chronic prostatitis, there are various mental disorders that require correction. In these cases, patients are prescribed tranquilizers and antidepressants.

In some cases, a prostate gland massage can be performed to evacuate the congestive inflammatory discharge that forms in the prostate gland. The restoration of complete microcirculation in the pelvic organs is promoted by the appointment of physiotherapy, physical therapy and local procedures (warm microclysters with chamomile, sage).

Patients are shown an active lifestyle, playing sports to eliminate stagnation in the pelvic organs and increase the muscle tone of the pelvic diaphragm.

Diet therapy is a full-fledged healthy diet with a high content of B vitamins and ascorbic acid. It is necessary to exclude spicy dishes, alcohol [5, 74]

Regular sex life contributes to the prevention and elimination of congestive phenomena in the prostate gland.

6.6 Epididymitis and orchitis

Epididymitis - inflammation of the epididymis. Epididymitis develops mainly due to the penetration of an infection into the appendage or by hematogenous from foci of purulent infection (sore throat, furuncle, hydradenitis, pneumonia, etc.), or canalicular, through the vas deferens, in the presence of inflammation in the urethra or prostate gland. Epididymitis may develop after instrumental (bladder catheterization, urethral dilation) and endoscopic (urethrocystoscopy) interventions.

Much less often, abnormal development of the lower urinary tract (diverticula, valves of the posterior urethra) and injuries of the scrotum organs can cause epididymitis.

Aseptic inflammation of the epididymis may develop as a result of selective accumulation of amiodarone in it - a drug used in cardiology practice.

Symptomatology. Acute epididymitis begins with a rapidly increasing increase in the epididymis, sharp pains in it, and increase in body temperature to 40°C with chills. Inflammation and swelling spread to the shell of the testicle and scrotum, with the result that its skin stretches, loses its folding, and becomes hyperemic.

With the involvement in the pathological process of the testicle (epididimoorchitis) the boundary between them ceases to be determined. Usually develops reactive hydrocele. Pain radiating to the groin area, sharply aggravated by movement, and therefore patients are forced to stay in bed. Due to the delayed or inadequate treatment of acute epididymitis, the disease can abscess or become chronic.

Chronic epididymitis is characterized by a latent course. Pain is insignificant. The presence of a node or a limited seal in the head of the epididymis indicates its hematogenous origin. During the process in the tail of the appendage, a connection with a disease of the urethra or instrumental examination should be sought.

Diagnostics

Diagnosis in most cases is not difficult. The diagnosis is established on the basis of the inspection data and palpation of the scrotum organs.

The enlarged and edematous corresponding half of the scrotum is determined, its skin is hyperemic, and its folding is smoothed. The appendage is considerably increased, condensed, sharply painful.

The appearance of symptomatic dropsy is confirmed by diaphanoscopy and ultrasound. In blood tests, leukocytosis is determined by shifting the formula to the left, increasing the ESR.

The three-glass urine sample and its bacterioscopic and bacteriological examination allow for a more accurate diagnosis.

Differential diagnosis. Nonspecific epididymitis in its clinical picture is sometimes difficult to

distinguish from epididymis of tuberculosis. Crucial is the careful collection of epidemiological history, the detection of mycobacterium tuberculosis in the appendage punctate, the presence of bilateral lesions with the formation of purulent fistulas of the scrotum.

Acute epididymitis should be distinguished from the hydatid or testicle torsion, requiring emergency surgical treatment, and testicular neoplasms. Torsion of the testicle is characterized by the sudden appearance of severe pain in the corresponding half of the scrotum, the absence of a temperature reaction, hyperemia of the skin of the scrotum and a significant increase in the epididymis.

Testicular neoplasms often develop at a young age. Testicle significantly increased in size; there are no signs of the inflammatory process. Ultrasonography of the scrotum organs and the determination of tumor markers in blood serum help to clarify the diagnosis.

Treatment

A patient with acute epididymitis is shown bed rest. To ensure the rest of the inflamed organ, a suspensory is used (tight melting), in the first 2-3 days - local cold.

Assign broad-spectrum antibiotics (doxycycline - 200 mg / day; ciprofloxacin - 500 mg / day; ofloxacin - 400 mg / day; ceftriaxone - 500 mg / day). Locally used compresses with 10-15% solution of dimexide, electrophoresis with potassium iodide, novocaine. Magnetic laser therapy has proven itself well.

After the inflammation subsides, heat is assigned to the scrotum, diathermy, and UHF [74].

In case of an abscess of the epididymis, operative treatment is indicated - opening and drainage of the abscess, and with massive organ damage, epididimectomy is performed.

Urinary tract infections

Urinary tract infections (UTI) are among the most prevailing infectious diseases with a substantial financial burden on society.

The symptoms focus on the anatomical level of infection, defined as:

1. Urethra: urethritis;

2. Urinary bladder: cystitis;

3. Kidney: pyelonephritis;

4. Prostate gland: prostatitis;

5. Testicle (epidydimis): orchitis (epidydimidis);

6. Bloodstream: sepsis.

Symptoms and signs of UTI in the adult are as follows:

1. Dysuria;

2. Urinary urgency and frequency;

3. A sensation of bladder fullness or lower abdominal discomfort;

4. Suprapubic tenderness;

5. Flank pain and costovertebral angle tenderness (may be present in cystitis but suggest upper UTI);

6. Bloody urine;

7. Fevers, chills, and malaise (may be noted in patients with cystitis, but more frequently associated with upper UTI).

Acute pyelonephritis in adults (uncomplicated, complicated). Pyelonephritis is an inflammation of the kidney tissue, calyces, and renal pelvis. Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (> 38°C), or costovertebral angle tenderness, and it can occur in the absence of symptoms of cystitis.

Diagnostic. Urinalysis and urine culture confirm the diagnosis of acute pyelonephritis. The consensus definition of pyelonephritis established by the Infectious Diseases Society of America (IDSA) is a urine culture showing at least 10,000 colony-forming units (CFU) per mm3 and symptoms compatible with the diagnosis.

Imaging. The purpose of imaging is to identify an underlying structural abnormality, such as occult obstruction from a stone or an abscess. Although renal ultrasonography and magnetic resonance imaging are sometimes used, computed tomography with contrast media is considered the imaging modality of choice for nonpregnant women.

Treatment. Empirical antibacterial therapy should include parenteral administration of broad-spectrum drugs that primarily affect the Gram-negative flora (fluoroquinolones, cephalosporins, aminoglycosides).

Acute episode of cystitis (lower UTI) in adults (uncomplicated, complicated). Cystitis is an infectious-inflammatory disease of the wall of the bladder with a predominant lesion of its mucous membrane.

Diagnostic. The diagnosis of acute uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation, in those

7.2 Diagnostics

Urinalysis. If hematuria is detected, further examination is required (ultrasound and CT of the urinary organs, intravenous urography, cystourethroscopy). Detection of urinary tract infections requires antibacterial treatment.

Blood test. Leukocyte formula, ESR, prostate-specific antigen level, urea, creatinine and other indicators are needed to clarify the etiology of the disease and its complications.

An **urination diary** allows a more objective assessment of the patient's symptoms. When filling, the amount of fluid consumed, the frequency and volume of urination, the presence of imperative urges and incontinence of urine are taken into account.

The cough test (Valsalva maneuver) is a simple provocative test to diagnose stress urinary incontinence. The test is positive if coughing or straining is marked by involuntary loss of urine during pre-filling of the bladder to 150-200 ml.

PSA and the prediction of prostatic volume. Pooled analysis of placebo-controlled BPH trials showed that PSA has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76 - 0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively.

The American Association of Urology recommended the International Prostate Symptom Score (IPSS). This is a self-assessment questionnaire, which includes seven questions regarding LUTS. Answers to the first 7 vary in points from 0 to 5, depending on the severity of the symptom (maximum - 35 points). With a score of 0–7, the symptoms are mild, 8–19 points - moderate, 20–35 points - severe. The 8th question finds out the effects of the disease on the patient's quality of life and is estimated from 0 to 6 points. An incontinence symptom assessment scale (LISS) and other questionnaires are also used.

Ultrasound is performed to exclude concomitant diseases of the bladder and to determine residual urine.

Cystourethrography is an X-ray examination method for diagnosing urethral stricture and bladder neck sclerosis.

Uroflowmetry is a method of registering violations of the act of urination. It determines the maximum volumetric flow rate of urine, the time to reach the maximum value of the flow rate of urine, the volume and time of urination.

Urodynamic study is an objective examination method, which makes it possible to assess in detail the functional state of the bladder and urethra. Includes cystometry, uroflowmetry, profilometry of the urethra. [32, 33, 34]

7.3 Conservative treatment

The choice of treatment is determined by the etiology and severity of the clinical manifestations of the disease. Patients with mild or moderately severe symptoms in the absence of indications for surgical treatment in the first stage are prescribed conservative therapy: lifestyle changes (exercise, weight loss, nutrition correction, smoking cessation); urination on schedule; physical therapy (Kegel exercises to strengthen the muscles of the pelvic floor).

Electrostimulation of the pelvic floor muscles. Electrostimulation options: perineal, vaginal, anal and sacral. The mechanism of action of the method is indirect stimulation of the pelvic floor muscles through the branches of the genital nerve.

Extracorporeal magnetic stimulation of the pelvic floor (ExMI method). The method has advantages over electrostimulation. In the course of treatment, magnetic stimulation of the neuromuscular apparatus of the pelvic floor and organs of the small pelvis is carried out. This leads to a reduction in the urethral sphincter, a decrease in the instability of the detrusor, an increase in the pressure of the urethra closure and inhibition of the activity of the bladder, an increase in its capacity. Magnetic radiation has anti-inflammatory, anti-edematous, analgesic effect.

The technique is intended to treat patients not only with urinary incontinence, but also with urgent urination, pelvic pain, chronic prostatitis.

Drug therapy. A-adrenoreceptor antagonists (α1-blockers) are first-line drugs for the treatment of LUTS in men. By binding to α1-adrenoreceptors, α1-blockers prevent endogenous catecholamines (norepinephrine and adrenaline) from binding to them, which interrupt the pathologically increased stimulation of smooth muscle cells and leads to relaxation of the urinary tract and a decrease in the severity of LUTS. The ultraselective drug of this group is silodozin. [31]

5α-reductase inhibitors. Free testosterone in the cell of the prostate with the help of the enzyme 5α-reductase is restored to dihydrotestosterone. The latter, by binding to a specific receptor, stimulates the synthesis of specific RNA, affects cellular activity and promotes BPH. [44]

5α-reductase inhibitors (finasteride, dutasteride) are used in

men with LUTS and an enlarged prostate.

Muscarinic receptor antagonists (anticholinergics, M-cholinolytics). The detrusor contraction occurs when M-cholinergic receptors are stimulated with acetylcholine. M-cholinolytics block muscarinic receptors, inhibiting the binding of acetylcholine to the receptor, thereby preventing the contraction of the muscle fibers of the bladder wall. Anticholinergic drugs - trospia chloride, solifenacin, oxybutynin. These drugs are not recommended for intravesical obstruction due to the likelihood of an increase in residual urine volume.

Combination therapy includes α1-blockers and 5α-reductase inhibitors, α1-blockers and muscarinic receptor antagonists.

Herbal preparations - extracts of the fruit Serenoa repens, Pygeum africanum and others.[31]

Type 5 phosphodiesterase inhibitors with or without α-blockers. Conducted clinical trials on the effectiveness of the use of these drugs in patients with LUTS.

7.4 Surgical treatment

The type of surgical treatment is determined by the etiology of the disease, its stage, and the presence of complications. The main purpose of the surgical treatment of LUTS is the elimination of infravesical obstruction due to an enlarged prostate or sclerosis of the vesicourethral segment. For sclerosis of the bladder neck, transurethral resection of scar tissue is used.

In prostate cancer stage I – II, radical prostatectomy and radiotherapy are used. Treatment options for locally advanced prostate cancer are combinations of radiation and hormone therapy, radical prostatectomy with adjuvant radiation therapy and hormone therapy. With common forms of the disease (with distant metastases), the only effective treatment is hormone therapy with blockade androgen stimulation of the tumor. Types of hormone therapy: LHRH agonists, anti-androgens, bilateral orchidectomy, estrogen therapy.

Methods of surgical treatment of BPH:

- transurethral resection and incision of the prostate gland;
- open adenomectomy;
- transurethral microwave therapy;
- transurethral needle ablation of the prostate gland;
- laser treatment of diseases of the prostate gland (enucleation and resection of the prostate gland with holmium laser, vaporization of the prostate gland using a "green" laser with a wavelength of 532 nm);

- minimally invasive method (installation of a prostatic stent). [38, 39]

Male lower urinary tract symptoms

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and substantial economic burden.

Causes of male lower urinary tract symptoms:

1. Distal ureteral stone;
2. Bladder tumor;
3. Urethral stricture;
4. Prostatitis;
5. Foreign body;
6. Urinary tract infection;
7. Neurogenic bladder dysfunction;
8. Detrusor underactivity;
9. Noctural polyuria;
10. Overactive bladder – detrusor overactivity;
11. Benign prostatic obstruction.

Diagnostic. The International Prostate Symptom Score (IPSS) is an 8-item questionnaire, consisting of seven symptom questions and one QoL question. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points).

Digital-rectal examination and prostate size evaluation. Digital-rectal examination (DRE) is the simplest way to assess prostate volume.

Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL.

Urinalysis. Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infections (UTI), microhaematuria and diabetes mellitus.

PSA and the prediction of prostatic volume. To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively.

Renal function measurement. Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR).

Post-void residual urine. Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation.

Uroflowmetry. Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Qmax and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. Qmax is prone to within-subject variation; it is therefore useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Qmax or flow pattern is abnormal.

Treatment:

1. Watchful waiting;

2. Behavioural and dietary modifications;

3. Transurethral resection of the prostate and transurethral incision of the prostate;

4. Open prostatectomy;

5. Transurethral needle ablation of the prostate (TUNA™);

6. Holmium laser enucleation and holmium laser resection of the prostate (Ho:YAG);

7. 532 nm ('Greenlight') laser vaporisation of prostate, the Kalium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers.

Theme # 8: Benign prostatic hyperplasia: diagnostic, conservative and surgery methods of treatment.

8.1 Epidemiology, aetiology and pathogenesis

One of the main causes of the lower urinary tract symptoms (LUTS) in men over the age of 40 years is benign prostatic hyperplasia (BPH). The histological prevalence of BPH, which has been examined in several autopsy studies around the world, ranges from 20% for men at the age of 40 years and reaches 80-90% for men aged 70-80 years old [22, 76].

By the age of 80 BPH occurs in 81.4% of men. Symptoms of the disease in 43% of patients begin to appear at the age of 60, although, according to autopsies, the pathological and morphological signs of BPH already exist at the age of 30, and by the age of 45, its frequency reaches 30%, and in men older than 60 – 70 %. The steady increase in the incidence of BPH is due primarily to an increase in the life expectancy of the male population.

However, not all people with histological BPH will have the significant symptoms of the lower urinary tract developed, and only about 1/3 of men with BPH will come to the doctor [17].

According to a meta-analysis conducted in 2017, based on 30 large epidemiological studies, it was found that the prevalence of BPH was more than 45% in the USA [17], and the lowest prevalence was found in Shanghai, China, and it was only about 12% [7]. The average total prevalence (according to meta-analysis) was 26.2% (95% CI: 22.8-29.8%), that is it occurs in every forth man. Moreover, the prevalence of BPH for every decade from 1990 to 2017 was 26.6%, 27.8% and 22.8% respectively, which means that it has not changed significantly for almost 30 years [14].

According to the Statistics Agency of the Republic of Kazakhstan, in 2012 the population was 16.7 million inhabitants, about 2.9 million of whom were men aged 40 years and older (17.4% of the total). From 2012 to 2017, the percentage of men in this age group was in the range of 17.2-17.5% [11]. Considering the data on prevalence of BPH among men aged above 40 years old (26.2%), it can be assumed that by the beginning of 2018, with population of 18.3 million people and an increase in life expectancy, this problem will happen in more men's life which is more than 800000 people.

The prostate gland has three main functional zones: central (25%), peripheral (70%) and transitional, or transient (5%). From the modern point of view, the essence of the pathological process consists in the formation of multiple proliferative centers (nodal hyperplasia) mainly from epithelial and to a lesser extent from stromal cells of the transition zone of the prostate, as well as acinar cells of the mucous (paraurethral) glands.

With increasing hyperplastic tissue compresses the prostatic section of the urethra, which lengthens, changes the angle of the bend, and its lumen acquires a slit shape. As a result, develops an infravesical obstruction (or sub-tubular compression of the urethra), which prevents adequate emptying of the bladder. The benign tumor that grows in size pushes to the periphery its own prostate tissue, which gradually atrophies.

Thus, the main causes of urinary disorders in patients with BPH are intravesical obstruction and changes in detrusor function. Intravesical obstruction consists of two components:

- mechanical (or static) – occurs due to compression of the urethra enlarged in the prostate gland, due to hyperplasia of the glandular tissue, proliferation of fibromuscular stroma and inflammatory edema;
- dynamic – characterized by increased tone and spasm of smooth muscle fibers of the prostate, neck of the bladder and posterior urethra.

Detrusor function is disrupted as a result of spasm of vessels and ischemia of the wall of the bladder, disturbance of the bioenergetics of muscle cells and neurotrophic changes occurring both in the course of aging and against the background of the infravesical obstruction. [37]

Understanding of the pathogenesis of infravesical obstruction, diagnostic methods and methods of its treatment is the key to the management of patients with clinical BPH, because if the obstruction is serious, it can lead to damage of the bladder and kidneys (hydronephrosis, the activation of the urological infection, the formation of kidney failure, formation of concrements and diverticula), and the question is not only about improving the quality of life, but about saving the functions of organs or even the life of the patient.

8.2 Classification

In this proposed classification (Tab. 11), which has not yet been validated, four parameters, which are not inter-correlated, are used:

- Prostate weight, P, evaluated by transrectal ultrasound
- Quality of life, Q, evaluated by IPSS, question no. 8
- Symptoms, S, evaluated by IPSS
- Maximum flow rate, F, evaluated for a single micturition over 120 mL.

Tab. 11 - PQSF classification of BPH Adapted from Vallancien et al.

Parameter Stage	1	2	3
P: weight (g)	< 40	40-70	> 70
Q: quality of life	0-2	3, 4	5, 6
S: score	< 8	8-20	> 20
F: flow (ml./s)	> 12	8-12	< 8

8.3 Symptoms and clinical manifestation

The onset of symptoms of BPH is caused by mechanical compression of the urethra by nodes of hyperplasia and an increase in the tone of the smooth muscles of the prostate gland and the bladder.

These changes determine the presence of two main groups of symptoms characteristic of adenoma: obstructive and irritative symptoms.

- Obstructive symptoms are characterized by difficult onset of urination; the urine stream in patients is thin, "sluggish" and intermittent. The patient has to push for urination, notes the feeling of incomplete emptying of the bladder.
- Irritative symptoms manifest in the form of frequent urination, including at night, imperative urge to urinate, inability to keep urine at urge.

If the nature of the first group of symptoms is clear, then the mechanism for the development of irritative symptoms requires some explanation.

It is believed that if there is a long-term infravesical obstruction, the a-adrenoreceptor density in the lower urinary tract muscles (bladder, prostatic urethra) increases, which increases its sensitivity to the effect of catecholamines circulating in the peripheral blood.

And since stimulation of the a-adrenoreceptors of the bladder leads to its reduction, the main clinical manifestation of this condition will be an increase in urination urination.

The age-related change in blood circulation in the wall of the bladder, leading to a change in the metabolism of its smooth muscle cells, also plays a role in increasing the detrusor tone. [35]

Obstructive symptoms are more dangerous in terms of prognosis and more often determine the need for surgical treatment. Irritative symptoms, while significantly reducing quality of life, are less dangerous and respond well to conservative therapy.

It should be noted that the clinical course of BPH depends not only on the symptoms described, but also on a number of complications, such as hematuria, acute urinary

retention and inflammatory complications against the background of impaired urine flow.

8.4 Diagnostics

Diagnosis of BPH includes:

- collecting anamnesis, filling the diary of urination (recording the daily frequency and volume of urination);
- physical examination and digital rectal examination;
- performing a general urine test;
- determination of blood creatinine to assess total renal function;
- determination of PSA level for the exclusion of prostate cancer
- filling out the IPSS questionnaires (International Prostate Symptom Score, international summary assessment of prostate disease symptoms) and QOL (Quality of Life quality of life) for prostate diseases.

More accurate information about the prostate gland gives ultrasound transrectal sensor, which allows to determine the direction of growth, the true boundaries, size and volume of hyperplastic prostate tissue. The prostate gland is considered enlarged if its size exceeds 4 cm and the volume is more than 25 cm3. New devices that work in 3D mode give a three-dimensional layered image of the organ. With the help of transrectal Doppler duplex sonography, the features of blood flow in the prostate are clarified.

Uroflowmetry is the main method for quantifying the volume flow rate of urine. The main parameters used are the maximum flow rate of urine Qmax, ml / s and the isolated Volume of urine Vcomp ml. The results of the study are considered reliable if it was performed at least 2 times under conditions of physiological filling of the bladder to 200-350 ml with the appearance of a natural urge to urinate. A decrease in Qmax to values less than 15 ml / s indicates an infravesical obstruction or deficiency of the detrusor contractile function

8.5 Treatment

There is no ideal drug for the treatment of BPH, therefore, it is necessary to select therapy strictly individually taking into account its effectiveness and safety. Currently, a large number of medicines have been proposed for the treatment of BPH:

- α-adrenoblockers (α-AB): selective (α1) - tamsulosin;

Superselective (α1A) - silodosin;

- inhibitors of 5-α-reductase: synthetic - finasteride, dutasteride;
- plant - extracts of Serenoa repens, Pygeum africanum, etc .;
- tissue preparations - prostate extract (raverone, prostatilen);
- polyene antibiotics - levorin, iprotrophane;
- hormones: analogues of the luteinizing releasing hormone - goserelin (zoladex), buserelin; Antiandrogens - flutamide, bicalutamide (casodex), cyproterone (androkur); Gestagens - depostat; Androgens, estrogens, anti-estrogens, aromatase inhibitors, prolactin antagonists;
- phytopreparations - extracts of palm sabal, urtiron, pumpkin seed oil, etc .;
- homeopathic remedies.

Minimally invasive methods of treatment: the installation of permanent, temporary (removable) or resorbable stents (endoprostheses) in the prostatic section of the urethra under endovideoorientologic control, thermal methods - are used with absolute contraindications to surgical interventions. [34, 35]

Urethral stents prevent squeezing of the urethral lumen by hyperplastic prostate tissue, but have a high risk of complications associated with salt incrustation, infection and pain syndrome.

Numerous thermal methods are based on physical effects on hyperplastic tissue of high and low temperatures from thermal, radiofrequency (electromagnetic), laser and ultrasound sources located in the urethra or rectum at the prostate level. Depending on the type and focus of radiation, as the temperature rises from 42-45 to 120°C, morphological changes occur in the tissue of the hyperplastic prostate, characterized by impaired microcirculation, destruction of α-adrenergic receptors, suppression of cell proliferation, dystrophy and the formation of necrosis foci with their subsequent sclerosis.

Nonendoscopic methods of electromagnetic influence include transrectal (40-42°C) and transurethral hyperthermia (40-45°C), transurethral thermotherapy (45-70°C), thermal destruction or thermoablation (70-82°C). Transurethral radiofrequency thermotherapy (TUMT) and thermal destruction (TUNA) lead to the formation of foci of coagulation necrosis in the depth of the prostate. Unlike the above methods, high-intensity focused ultrasound (HIFU) with the help of a special transrectal probe and computer guidance program allows to create a local temperature increase up to 80-120°C. As a result, destruction occurs only at specified points of the prostate, without affecting the surrounding organs and tissues.

Surgery. Indications for surgical treatment of BPH are:

- lack of the effect of prolonged drug therapy with the increase of obstructive and irritative symptoms, which adversely affect the daily activity of the patient;
- an increase in the amount of residual urine (more than 100 ml);
- repeated acute urinary retention;
- recurrent urinary tract infection;
- stones of the bladder;
- repeated macrohematuria, refractory to therapy with 5-a-reductase inhibitors;
- hydroureteronephrosis and chronic renal failure.

Operative intervention should not be performed in the early stages of BPH, when irrational symptoms predominate, as it does not bring relief to the patient.

Radical method - adenomectomy (prostatectomy), which can be performed as endoscopically (transurethral) - transurethral adenomectomy with electroenucleation of the hyperplastic prostate with a single block or removal of the entire adenomatous tissue by transurethral sections, and by the open method (transhepatic or retropubic access).

The prognosis is favorable for properly selected and timely treatment. In rare cases, after an adenomectomy, a relapse of the disease may occur, which is caused by incomplete removal of hyperplastic tissue. In the absence of treatment, the prognosis is unfavorable and is associated with the progression of the disease, the development of hydroureteronephrosis, chronic pyelonephritis, and terminal chronic renal failure.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is one of the most common diseases in men over 45 years of age worldwide.

Micturition disorders, dysuria or lower urinary tract symptoms (LUTS) occur in more than 50% of patients with BPH, but not all patients with LUTS have BPH.

LUTS with BPH are divided into two groups - obstructive and irritive.

Diagnosis of BPH includes:

1. Collecting anamnesis, filling the diary of urination (recording the daily frequency and volume of urination);

2. Physical examination and digital rectal examination;

3. Performing a general urine test;

4. Determination of blood creatinine to assess total renal function;

5. Determination of PSA level for the exclusion of prostate cancer

6. Filling out the IPSS questionnaires (International Prostate Symptom Score, international summary assessment of prostate disease symptoms) and QOL (Quality of Life quality of life) for prostate diseases.

Currently, a large number of medicines have been proposed for the treatment of BPH:

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2. Inhibitors of 5-α-reductase: synthetic - finasteride, dutasteride;

3. Plant - extracts of Serenoa repens, Pygeum africanum, etc .;

4. Tissue preparations - prostate extract (raverone, prostatilen).

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The prognosis is favorable for properly selected and timely treatment. In rare cases, after an adenomectomy, a relapse of the disease may occur, which is caused by incomplete removal of hyperplastic tissue. In the absence of treatment, the prognosis is unfavorable and is associated with the progression of the disease, the development of hydroureteronephrosis, chronic pyelonephritis, and terminal chronic renal failure.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is one of the most common diseases in men over 45 years of age worldwide.

Micturition disorders, dysuria or lower urinary tract symptoms (LUTS) occur in more than 50% of patients with BPH, but not all patients with LUTS have BPH.

LUTS with BPH are divided into two groups - obstructive and irritive.

Diagnosis of BPH includes:

1. Collecting anamnesis, filling the diary of urination (recording the daily frequency and volume of urination);

2. Physical examination and digital rectal examination;

3. Performing a general urine test;

4. Determination of blood creatinine to assess total renal function;

5. Determination of PSA level for the exclusion of prostate cancer

6. Filling out the IPSS questionnaires (International Prostate Symptom Score, international summary assessment of prostate disease symptoms) and QOL (Quality of Life quality of life) for prostate diseases.

Currently, a large number of medicines have been proposed for the treatment of BPH:

1. α-adrenoblockers (α-AB): selective (α1) -prasozin, alfuzosin, doxazosin, terazosin, tamsulosin etc .; Superselective (α1A) - silodosin;

2. Inhibitors of 5-α-reductase: synthetic - finasteride, dutasteride;

3. Plant - extracts of Serenoa repens, Pygeum africanum, etc .;

4. Tissue preparations - prostate extract (raverone, prostatilen).

Radical method - adenomectomy (prostatectomy), which can be performed as endoscopically (transurethral) - transurethral adenomectomy with electroenucleation of the hyperplastic prostate with a single block or removal of the entire adenomatous tissue by transurethral sections, and by the open method (transhepatic or retropubic access).

Theme # 9: Oncology diseases of urinary tract: main symptoms, diagnostic and methods of treatment.

In this chapter we describe the most common tumor diseases of the urogenital system (renal cell carcinoma, bladder cancer, prostate cancer and primary urethral carcinoma).

9.1 Renal cell carcinoma

Epidemiology and aetiology

Kidney tumors make up about 3% of the total number of neoplasms of different localizations. There are carcinomas of the renal parenchyma (renal cell carcinoma), which emanate directly from the kidney tissue, and tumors from the urethropy of the pyelocaliceal system and the ureter (transitional cell carcinoma). Wilms tumor is usually found in children.

The etiology and pathogenesis of kidney parenchyma cancer, as well as other tumors, are not definitively established. The disease may be hereditary. In genetic studies in patients with renal parenchyma cancer, a 3p deletion, trisomy of chromosomes 7, 16, 17, monosomy of chromosomes 1, 2, 6 and 10 were identified. Individual families characterized by multiple cases of kidney cancer were identified. In such pedigrees, the transfer from generation to generation of a dominant mutation with a high penetration potential is assumed. In these families, the development of the disease is observed at a young age, bilateral tumor of the kidneys, as well as multicentric growth of tumors. These include familial clear cell renal cell carcinoma, familial papillary kidney cancer, von Hippel-Lindau syndrome.

This syndrome has an autosomal dominant mode of inheritance with a frequency of occurrence in a population of 1 in 40,000 people. It is characterized by the development of renal cell carcinoma, kidney cysts, pheochromocyte, cysts and pancreatic cancer, brain and spinal cord hemangioblastoma, retinal angioma.

More frequent development of kidney cancer was noted in patients with chronic renal failure undergoing constant dialysis. Renal cell carcinoma occurs in recipients of a renal transplant many times more often than in a population, which is associated with uremic immunodeficiency and prolonged drug immunosuppression.

Risk factors for disease include contact with carcinogens (nitroso compounds, asbestos, cyclic hydrocarbons, cadmium, industrial dyes), abuse of analgesics, smoking, obesity, cystic disease, and kidney injury. [40,42]

TNM classification described in 12. Tab.

12 - TNM classification of renal cell carcinoma

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour < 7 cm in greatest dimension, limited to the kidney		
T1a	Tumour < 4 cm in greatest dimension, limited to the kidney		
T1b	Tumour > 4 cm but < 7 cm in greatest dimension		
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
T2a	Tumour > 7 cm but < 10 cm in greatest dimension		
T2b	Tumours > 10 cm limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota's fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota's fascia		
T3b	Tumour grossly extends into the vena cava (VC) below the diaphragm		
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC		
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
N – Regional lymphatic nodes			
NX	Regional lymphatic nodes cannot be assessed		
N0	No regional lymphatic node metastasis		
N1	Regional lymphatic node metastasis		
M - Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Symptoms

There are local and common symptoms of kidney parenchyma cancer. **Local causes** include hematuria, pain in the lumbar region and palpable formation. This triad of symptoms in connection with the improvement of diagnosis is now less common and indicates, as a rule, the late stages of the tumor.

Theme # 9: Oncology diseases of urinary tract: main symptoms, diagnostic and methods of treatment.

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	Any T	Any N	M1

Symptoms

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Among the local, the most frequent and first symptom is hematuria, which is observed in 50-70% of patients. The reasons for its occurrence are germination of a Forniks tumor, a cup pelvis system, destruction and rupture of tumor vessels. Hematuria is micro and macroscopic. A total painless macroscopic hematuria with a discharge of shapeless, and more often worm-like blood clots, which are casts of the ureter, is characteristic of a kidney tumor. In some cases, after its termination, an attack of renal colic may occur. It is caused by obturation of the lumen of the ureter by a blood clot and indicates the source of hematuria and the side of the lesion. Unlike nephrolithiasis, in which hematuria appears after pain (renal colic), with a kidney tumor, total hematuria first occurs, and then pain syndrome. That is why hematuria in a kidney tumor is called "pre-pain", unlike "post-pain" in urolithiasis. [42]

Constant aching pain on the side of the lesion develops as a result of: germination and/or stretching of the fibrous capsule by the tumor, squeezing of the vascular pedicle and renal pelvis by the growing neoplasm, invasion of perirenal fiber, muscles and adjacent organs. The intensity of the pain varies from a slight feeling of mild discomfort to a very significant one. In some cases, their enhancement is associated with the development of a heart attack of a destructively altered kidney. Palpation of the abdomen and lumbar region can reveal a dense, nodular, painless formation in the case of localization of a tumor of the kidney in the lower pole or its large size. Its mobility depends on the presence or absence of germination of the tumor in neighboring organs.

Renal cell carcinoma in men may be accompanied by the development of varico-celi - varicose veins of the spermatic cord. It is caused by compression of the inferior vena cava, renal and gonadal veins, enlarged lymph nodes or tumor thrombosis of these veins, which leads to disruption of blood flow through the testicular vein.

Common or extrarenal kidney tumor symptoms include fever, hypertension, toxic anemia, erythrocytosis (due to increased production of erythropoietin by tumor tissue), hypercalcemia, abnormal liver function, loss of appetite, weight loss, weakness. Often they are the first or only symptoms of the disease. The most frequent of them is an increase in body temperature. Fever with renal cell carcinoma is usually subfebrile, constant, and lasting for a long period of time. Increased body temperature is associated with the release of endogenous pyrogens by the tumor. Occasionally fever accompanied by chills or reaches 38-39 ° C.

Hypertension occurs in 15–20% of patients with a kidney tumor. It is explained by thrombosis and compression of the renal veins by the tumor or enlarged regional lymph nodes, the effect of the tumor on the renin-angiotensin system, its compression of the intrarenal vessels with impaired intrarenal blood flow and the production of pressure agents.

This type of hypertension is characterized by poor clinical manifestations, lack of crises, resistance to antihypertensive therapy.

Clinical manifestations of metastatic lesions correspond to their localization. Metastases in the lungs can be asymptomatic for a long time and can be detected by prophylactic X-ray examination. With the development of their patients complain of chest pain, cough, and hemoptysis. Bone metastases are characterized by severe pain in the area of the affected bone tissue. Sometimes their first manifestation, as well as a symptom of a kidney tumor, can be a pathological fracture.

Diagnostics

Diagnosis of kidney tumors includes the collection of complaints and anamnesis, an objective examination, laboratory and special methods of research. It is necessary not only to establish the presence of a tumor, but also to determine the stage of the disease. Before planned surgery, an assessment is made of the functional state of the contralateral kidney.

Laboratory studies help to suspect the presence of a tumor process in a patient, including kidney cancer. Laboratory signs that can cause oncological alertness include: increased ESR, anemia, polycythemia, hypercalcemia, Stauffer syndrome, hyperuricemia.

Elevated ESR is a non-specific symptom of many cancers. Anemia is caused by the toxic effects of the tumor on the red bone marrow. In 1-2% with kidney tumors, polycythemia is observed, which is associated with both the pathological synthesis of erythropoietin by the tumor and its production by normal kidney tissue in response to ischemia. Hypercalcemia is the result of osteolytic bone metastases or paraneoplastic reactions in kidney tumors. It is expressed in nausea, loss of appetite, drowsiness, convulsions, decrease in deep tendon reflexes.

Stauffer syndrome is a non-metastatic dysfunction of the liver. It is manifested by an increase in the level of indirect bilirubin, alpha-2-globulins, gamma-globulins, blood alkaline phosphatase and prolongation of the prothrombin time.

The urine color is red with gross hematuria, erythrocytes cover the entire field of view, and false proteinuria is observed.

Total kidney function is determined according to serum levels of creatinine, urea, sodium, potassium, and blood clotting parameters. With a one-way process, it does not suffer.

The main screening and one of the main methods for diagnosing cancer of the parenchyma of the kidney is **ultrasound**. When a volume neoplasm is detected, its size, localization, depth, prevalence, boundaries, connection with surrounding organs and tissues, germination in large vessels are assessed. Characteristic ultrasound signs of kidney cancer are an increase in the size of the organ, the unevenness of its contour, a change in the borders of the kidney due to the formation of

tissue acoustic density, the difference in the echostructure of the revealed formation from the normal parenchyma of the organ. The presence of hypoechoic sites in this neoplasm indicates the processes of tumor necrosis, the heterogeneity of the structure of the neoplasm is due to the presence of calcification and cystic areas. Sometimes the tumor deforms the sinus and renal pelvic system. Sonography makes it possible to visualize well the inferior vena cava and the right heart sections, which makes it possible to determine the border of the tumor thrombus propagating upwards.

Excretory urography allows to establish the characteristic signs of a tumor lesion and evaluate the function of the contralateral kidney. It is not very informative in the initial stages of the disease and the small size of the tumor. With tumors of more than 3-4 cm on the excretory urogram, you can see a defect in the filling of the pelvis and / or cups, up to their amputation, a segmental expansion of the cup-pelvis plaster complex. deformation or shortening of the cups with pushing them aside, medial deviation of the ureter.

CT is the method of choice in the diagnosis and staging of renal cell carcinoma. It allows not only to reveal the fact of the presence of a neoplasm, but also to estimate its size, localization, attitude to the cup and pelvis system, surrounding organs and tissues, as well as the presence of regional and distant metastases. On CT scan, kidney cancer is visualized as a volume with a homogeneous or heterogeneous internal structure, with a density lower or higher than the normal renal parenchyma. It can spread to the perirenal fiber and the renal sinus, deform and involve the calyx-pelvis system in the tumor process. [40]

MRI allows you to establish the diagnosis and is the method of choice when identifying the size and boundaries of a tumor thrombus in the renal and inferior vena cava. This method is indispensable for patients with allergies to iodine-containing radiopaque drugs and for patients with a kidney tumor and chronic renal failure.

Radionuclide studies are used to identify focal lesions of the kidney caused by a tumor, assess the separate functional status of the kidneys, and detect metastatic bone lesions.

When examining a patient with a kidney tumor, it is necessary to conduct research aimed at identifying possible metastasis. Metastatic lesion of the lymph nodes, brain, spine, lungs, liver is diagnosed using **radiation techniques and MRI**. Bone metastases can reveal radiography and osteoscintigraphy.

Cystoscopy, performed with gross hematuria, allows you to detect the release of blood from the mouth of the ureter and thereby determine the direction of the lesion, as well as to exclude its source in the bladder.

Treatment

Treatment of kidney cancer is surgical. Conservative therapy is an auxiliary method, ineffective and is

used mainly in metastatic or recurrent kidney cancer. It includes immunotherapy (interferon-alpha, interleukin-2), chemotherapy (vinblastine, fluorouracil) and hormone therapy. Certain perspectives are associated with the achievements of the molecular genetics of renal cell carcinoma, which have allowed the development of targeted drugs.

These drugs are divided into three groups:

- tyrosine kinase (multi kinase) inhibitors - sorafenib and sunitinib;
- mTOR inhibitors - temsirolimus and everolimus;
- monoclonal antibodies - bevacizumab.

At present, they are being studied further, which allows us to hope for the early appearance of new drugs for the treatment of patients with kidney cancer.

The low effectiveness of chemotherapy in renal cell carcinoma is due to the phenomenon of multidrug resistance associated with the p170 gene. This protein, changing the intracellular structure of carcinoma, reduces the flow of anticancer drugs into the cell and enhances their elimination from it. The most commonly prescribed cytotoxic drugs include vinblastine (effective in 6–9% of patients) and 5-fluorouracil (effective in 5–8% of patients).

Radiation therapy due to the radioresistance of kidney cancer is also not widespread. It is used for palliative purposes to reduce pain in patients with bone metastases.

As a palliative treatment method, a number of patients with renal cancer perform embolization of the renal artery. It is used in cases of threatening bleeding in patients with inoperable large kidney tumors and metastases to regional lymph nodes.

Surgical treatment includes:

- radical nephrectomy;
- kidney resection;
- minimally invasive percutaneous methods of tumor destruction (radio ablation, cryoablation, microwave and laser ablation, ablation of HIFU).

Surgical removal of the tumor is the only radical treatment for kidney cancer. It consists in performing radical nephrectomy or resection of the kidney with a tumor within healthy tissue. In this regard, the indications for surgical treatment of kidney cancer are maximally expanded. Absolute contraindications are only the late stages of the disease with multiple metastases and cachexia or severe comorbidities that do not allow for extended surgery under anesthesia. [40,42]

Targeted therapies

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis. This

process substantially contributes to the development and progression of RCC. There are several targeting drugs approved for treating mRCC in both the USA and Europe:

- sorafenib (Nexavar®);
- sunitinib (Sutent®);
- bevacizumab (Avastin®) combined with IFN-α;
- pazopanib (Votrient®);
- temsirolimus (Torisel®);
- everolimus (Afinitor®);
- axitinib (Inlyta®).

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes. In major trials leading to registration of the approved targeted agents, patients were stratified according to the MSKCC risk model. Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to yield an accurate prognosis for patients treated in the era of targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while LDH has been removed. The IMDC published data on conditional survival which may be used in patient counselling. The IMDC risk model has been validated and compared with the Cleveland Clinic Foundation (CCF) model, the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The IMDC model did not differ from the other models, indicating that a ceiling has been reached in predicting prognosis based solely on clinical factors.

9.2 Bladder cancer (non-muscle-invasive bladder cancer (Ta, T1 and CIS))

Epidemiology and aetiology

Bladder cancer (BC) is 3-4% of all malignant tumors. Among all oncological diseases, it ranks fourth in men (after prostate, lung and colon cancer) and ninth in women, being on the 11th line in world oncological statistics. BC men are found 5-6 times more often than women. With age, its frequency increases, and 75% of cases occur in people over 65 years of age.

The incidence depends not only on age and gender, but also on geographic location and race. In North America, Western Europe, Russia, it is 5-10 times higher than in Central and South America, Central Africa and Asia. In black men and American Indians living in the United States, BC is found, respectively, 2 and 8 times less frequently than whites. There are pathological features of this disease. Surface tumors are diagnosed in 70%, and invasive tumors - only in 30% of patients with primary diagnosed BC.

The causes of BC are not fully understood. The proven risk factors for its formation include contact with chemicals (aromatic amines and their derivatives, cyclophos family), tobacco smoking, radiation, schistosomiasis, prolonged use of chlorinated water, chronic cystitis, which increase the incidence of BC several times. In 20%

of patients (15-30% of men, 1-6% of women), the development of the disease is due to professional factors. The most dangerous professions in relation to the development of malignant tumors of the urothelia are associated with work on vehicles, the production of paints and rubber, the use of resins and plastics.

Urinary stagnation and long-term contact of urothelia with carcinogenic substances with infarctional obstruction and features of the histological structure of the mucous membrane of the bladder in the elderly are important pathogenetic. It has now been established that in some cases, malignant proliferation of urothelia is caused by cell DNA damage as a result of mutation of the p21 ras and p53 oncogenes, activation of the c-myc and c-jun oncogenes, and suppression of tumor suppressor genes. The sun is a disease of the entire mucosa (urothelia) of the bladder, and its relapses can appear in various places at any time after a conserving operation. The risk of BC increases with an increase in the diet of protein and salt, but decreases with the inclusion of vegetable oil, margarine, beta-carotene, potassium, and vitamin C.

A feature of BC is that it remains a local process for a long time. Most often it metastasizes to regional lymph nodes (obturator and external iliac). Less hematogenous distant metastases in the liver, lungs and bones are detected.

Classification

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system (Tab. 13). Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder and/or intravesical instillations. However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions. [40]

Tab. 13 - TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue

T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Symptomatic. In the early stages of BC, most patients are asymptomatic. As a rule, the first and most characteristic manifestation of the disease is micro-, and more often, gross hematuria, which can be terminal, total, single, permanent, and episodic. The degree of bleeding does not depend on the size and stage of the tumor. Massive and prolonged gross hematuria can lead to tamponade of the bladder with blood clots and cause anemization of the patient.

An important symptom of BC is dysuria, which most often manifests itself in the form of pollakiuria, stranguria, imperative urges and acute urinary retention. It occurs due to a decrease in the capacity of the bladder due to a tumor, irritation of the receptor apparatus as a result of wall sprouting, the addition of infection and obstruction of the lumen of the urethra by flotation of a tumor or blood clots.

The pains in patients with BC are mainly localized in the supralonal and sacral areas, are diverse and depend on the stage. As the tumor invades the muscle wall and beyond, the pain becomes more pronounced, permanent and radiates to the affected adjacent pelvic organs (rectum, vagina, prostate). Pain in the lumbar region occurs in violation of the outflow of urine from the kidneys as a result of obstruction of the mouths and pre-bladder sections of the ureters by a growing tumor with the development of hydroureteronephrosis.

The addition of chronic pyelonephritis leads to chronic renal failure. With bone metastases, pain appears at the sites of tumor foci.

The progression of the disease is accompanied by general weakness, fatigue, decreased appetite, weight loss, which is associated with the spread of the tumor process and symptoms of chronic renal failure.

Diagnostics

Diagnosis is based on characteristic complaints, anamnesis and objective data. On examination, the general condition of the patient is assessed; attention is paid to the skin color, which acquires a pale tinge with post-hemorrhagic anemia or the presence of metastases in the bone marrow (toxic anemia). A tamponade of the bladder or a large tumor leads to a retention of urine, and an overblown bladder swelling out above the bosom is easily determined visually and by palpation. The appearance of edema of the lower limbs indicates a metastatic lesion of the pelvic lymph nodes. Important information is given by bimanual palpation, which is performed under general anesthesia with an empty bladder after cystoscopy and tumor biopsy. The study determines the mobility of the tumor between the index finger of the left hand, inserted into the rectum in men or into the vagina in women, and the right palm, located on the front wall of the abdomen above the womb. A fixed tumor indicates its germination in the pelvic organs (T4).

In the blood tests are determined: anemia, increased ESR, azotemia. In the urine there is a large number of red blood cells, and in the presence of infection - leukocytes, false proteinuria is noted. Cystological examination of urine sediment has sensitivity up to 50% and high specificity (up to 95-100%). The informativeness of the method is reduced with highly differentiated tumors, accompanied by inflammation, hematuria and bacteriuria. It is recommended to use it for screening, in diagnosing primary cancer and monitoring the results of treatment.

Ultrasound due to its wide availability, simplicity, low invasiveness, safety and high accuracy has become one of the main methods for early detection of BC, determining the stage of the disease and postoperative monitoring of possible tumor recurrence. For this purpose, transabdominal, transrectal, transvaginal and in rare cases transurethral sensors are used. Exophytic tumors of the bladder in the sonograms are the formation of various sizes with uneven contours and heterogeneous structure, protruding into the lumen of the bladder. Superficial (non-muscle-invasive) tumors appear small in size, not extending to the muscular layer of the bladder wall. Muscle-invasive formations, as a rule, are large in volume with a wide base penetrating the bladder wall. When localized in the area of the mouth, they can squeeze it or germinate, causing obstruction of the ureter with the development of hydroureteronephrosis. Transrectal sonodoplerography allows revealing the degree of tumor angiogenesis.

Excretory urography allows you to identify the level of violation of urine outflow from the kidneys, to judge their separate functional state and

to detect a tumor in the upper urinary tract by defect filling. The presence of hydroureteronephrosis indicates squeezing or invasion of the mouth and pre-vesicular ureter by a tumor. On the descending cystogram appear filling defects with uneven, corroded contours and asymmetry of the bladder contour. CT and MRI are the most informative and are now widely used in the diagnosis of BC, the staging of the disease and the detection of affected regional lymph nodes. These studies allow us to distinguish the anatomical layers of the bladder wall and with high accuracy to determine the degree of invasion of the tumor in them.

Urethrocystoscopy under general anesthesia with biopsy of the modified urothelium sites is the main method for diagnosing and determining the stage of BC.

Cystoscopy in normal light and radiation examination methods do not allow to detect papillary formations less than 0.3 cm in diameter and flat tumors (cancer in situ). For this purpose, **fluorescent cystoscopy** (photodynamic diagnostics) is used, with which it is possible to detect superficial cancer (CIS, Ta, T1) in 97% of patients. It is carried out by illuminating the cavity of the bladder with blue-violet light after preliminary intravesical administration of 5-aminolevulemic acid, which selectively accumulates in tumor cells. As a result, fluorescence of tumor tissues that are invisible with conventional cystoscopy occurs. The method is widely used not only for the early diagnosis of primary and recurrent tumors, but also for more accurate determination of their boundaries during TURP.

Treatment failure of non-muscle invasive bladder cancer

BC treatment is combined and aimed at radical removal of the tumor, prevention of recurrence, metastasis and progression of the disease. The main method is surgical treatment.

Surgical tactics are fundamentally different in patients with superficial and muscle-invasive BC.

Transurethral electroresection of the bladder wall with a tumor within healthy tissue followed by intravesical immuno or chemotherapy is the main treatment method for patients with superficial (non-invasive) BC. The operation consists in sequential cutting of the tumor sites with a loop of the resectoscope up to its base. Bleeding vessels coagulate. The base is resected together with the muscle layer of the bladder around the circumference, some distance from the tumor 1.5-2 cm, and in a separate container is sent for histological examination. In order not to miss tumors less than 0.2-0.3 cm in diameter and cancer in situ, TURP is performed under fluorescent control.

BCG therapy is the most effective method of preventing recurrence of superficial BC, but it is accompanied by a number of complications. Most patients develop cystitis, the frequency of which increases with an increase in the number of instillations and the dose of the drug administered. Among the common complications, fever is most often observed, usually not exceeding

38.5°C. The reduction of the hyperthermic reaction is achieved by the use of traditional antipyretics, primarily paracetamol. The reason for the termination of instillations - temporarily or permanently - can be a fever that persists for more than two days, multiorgan pain, a distinct malaise, joint pain and skin rashes. [42]

Treatment of muscle-invasive BC is more difficult. It consists of the combined or separate use of surgical, chemo- and/or radiation treatment. Organ-sparing surgical treatment (TURP of the bladder wall with a tumor and its open resection), although it allows to preserve the bladder, is not radical and is used in combination with adjuvant chemo- and radiation therapy in elderly patients with severe somatic status and due to continued bleeding. Tumor recurrences after open bladder resection for muscle-invasive cancer occur in 50-80% of patients.

Cystectomy with various methods of urinary derivation is the main and only radical method of treating patients with invasive BC. Radical cystectomy includes the removal of the bladder with the area of the adjacent peritoneum and paravesical fiber, regional lymph nodes, prostate gland and seminal vesicles (in men), ovaries, fallopian tubes, uterus and the anterior wall of the vagina (in women).

9.3 Primary urethral carcinoma

Epidemiology and actiology

Primary urethral carcinoma (UC) is considered a rare cancer, accounting for < 1% of all malignancies.

For male primary UC, various predisposing factors have been reported, including urethral strictures, chronic irritation after intermittent catheterisation/urethroplasty, external beam irradiation therapy, radioactive seed implantation, and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16). In female urethral carcinoma, urethral diverticula and recurrent urinary tract infections have been associated with primary urethral carcinoma. Clear cell adenocarcinoma may also have a congenital origin.

TNM classification of urethral carcinoma is shown in Tab. 14.

Tab. 14 - TNM classification of urethral carcinoma

T - Primary Tumour (men and women)	
TX	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma

T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumour invades other adjacent organs
Primary tumour in prostatic urethra	
TX	Primary tumour cannot be assessed
Tis pu	Carcinoma in situ in the prostatic urethra
Tis pd	Carcinoma in situ in the prostatic ducts
T0	No evidence of primary tumour
T1	Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumour invades other adjacent organs
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastasis
N1	Metastasis in a single lymph node $\leq$ 2 cm in greatest dimension
N2	Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Dignostics

Clinical examination. In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size and mobility.

Urinary cytology. The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59%. Detection rates

depend on the underlying histological entity. In male patients, the sensitivity for UC and SCC was reported to be 80% and 50%, respectively, whereas in female patients sensitivity was found to be 77% for SCC and 50% for UC.

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist. Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate.

Radiological imaging of UC aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (> cT1N0M0). If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase.

Regional lymph nodes. Enlarged lymph nodes in UC often represent metastatic disease. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes. Nodal control in UC can be achieved either by regional lymph node dissection, radiotherapy or chemotherapy. Currently, there is still no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with UC. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease.

Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior UC has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours. Therefore, optimising treatment of distal UC has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penispreserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have also been reported in a recent series.

Treatment of localised urethral carcinoma in females

Urethrectomy and urethra-sparing surgery. In women with localised UC, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure via an appendicovesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women. Recent series have reported outcomes in women with mainly anterior UC undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery. Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal UC, have also resulted in a considerable local failure rate of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal UC to prevent local and systemic progression. [40, 42]

Radiotherapy. In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year CSS was 49%. Most local failures (95%) occurred within the first two years after primary treatment. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam radiotherapy [EBRT] vs.

interstitial brachytherapy) was not. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe.

Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%). Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75%. Some earlier series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement.

9.4 Prostate cancer

Epidemiology. Prostate cancer (PCa) is the most common cancer in elderly males (> 70 years of age) in Europe. It is a major health concern, especially in developed countries with their greater proportion of elderly men in the general population.

With the expected increase in the life expectancy of men and in the incidence of prostate cancer, the disease's economic burden in Europe is also expected to increase substantially. It is estimated that the total economic costs of PCa in Europe exceed € 8.43 billion, with a high proportion of the costs of PCa care occurring in the first year after diagnosis. In European countries with available data (UK, Germany, France, Italy, Spain, the Netherlands), this amounted to € 106.7-179.0 million for all PCa patients diagnosed in 2006.

Risk factors and chemoprevention. The factors that determine the risk of developing clinical PCa are not well known, although a few have been identified. There are three well-established risk factors for PCa:

- increasing age;
- ethnic origin;
- heredity.

If one first-line relative has PCa, the risk is at least doubled. If two or more first-line relatives are affected, the risk increases by 5-11-fold. A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected

relatives, or at least two relatives who have developed early-onset disease, i.e. before age 55. Patients with hereditary PCa usually have an onset six to seven years earlier than spontaneous cases, but do not differ in other ways. The frequency of incidentally- and autopsy-detected cancers is roughly the same in different parts of the world.

This finding is in sharp contrast to the incidence of clinical PCa, which differs widely between different geographical areas, being high in the USA and northern Europe and low in South-East Asia. However, if Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men. These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as the foods consumed, the pattern of sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure have all been discussed as being aetiologically important. PCa may be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to the following specific features:

- high prevalence;
- long latency;
- endocrine dependency;
- availability of serum markers (PSA);
- the histological precursor lesion prostatic intraepithelial neoplasia.

Nevertheless, there is currently no evidence to suggest that dietary interventions would reduce the risk of PCa. The outcome of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was negative, and therefore vitamin E and selenium are not recommended for the prevention of PCa.

Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography. Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low HDL cholesterol) only hypertension and waist circumference >102 cm were associated with a significantly greater risk of PCa, increasing it by 15% ($p = 0.035$) and 56% ($p = 0.007$), respectively.

Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa. Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing the risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in preventing or delaying the development of PCa (~25%, only of Gleason 6 cancer), this must be weighed against treatment-related sideeffects as well as the potential increased risk of high-grade PCa. None of the available 5-ARIs have been approved for this indication. In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on the risk of

progression. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk. [66]

TNM classification of prostate cancer is shown in Tab. 15.

Tab. 15 - TNM classification of prostate cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)
T2	Tumour confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Diagnostics

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and/or prostate-specific antigen (PSA) levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement (BPE).

Digital rectal examination. Most prostate cancers are located in the peripheral zone and may be detected by DRE when the volume is >0.2 mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level. Suspect DRE in patients with PSA level <2 ng/mL has a positive predictive value of 5-30%. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy.

Prostate-specific antigen. The use of PSA as a serum marker has revolutionised PCa diagnosis. PSA is organ- but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than DRE or transrectal ultrasound (TRUS).

There are no agreed standards defined for measuring PSA. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA.

PSA density. PSA density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely that PCa is clinically significant.

PSA velocity and doubling time. There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year);
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time.

PSAV and PSA-DT may have a prognostic role in treated PCa, but limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time. These measurements do not provide additional information compared with PSA alone.

Free/total PSA ratio. Free/total (f/t) PSA ratio is widely used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. f/t PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow-up of known PCa. f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates).

Prostate Health Index (PHI) test. The Prostate Health Index (PHI)

test is a recently approved diagnostic blood test, combining free and total PSA and the (-2) pro PSA isoform (p2PSA), intended to reduce the number of unnecessary prostate biopsies in PSA tested men. A few prospective multicentre studies demonstrated that the PHI test not only outperforms free and total PSA PCa detection, but has an improved prediction of clinically significant PCa, both in men with a PSA between 4-10 ng /mL and between 2-10 ng /mL. The PHI test may therefore also have a role in monitoring men under active surveillance. Its clinical impact is, as yet undetermined, given the slight net benefit for clinical decision-making. [66]

PCA3 marker. PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The Progensa urine test for PCA3 is now commercially available. PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies.

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts Gleason score, and its use for monitoring in active surveillance is unconfirmed. Currently, the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy.

Prostate biopsy. The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand. Risk stratification is a potential tool for reducing unnecessary biopsies.

Limited PSA elevation alone, should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken.

Ultrasound-guided biopsy is now the standard of care. A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Cancer detection rates are comparable with both approaches.

Transrectal ultrasound. Classic hypoechogenicity in the peripheral prostate is not always seen. Grey-scale TRUS is not reliable at detecting PCa. Thus, there is no evidence that targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography, contrast-enhanced ultrasound or computerised ultrasound (Histoscanning™) are being investigated. There is not currently enough evidence for their routine use.

Multiparametric MRI (mpMRI). Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted

imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, or H1-spectroscopy, has excellent sensitivity for Gleason score >7 cancers.

Treatment

Radical prostatectomy (RP). Information about having surgery to remove the prostate. Surgery may be a treatment option for men with localised prostate cancer.

This involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency. There is no age threshold for RP and a patient should not be denied this procedure on the grounds of age alone. However, patients with a life expectancy of >10 years are more likely to benefit from the procedure. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes. An estimation of life expectancy is paramount in counselling a patient about surgery.

External beam radiotherapy uses high energy X-ray beams to treat prostate cancer.

Permanent seed brachytherapy involves implanting tiny radioactive seeds into prostate gland. This is also called low dose rate brachytherapy. Radiation from the seeds destroys cancer cells in the prostate. Pacient may have this treatment on its own or together with external beam radiotherapy or hormone therapy.

Hormone therapy. Androgen deprivation therapy (ADT) can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as anti-androgens.

In addition, these two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB).

Testosterone-lowering therapy (castration). Surgical castration is still considered the 'gold standard' for ADT, against which all other treatments are rated. It leads to a considerable decline in testosterone levels and induces a hypogonadal status, known as the 'castration level'.

The standard castrate level was < 50 ng/dL (1.7 nmol/L). It was defined more than 40 years ago, when testosterone level testing was limited. Current testing methods have found that the mean value of testosterone after surgical castration is 15 ng/dL. This has led to a revisiting of the current definition of castration, with a more appropriate level defined as below 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with levels around or below 1 nmol/l compared to 1.7 nmol/L. However, the castrate level considered by the regulatory authorities is still 50 ng/dL (1.7 mmol/L), which is also the threshold that has been used in

all clinical trials addressing castration in PCa patients.

Bilateral orchiectomy. Bilateral orchiectomy, either total or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia and is the quickest way to achieve a castration level, usually within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

Oestrogens. Opposed to castration, oestrogens resultant testosterone suppression is not associated with bone loss.

Diethylstilboesterol (DES). Early studies by the Veterans Administration (VACURG) tested oral Diesthylstilboesterol (DES) at 5 mg/day. This dosage was associated with high cardiovascular morbidity and mortality, which was secondary to first-pass hepatic metabolism and the formation of thrombogenic metabolites. Lower doses of 1 mg/day and 3 mg/day were found to be as effective as bilateral orchiectomy, with still more side effects compared to castration.

Luteinising-hormone-releasing hormone (LHRH) agonists. Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they stimulate pituitary LHRH receptors, inducing a transient rise in LH and FSH leading to the 'testosterone surge' or 'flare-up' phenomenon, which begins 2-3 days later and lasts for about 1 week. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

Luteinising-hormone-releasing hormone (LHRH) antagonists. LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation.

Anti-androgens. These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate, megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal antiandrogens that leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal antiandrogens have progestational properties leading to a central inhibition by crossing the blood-brain barrier.

Steroidal anti-androgens compounds are synthetic derivatives of hydroxyprogesterone. Their main

pharmacological side-effects are secondary to castration, while gynaecomastia is quite rare. The non-pharmacological side effects are cardiovascular toxicity and hepatotoxicity.

Non-steroidal anti-androgens monotherapy have been promoted on the basis of improved quality of life (QoL) and compliance compared to castration. They do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are preserved. Non-androgen pharmacological side-effects differ, with bicalutamide showing a more favourable safety and tolerability profile than nilutamide and flutamide. All three agents share a common liver toxicity (occasionally fatal) and liver enzymes must be monitored regularly.

High dose-rate brachytherapy is also known as HDR brachytherapy, or temporary brachytherapy. It is a type of internal radiotherapy used to treat prostate cancer.

Cryotherapy. Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis.

Freezing of the prostate is ensured by the placement of 12-15 x 17 gauge cryoneedles under transrectal ultrasound (TRUS) guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, the so-called third-generation cryosurgery devices are mainly used.

High-intensity focused ultrasound of the prostate (HIFU). HIFU consists of focused ultrasound waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation. The goal of HIFU is to heat malignant tissues above 65°C so that they are destroyed by coagulative necrosis.

HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position. The procedure is time-consuming, with about 10 g prostate tissue treated per hour. In a 2006 review, 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters. No controlled trial was available for analysis, and no survival data were presented. No validated biochemical, surrogate end-point was available for HIFU therapy. Potential candidates are patients with low to moderate risk in investigational settings. The patient should be informed about the lack of long-term outcome data at > 10 years.

Oncology diseases of urogenital organs

The most common tumor diseases of the urogenital system (renal cell carcinoma, bladder cancer, prostate cancer and primary urethral carcinoma).

Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence in Western countries. Aetiological factors include smoking, obesity, hypertension, acetaminophen and non-aspirin nonsteroidal anti-inflammatory drugs, and viral hepatitis.

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging used to investigate various non-specific symptoms and other abdominal diseases. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease.

Laboratory findings. Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium, coagulation study, and urinalysis.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

Traditionally, **US, CT and MRI (magnetic resonance imaging)** are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases.

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients.

Radiographic investigations for metastatic RCC. Chest CT is accurate for chest staging. However, routine chest radiography must be performed for metastases, but is less accurate than chest CT.

Surgical treatment.

Nephron-sparing surgery versus radical nephrectomy. Based on current available oncological and quality of life (QoL) outcomes, localised renal cancers are better managed by NSS (PN) rather than RN, irrespective of the surgical approach. Complete resection of the primary tumour by open or laparoscopic surgery offers a reasonable chance of cure.

Associated procedures.

Adrenalectomy.

Lymph node dissection for clinically negative lymph nodes (cN0).

Embolisation. Before routine nephrectomy, tumour embolisation has no benefit.

Targeted therapies. In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis. This process substantially contributes to the development and progression of RCC. There are several targeting drugs approved for treating mRCC in both the USA and Europe:

sorafenib (Nexavar®);

sunitinib (Sutent®);

bevacizumab (Avastin®) combined with IFN-α;

pazopanib (Votrient®);

temsirolimus (Torisel®);

everolimus (Afinitor®);

axitinib (Inlyta®).

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, while it drops to 11th when both genders are considered.

Symptoms. Painless haematuria is the most common presenting complaint. Other clinical signs include urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

Physical examination should include rectal and vaginal bimanual palpation.

Bladder imaging. Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging.

Urinary cytology and urinary markers. Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or CIS.

Cystoscopy. Ultimately, the diagnosis of bladder cancer is made by cystoscopy and histological evaluation of resected tissue.

Transurethral resection of invasive bladder tumours. The goal of transurethral resection of bladder is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection biopsies.

Prognostic markers. Currently, insufficient evidence exists to recommend the standard use of the prognostic marker p53 in highrisk muscle-invasive disease, as it will not yield sufficient data upon which to base treatment in an individual patient.

Treatment.

Large cystectomy series show a risk of an understaging error in TaT1 tumours of 35-62%. This may be caused by the presence of persisting or recurrent tumours due to omission of a second TURB or re-TURB, and the absence of neoadjuvant therapy. Second TURB identifies upstaging to > T2 tumours in 10-20%.

Radical cystectomy is also strongly recommended in patients with BCG-refractory tumours.

Primary urethral carcinoma (UC) is considered a rare cancer, accounting for < 1% of all malignancies.

Clinical examination. In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding.

Urinary cytology. The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59%.

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology.

Radiological imaging of UC aims to assess local tumour extent and to detect lymphatic and distant metastatic spread.

Regional lymph nodes. Enlarged lymph nodes in UC often represent metastatic disease.

Treatment of localised primary urethral carcinoma in males. Previously, treatment of male anterior UC has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours.

Treatment of localised urethral carcinoma in females. Urethrectomy and urethra-sparing surgery. In women with localised UC, to provide the highest chance

of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck.

Radiotherapy.

Treatment of urothelial carcinoma of the prostate. Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC.

Prostate cancer (PCa) is the most common cancer in elderly males (> 70 years of age) in Europe.

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and/or prostate-specific antigen (PSA) levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from TURP or prostatectomy for benign prostatic enlargement (BPE).

Free/total PSA ratio. Free/total (f/t) PSA ratio is widely used to differentiate BPH from PCa.

Prostate Health Index (PHI) test. The Prostate Health Index (PHI) test is a recently approved diagnostic blood test, combining free and total PSA and the (-2) pro PSA isoform (p2PSA), intended to reduce the number of unnecessary prostate biopsies in PSA tested men.

PCA3 marker. PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE.

Prostate biopsy. The need for prostate biopsy is based on PSA level and/or suspicious DRE.

Transrectal ultrasound. New sonographic modalities such as sonoelastography, contrast-enhanced ultrasound or computerised ultrasound (Histoscanning™) are being investigated. There is not currently enough evidence for their routine use.

Multiparametric MRI (mpMRI). Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, or H1-spectroscopy, has excellent sensitivity for Gleason score >7 cancers.

Treatment.

Radical prostatectomy (RP). Surgery may be a treatment option for men with localised prostate cancer.

External beam radiotherapy uses high energy X-ray beams to treat prostate cancer.

Permanent seed brachytherapy involves implanting tiny radioactive seeds into prostate gland.

Hormone therapy. Androgen deprivation therapy (ADT) can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor using competing compounds known as anti-androgens.

Testosterone-lowering therapy (castration). Surgical castration is still considered the 'gold standard' for ADT, against which all other treatments are rated.

Bilateral orchiectomy. Bilateral orchiectomy, either total or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure.

Oestrogens. Opposed to castration, oestrogens resultant testosterone suppression is not associated with bone loss.

Diethylstilboesterol (DES).

Luteinising-hormone-releasing hormone (LHRH) agonists. Long-acting LHRH agonists are currently the main forms of ADT.

Luteinising-hormone-releasing hormone (LHRH) antagonists. LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland.

Anti-androgens.

High dose-rate brachytherapy is also known as HDR brachytherapy, or temporary brachytherapy.

Cryotherapy. Cryosurgery uses freezing techniques to induce cell death.

High-intensity focused ultrasound of the prostate (HIFU). HIFU consists of focused ultrasound waves, emitted from a transducer, that cause tissue damage by mechanical and thermal effects as well as by cavitation.

Theme # 10: Urological trauma: basic provisions.

10.1 Actuality, classification

Damage to the genitourinary system is 1.5-3% in the total structure of injuries of all human organs. In peacetime, 75-80% of the injured caused damage during road accidents and falls from height. Genito-urinary trauma is seen in both sexes and in all age groups, but is more common in males. The kidney is the most commonly injured organ in the genito-urinary system and renal trauma is seen in up to 5% of all trauma cases, and in 10% of all abdominal trauma cases.

Renal trauma is seen after direct impact into the seatbelt or steering wheel (frontal crashes) or from body panel intrusion in side-impact crashes.

Ureteral trauma is relatively rare and mainly due to iatrogenic injuries or penetrating gunshot wounds – both in military and civilian settings.

Traumatic bladder injuries are usually due to blunt causes and associated with pelvic fracture, although may also be a result of iatrogenic trauma.

The anterior urethra is most commonly injured by blunt or "fall-astride" trauma, whereas the posterior urethra is usually injured in pelvic fracture cases.

Genital trauma is much more common in males due to anatomical considerations and more frequent participation in physical sports, violence and war-fighting. Of all genito-urinary injuries, 1/3-2/3 involve the external genitalia.

Classification. There are injuries of the kidneys (renal trauma), ureters, bladder, urethra and male genital organs.

Injuries can be isolated, multiple and combined. Isolated is considered to be the injury of one organ of the genito-urinary system, multiple - when, in addition to injury of the urogenital organs, there are injuries of other organs within one anatomical area, for example, trauma to the kidney and abdominal organs.

Concurrent damage – injury of organs located in different anatomical areas, for example, bladder trauma and craniocerebral injury.

Urogenital trauma can be light, medium and heavy; penetrating and non-penetrating; one- and two-sided. [44, 45]

10.2 Trauma of the kidney (renal trauma)

Epidemiology, actiology and pathophysiology

Kidney injury occurs most frequently and is about 60-65% in the

structure of damage to the organs of the urinary system. In peacetime, the closed ones prevail, and in the wartime - open kidney damage.

Closed kidney damage is usually caused by the application of force to the lumbar region or abdomen in the form of impact or compression. The hydrodynamic factor also plays a role in the mechanism of rupture, due to the significant predominance of the liquid component in the kidney parenchyma (blood, lymph, urine) surrounded by a dense fibrous capsule. Direct impact and detonation of the fluid inside the organ leads to rupture of the fibrous cap and the kidney parenchyma. In the domestic environment, trauma is most often caused by a lumbar area falling on a protruding solid object. The rupture of an organ occurs as a result of a direct impact and the damaging action of the adjacent bone structures - the ribs and the spine.

Kidney damage can occur as a result of minimally invasive and endoscopic methods for the diagnosis and treatment of urological diseases, which are now widespread. First of all, they are associated with careless or erroneous actions of the doctor. After remote shock-wave nephrolithotripsy, subcapsular hematomas are often diagnosed, and the hematuria that arises after it can be the result not only of the damaging effect on the urothelium of the stone and its fragments, but also of Fornicus ruptures. Trauma to the renal parenchyma can be observed during catheterization (stenting) of the ureter, ureteroscopy, nephroscopy, nephrobiopsy, and even perirenal blockade.

Kidney disease (tumor, cyst, hydronephrosis) make it more susceptible to various traumatic effects. Severe damage to the diseased kidney can occur even with minimal trauma.

Open injuries - knife or gunshot - are usually multiple.

Tab. 16 – Renal injury grading scale

Grade*	Description of injury
1	Contusion or non-expanding subcapsular haematoma
	No laceration
2	Non-expanding peri-renal haematoma
	Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation
4	Laceration: through corticomedullary junction into collecting system or Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney or Vascular: renal pedicle or avulsion

*Advance one grade for bilateral injuries up to grade III.

The most severe forms of kidney damage are crush injury, that is, the formation of multiple organ ruptures that penetrate into the renal pelvis with possible tearing off of parenchyma (pole) sections, and tearing (tearing) of the vascular pedicle. The latter has no

clinical significance, since it is almost always combined with equally severe injuries of other organs, which makes this kind of damage incompatible with life. [45]

Symptoms and clinical manifestation

The clinical picture depends on the degree of damage and the presence of injuries to other organs. Patients complain of pain in the lumbar region and/or in the abdomen, deepening with deep breathing, bloating, nausea, vomiting, general weakness. Total hematuria is observed with severe renal trauma.

Macrogematuria is a sign of severity of organ damage. But when the kidney is crushed, the hematuria may be insignificant or absent as a result of tamponade of the cavity system by blood clots and/or damage of the renal pelvis, ureter and its vascular pedicle.

A rupture of a parenchymal organ rich in blood vessels, such as a kidney, is accompanied by signs of internal bleeding. In combination with severe hematuria, it can quickly lead to anemization and severe condition of the patient, which is manifested by pallor of the skin, cold sweat, tachycardia, a decrease in blood pressure, an increase in retroperitoneal urohematoma. An objective study on the skin of the abdomen and lumbar region can be determined by abrasions, hemorrhages, swelling of tissues, as well as bulging in this area, due to urohematoma of large sizes. The location and course of the wound canal with the outflow of urine from it makes it possible to suspect open kidney damage. Palpation of the chest and spine may be accompanied by a sharp pain due to the fracture of these bone formations. On palpation of the abdomen, pain and protective tension of the muscles on the affected side are determined, and for large urohematomas, a rounded education in the hypochondrium and lumbar region.

Distant complications of closed kidney damage are hematoma, which is compressed, squeezing the kidney, stone formation, hydronephrosis, arterial hypertension, etc.

Diagnostics

In diagnosis, pay attention to the type and nature of the injury, its objective local and general manifestations. In blood tests, a decrease in the number of erythrocytes and hemoglobin is determined, in later terms, from the moment of injury, leukocytosis joins. In the analysis of urine, the erythrocytes cover the whole field of vision. The total renal function makes it possible to evaluate the determination of residual nitrogen, urea and serum creatinine, which is especially important when the only kidney is damaged and the surgical treatment is planned.

The most informative methods of diagnosing kidney damage are computed tomography and magnetic resonance imaging; it provides the highest degree of accuracy in assessing anatomical details. [45]

The use of **intravenous pyelography** is recommended only when it is the only modality available. Intravenous pyelography can be used to establish the presence or absence of one or both kidneys, clearly define the parenchyma and outline the collecting system. The most significant findings are non-function and extravasation. Non-function is a sign of extensive trauma to the kidney, pedicle injury, or a severely shattered kidney. Extravasation of the contrast medium implies a severe degree of trauma, involving the capsule, parenchyma and collecting system. Non-visualisation, contour deformity or contrast extravasation should prompt further radiological evaluation. The sensitivity of intravenous pyelography is high (> 92%) for all grades of renal injury trauma. In unstable patients undergoing emergency laparotomy, intravenous pyelography may provide information on the presence of a normal functioning contralateral kidney. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after 10 minutes.

Computed tomography is the best method for assessment of stable patients. Computed tomography is more sensitive and specific than intravenous pyelography, ultrasonography or angiography, since it accurately defines the location of injuries, easily detects contusions and the entire retroperitoneum and any associated haematomas, and simultaneously provides a view of both the abdomen and pelvis. It demonstrates superior anatomical details, including the depth and location of lacerations and the presence of associated abdominal injuries, and establishes the presence and location of the contralateral kidney. Intravenous contrast should be administered for renal evaluation. A lack of contrast enhancement is a hallmark of pedicle injury. In cases where this typical finding is not demonstrated, central parahilar haematoma may also raise the possibility of pedicle injury. This sign should be considered even if the parenchyma is well enhanced. Renal vein injury is difficult to diagnose, but the presence on computed tomography of a large haematoma, medial to the kidney and displacing the vasculature, should raise the suspicion. Spiral computed tomography provides fewer artefacts in the examination of patients who cannot co-operate adequately. Three-dimensional post-processing modalities allow assessment of the vascular pedicle by computed tomography angiography and improve the demonstration of complex lacerations of the parenchyma. As injury to the collecting system may be missed during routine spiral computed tomography, in all cases of suspected trauma, repeat scans of the kidneys should be performed 10-15 minutes after contrast injection. Most blunt ureteral and UPJ injuries can be identified with delayed excretory computed tomography scans. Computed tomography scanning is an essential diagnostic modality in patients with gunshot wounds who are being considered for non-operative management. Missed injuries are common, but are mostly minor, and do not alter the patients' clinical course.

Magnetic resonance imaging is not commonly used in this setup, although it is sensitive for the evaluation of blunt renal trauma. Magnetic resonance imaging requires a longer imaging time and limits access to patients during the examination, and is therefore useful only if computed tomography is not available, in patients with iodine allergy, or in cases where computed tomography findings are equivocal.

Treatment.

Therapeutic tactics depends on the degree of damage to the kidney.

Conservative management

Conservative therapy is indicated for small organ breaks with subcapsular or perirenal hematoma with a volume of up to 300 ml and moderate hematuria. Assign strict bed rest for two weeks, cold on the lumbar region, hemostatic, antibacterial and improves microcirculation in the kidney drugs. In the process of treatment requires constant dynamic monitoring, including the assessment of the state of hemodynamics, blood tests, urine and ultrasound monitoring. It should be remembered about the possibility of the so-called two-stage organ damage, which implies a rupture of the fibrous capsule over a subcapsular hematoma with renewed bleeding from the damaged parenchyma into the retroperitoneal tissue. Such a rupture may occur if the patient does not comply with bed rest.

Surgical management

Surgical treatment requires 10-15% of patients with severe kidney damage. Emergency surgery indicated:

- with increasing internal bleeding and/or profuse hematuria;
- large and multiple breaks of the parenchyma with the formation of hematomas (urohematoma) with a volume of more than 300 ml;
- concomitant damage to the kidney and other internal organs requiring an urgent audit;
- infection of pararenal hematoma with the formation of perirenal abscess.

Planned operations are performed for remote complications of closed kidney damage.

Surgical interventions for kidney injury are divided into minimally invasive and open.

The percutaneous puncture and drainage of hematoma or post-traumatic perirenal abscess are minimally invasive; laparoscopic (lumboscopic) suturing of kidney rupture or nephrectomy, evacuation and drainage of hematoma; arteriography and selective embolization of a bleeding kidney vessel.

Open surgeries include suturing a renal parenchymal rupture with or

without nephrostomy, renal resection, and nephrectomy.

Even at present, nephrectomy is most often performed with kidney injury. It is performed by approximately 50% of patients who perform emergency lumbotomy (laparotomy) due to organ rupture. The kidney is removed when the vascular pedicle is ruptured, multiple and deep wounds of the parenchyma, the inability to perform a good audit and organ preservation treatment due to rapidly increasing, life-threatening bleeding, especially with combined injuries. In some cases, in rayon and small city hospitals, nephrectomy is performed without a proper revision of the kidney and an assessment of the extent of its damage in the process of laparotomy undertaken for intraperitoneal injuries.

A complete urological examination may not be possible due to the need for emergency laparotomy for concomitant intraperitoneal injuries. During the operation, a kidney revision is required if there is an increasing retroperitoneal hematoma of a large size. If after revision of the retroperitoneal space and kidney nephrectomy is planned, it is necessary to evaluate the function of the opposite kidney. First of all, it is necessary to determine the presence of an organ by palpation through the parietal peritoneum, and also to establish its functional viability. In emergency cases on the operating table, this can be done in one of two ways: by excretory urography or indigo carmine test (by intravenous administration of a coloring matter with compression of the ureter of the injured kidney and by monitoring its entry through the catheter from the bladder). [45]

When a gunshot wound of the kidney is necessary to take into account the cavitation effect of a bullet, splinter, that is, a concussion, crush of the parenchyma due to the impact of the pulsating cavity. In such cases, surgical treatment of the wound channel is necessary, which includes, in addition to stopping the bleeding, excision of non-viable tissues and removal of foreign bodies.

The prognosis depends on the degree of damage to the kidney and the proper treatment. Conservative therapy with small gaps and organ-sparing surgical treatment make the prognosis for anatomical and functional state of the kidney favorable. With pronounced organ ruptures and massive bleeding, the prognosis for the life of the patient is determined by timely surgical intervention.

10.3 Trauma of ureters

Epidemiology, aetiology, and pathophysiology

Injuries of the ureters due to their anatomical structure are rarely observed. In the structure of injuries of the urinary system, they account for no more than 1% of cases.

Open injuries of the ureters are extremely rare, as a rule, they are caused by knife or gunshot wounds and

are almost always combined. Gunshot wounds of the ureters are found in 3.3–3.5% of cases of all combat damage to the urinogenital system during modern warfare.

Closed damage to the ureters as a result of external exposure due to their anatomical and topographic features (depth of location, protection by muscle and bone structures, size, elasticity, mobility) are not much more frequently observed. Such an injury can occur as a result of damage to the ureters with bone fragments due to a fracture of the posterior half of the pelvis.

In peacetime, the vast majority of damage to the ureters is iatrogenic in nature, that is, it occurs as a result of accidental damage during surgery. Ligation, dissection or intersection of the ureter is most often observed during obstetric-gynecological and surgical operations. Damage to it as a result of endourological diagnostic and therapeutic interventions (ureteroscopy, stenting and catheterization of the ureter) should be regarded as a complication when performing manipulations.

Symptoms and clinical manifestation

Damage of the ureter is manifested by pain in the lumbar region, associated with a violation of the outflow of urine from the corresponding kidney, and short-term hematuria.

The ureteral lesions that were not detected during the surgical intervention are manifested by urine drainage from the abdominal cavity or retroperitoneal space already in the first hours after the operation.

The flow of urine into the abdominal cavity is manifested by the symptoms of the beginning peritonitis: irritation of the peritoneum and paresis of the intestine. [44]

Non-drained or poorly drained urinary blisters are infected with the formation of a retroperitoneal urinary phlegmon followed by the development of urosepsis.

Diagnostics

The diagnosis of ureteral trauma is challenging, therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intraoperatively during laparotomy, while it is delayed in most blunt trauma and iatrogenic cases.

External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spine injuries. Haematuria is an unreliable poor indicator of ureteral injury, as it is present in only 50-75% of patients.

Iatrogenic injury may be better noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. It is usually noticed later, when it is discovered by subsequent evidence of upper tract obstruction, urinary fistulae formation or sepsis.

The following clinical signs are characteristic of delayed diagnosis: flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever, uraemia or urinoma. When the diagnosis is missed, the complication rate increases. Early recognition facilitates immediate repair and provides better outcome.

Treatment

Treatment of ureteral trauma depends on their type, localization and time elapsed since the injury (Tab. 17). Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement.

With open injuries, urine diversion by puncture nephrostomy and drainage of the urinary flow are required. After the wound has healed, an operation is performed to restore the patency of the ureter. The marginal lesions of the ureter, which occurred as a result of endourological operations, are closed independently after the stent is established.

Iatrogenic lesions of the ureter, diagnosed during surgery, are subject to immediate correction, which depends on the type of damage. The marginal defect of the ureter is sutured with nodal vicryl sutures; with more extensive defects or ligation of the ureter perform resection of its modified areas with ureteroureteroor ureterocystanastomosis.

If iatrogenic damage to the ureter is not seen during surgery, its outcome can be urinary leakage, peritonitis, cicatricial contractions and ureteral-vaginal fistulas. In such cases, and especially with the development of postrenal anuria, percutaneous puncture nephrostomy with drainage of urinary flow is shown.

In the future, depending on the length and localization of the narrowing or obliteration of the ureter, reconstructive surgery is performed: ureteroureteroanastomosis, ureterocystanastomosis, and with extended or bilateral contractions, intestinal plasty of the ureters.

Tab. 17 - Reconstruction operations by site of injury

Site of injury	Reconstruction options
Upper ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Uretero-calycostomy
Mid ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Ureteral reimplantation and a Boari flap
Lower ureter	Ureteral reimplantation
	Ureteral reimplantation with a psoas hitch
Complete	Ileal interposition graft
	Autotransplantation

10.4 Trauma of the bladder

Epidemiology, aetiology and pathophysiology

Bladder injuries are severe injuries to the abdomen and pelvis. The severity of the condition of the victims and the outcome of treatment are determined not so much by damage to the bladder as by their combination with injuries of other organs and the dangerous complications caused by the flow of urine into the surrounding tissues and abdominal cavity.

Damage to the bladder is divided into closed and open, isolated and combined. They can be non-penetrating and penetrating when all layers of the bladder wall are damaged and urine is expelled beyond it. In peacetime, closed bladder injuries prevail. They can be intraperitoneal, extraperitoneal, and combined when there is a simultaneous intraperitoneal and bladder rupture.

The frequency of damage to the bladder with a closed abdominal injury is from 3 to 16%. In most cases, there are non-bruise-splitting organ.

Closed bladder damage in most cases (70-80%) is a consequence of pelvic bone fractures. With this mechanism of injury, extraperitoneal ruptures prevail, which occur as a result of the sudden movement of the bladder-prostatic and lateral ligaments of the bladder. The sharp tension of dense anatomical structures, which are its ligaments, leads to the rupture of a more pliable soft-elastic bladder wall. It is also possible direct damage to its wall by displaced bone fragments. Intraperitoneal injuries have a different mechanism of development. The rupture occurs as a result of hydrodynamic impact on the wall of the overflowing bladder. Such damage occurs even with minimal traumatic impact on the lower abdomen (sudden blow) with a relaxed anterior abdominal wall.

Symptoms and clinical manifestation

Bladder injuries are characterized by pain in the lower abdomen, which is especially pronounced for fractures of the pelvic bones. The bright symptoms of bone injury, especially with the development of a shock, mask the manifestations of intrapelvic organ damage, including damage to the bladder. It should be remembered that in patients with fractures of the pelvic bones, bladder and / or membranous urethral ruptures most often occur. These injuries should first be excluded from the examination of such victims. Clinic of acute abdomen is the main manifestation of intraperitoneal rupture of the bladder. The presence of a large amount of urine in the abdominal cavity causes a characteristic symptom of "Vanka-vstanka". Attempting to lay the victim leads to a sharp increase in pain throughout the abdomen, this is associated with the irritation of a large number of nerve endings due to the movement of fluid in the upper abdomen. As a result, he tends to take a vertical position. [44]

Penetrating ruptures of the bladder are always accompanied by urination disorders, the severity of which is directly related to the degree of the resulting defect. Despite the heightened urge to urinate, independent urination is impossible. An attempt to urinate leads to the movement of urine out of the organ, accompanied by a sharp increase in pain and the absence or minimal release of it with blood in the urethra.

In case of late treatment and damage not recognized in time, severe septic complications develop: in case of extraperitoneal injury, phlegmon of the pelvis, and in intraperitoneal disease, diffuse urinary peritonitis.

Diagnostics

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected iatrogenic bladder trauma in the post-operative setting. Both plain and computed tomography cystography have a comparable sensitivity (90-95%) and specificity (100%).

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 350 mL of dilute contrast material. With intraperitoneal extravasation, free contrast medium is visualised in the abdomen, highlighting bowel loops and/or outlining abdominal viscera such as the liver.

Extraperitoneal bladder injury is associated with flame-shaped areas of contrast extravasation in the perivesical soft tissues.

Cystoscopy is the preferred method for detection of intra-operative bladder injuries, as it may directly visualise the laceration. Cystoscopy can localise the lesion in relation to the position of the trigone and ureteral orifices. A lack of bladder distension during cystoscopy suggests a large perforation. Routine cystoscopy is advised at the end of a hysterectomy and every major gynaecological procedure.

Cystoscopy is recommended to detect perforation of the bladder (or urethra) following suburethral sling operations by the retropubic route. Routine cystoscopy after sling insertion through the obturator route is controversial because bladder injuries are, rare but not impossible. Cystoscopy after transvaginal mesh procedures is preferable, but not mandatory.

Treatment

Conservative management

Conservative treatment comprises clinical observation, continuous bladder drainage and antibiotics prophylaxis. This is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma, after TURB or after other operations in which the injury was not recognised during surgery. It is an option for an uncomplicated intraperitoneal injury after TURB or not recognised during surgery, but only in the absence of peritonitis and ileus. In addition to conservative treatment, placement of an intraperitoneal drain has been

advocated, especially when the lesion is larger.

Surgical management

The preferred method is two-layer vesicorraphy (mucosa-detrusor) with absorbable sutures.

Blunt non-iatrogenic trauma. Although most extraperitoneal ruptures can be treated conservatively, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal injury or entrapment of the bladder wall will necessitate surgical intervention. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material.

During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection. Similarly, during surgical exploration for other injuries, an extraperitoneal rupture should be sutured concomitantly in order to reduce infective complications. Intraperitoneal ruptures should always be managed by formal surgical repair because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death.

Penetrating non-iatrogenic trauma. This requires emergency exploration, debridement of devitalised bladder muscle and primary bladder repair. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters. In gunshot wounds, there is a strong association with intestinal and rectal injuries, requiring faecal diversion. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for those two lesions.

Non-iatrogenic bladder trauma with avulsion of lower abdominal wall or perineum and/or bladder tissue loss. In these cases, direct closure of the traumatised bladder will lead to excessive tension, resulting in ischaemia and eventually breakdown of the repair. A bladder wall substitute is needed to repair the bladder defects and to restore the lower abdominal wall or perineum. A pedicled vastus lateralis myocutaneous flap has been proposed for this.

Iatrogenic bladder trauma. Perforations recognised intra-operatively are primarily closed. For bladder injuries not recognised during surgery or for internal injuries, a distinction must be made between intraperitoneal and extraperitoneal injuries.

For intraperitoneal injuries, the standard of care is surgical exploration with repair. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury.

For extraperitoneal injuries, exploration is only needed for large perforations complicated by symptomatic extravesical collections. It requires drainage of the collection, with or without closure of the perforation. If bladder perforation is encountered during midurethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (1-2 days) should be performed. [43]

Intravesical foreign body. For perforated or eroded meshes, the intravesical portion must be removed by open cystotomy or endoscopically. The choice depends on the surgeon's level of experience and the location of the mesh. For other types of foreign bodies, cystoscopic removal is performed and if this fails cystotomy is needed.

10.5 Urethral trauma

Epidemiology, aetiology and pathophysiology

Iatrogenic urethral trauma. The most common type of urethral trauma seen in urological practice is iatrogenic, due to catheterisation, instrumentation, or surgery. New treatment methods and applied energy sources can also injure the urethra.

Transurethral catheterization. Iatrogenic urethral trauma usually results from improper or prolonged catheterisation and accounts for 32% of strictures. Most of these strictures affect the bulbar urethra, while the bladder neck is rarely affected in such cases. The size and type of catheter used have an important impact on urethral stricture formation. Current data indicate that silicone catheters and small-calibre Foley catheters are associated with less urethral morbidity. Implementing training programmes may significantly decrease the incidence of such injuries, increase patients' safety and reduce the negative long-term effects.

Transurethral surgery is a common cause of iatrogenic urethral trauma. Factors that may influence the development of iatrogenic endoscopic urethral strictures include electrical dispersion generated by unipolar current and the diameter of the instruments used. Predisposing factors most strongly associated with stricture formation in patients undergoing TURP are increased prostate volume, prostate cancer and the surgeon's experience. Meatal strictures occur as a result of a mismatch between the size of the instrument and the diameter of the urethral meatus. Bulbar strictures occur due to insufficient insulation by the lubricant, causing the monopolar current to leak. To prevent strictures, lubricant gel should be applied carefully in the urethra. The lubricant must be reapplied when the resection time is prolonged. Internal urethrotomy must be performed before TURP if there are pre-existing meatal or urethral strictures. There appears to be no relationship with the duration of the procedure or the method used (holmium laser or traditional TURP) on the rate of stricture formation.

Surgical treatment for prostate cancer. Urethral stricture following prostate cancer treatment can occur anywhere from the bladder neck to the urethral meatus. The rate of bladder neck constriction after radical prostatectomy varies with the definition of the stricture used and individual practice. The risk is greatest after radical prostatectomy if combined with

external-beam radiation therapy. In a multivariate analysis, primary treatment type, age, and obesity were found to be significant predictors for stricture development.

Symptoms and clinical manifestation

Blood at the meatus is the cardinal sign of urethral injury. The absence of it, however, does not rule out a urethral injury. An inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture. In addition, haematuria and pain on urination may be present. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour). Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) and may reveal a 'high-riding' prostate, which is an unreliable finding. Failure to detect a rectal injury will cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration. Another sign of urethral injury is difficulty or an inability to pass a urethral catheter.

A female urethral injury should be suspected from the combination of a pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling and/or urinary retention. Vaginal examination is indicated to assess vaginal lacerations. Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/ or perineal pain (100%) and urethral bleeding (86%). Failure to diagnose accurately and treat urethral injuries may lead to significant long-term sequelae, mostly presenting as strictures.

Diagnosis in males and females

Retrograde urethrography is the standard diagnostic investigation for the acute evaluation of a male urethral injury. A retrograde urethrography is conducted by injecting 20-30 mL of contrast material while occluding the meatus, with a balloon of a Foley catheter inflated in the fossa navicularis. Films should be taken in a 30°-oblique position, unless this is not possible because of the severity of the pelvic fractures and associated patient discomfort. In an unstable patient, retrograde urethrography should be postponed until the patient has been stabilised. A urethrogram allows for identification of the site of injury and assessment of the extent of any injury. Any extravasation outside the urethra is pathognomonic for urethral injury. However, the distinction between a complete and partial rupture is not always clear. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling.

Treatment

Anterior urethral injuries are usually not associated with other life-threatening injuries. Treatment

decisions are based mainly on the type of injury (blunt, penile fracture associated or penetrating).

Blunt anterior urethral injuries are associated with spongiosal contusion, which makes it more difficult to evaluate the limits of urethral debridement in the acute phase. Acute or early urethroplasty is therefore not indicated. The therapeutic options are suprapubic diversion or (a trial of) early endoscopic realignment with transurethral catheterisation. Urinary diversion is maintained for 2 and 3 weeks for partial and complete ruptures, respectively. Satisfactory urethral luminal recanalisation may occur in up to 68% after partial ruptures, but is rare after complete ruptures. [44]

Penile fracture-related anterior urethral injuries. In order to preserve erectile function, penile fractures require early exploration. The strategy consists of closing the tear in the cavernosal tunica albuginea, while the concomitant tear in the urethra is repaired at the same time. In these circumstances, there is no substantial urethral tissue loss. A small laceration can be repaired by simple closure, while a complete rupture requires an anastomotic repair.

Penetrating anterior urethral injuries. Immediate exploration is advised, except when this is precluded by other life-threatening injuries. Devitalised tissues should be debrided, although urethral and spongiosal debridement should be kept to a minimum due to the excellent vascularisation. For small lacerations and stab wounds, simple urethral closure might be sufficient. Defects of up to 2-3 cm in length in the bulbar urethra, and up to 1.5 cm in the penile urethra, can be treated by spatulation of the urethral ends and primary anastomosis. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation and a suprapubic catheter is needed. Peri- and post-operative antibiotic treatment is also necessary.

Blunt posterior urethral injuries. In posterior injuries, it is important to distinguish between complete and partial ruptures prior to treatment. The timing of the surgical intervention is classified as:

- immediate: < 48 hours after injury;
- delayed primary: 2 days to 2 weeks after injury;
- deferred: > 3 months after injury.

Immediate management. Although urinary diversion is not essential during the first hours after trauma, many prefer to perform an early urinary diversion for three main reasons:

- to monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;
- to treat symptomatic retention if the patient is still conscious;
- to minimise urinary extravasation and its secondary effects, such as infection and fibrosis. Insertion of a suprapubic catheter is always a

external-beam radiation therapy. In a multivariate analysis, primary treatment type, age, and obesity were found to be significant predictors for stricture development.

Symptoms and clinical manifestation

Blood at the meatus is the cardinal sign of urethral injury. The absence of it, however, does not rule out a urethral injury. An inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture. In addition, haematuria and pain on urination may be present. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour). Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) and may reveal a 'high-riding' prostate, which is an unreliable finding. Failure to detect a rectal injury will cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration. Another sign of urethral injury is difficulty or an inability to pass a urethral catheter.

A female urethral injury should be suspected from the combination of a pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling and/or urinary retention. Vaginal examination is indicated to assess vaginal lacerations. Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/ or perineal pain (100%) and urethral bleeding (86%). Failure to diagnose accurately and treat urethral injuries may lead to significant long-term sequelae, mostly presenting as strictures.

Diagnosis in males and females

Retrograde urethrography is the standard diagnostic investigation for the acute evaluation of a male urethral injury. A retrograde urethrography is conducted by injecting 20-30 mL of contrast material while occluding the meatus, with a balloon of a Foley catheter inflated in the fossa navicularis. Films should be taken in a 30°-oblique position, unless this is not possible because of the severity of the pelvic fractures and associated patient discomfort. In an unstable patient, retrograde urethrography should be postponed until the patient has been stabilised. A urethrogram allows for identification of the site of injury and assessment of the extent of any injury. Any extravasation outside the urethra is pathognomonic for urethral injury. However, the distinction between a complete and partial rupture is not always clear. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling.

Treatment

Anterior urethral injuries are usually not associated with other life-threatening injuries. Treatment

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- to minimise urinary extravasation and its secondary effects, such as infection and fibrosis. Insertion of a suprapubic catheter is always a

Diagnostics. The diagnosis of ureteral trauma is challenging, therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intraoperatively during laparotomy, while it is delayed in most blunt trauma and iatrogenic cases.

Treatment

Treatment of ureteral trauma depends on their type, localization and time elapsed since the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement.

Proximal and mid-ureteral injuries. Injuries shorter than 2-3 cm can usually be managed by a primary uretero-ureterostomy.

Distal ureteral injuries are best managed by ureteral reimplantation (ureteroneocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter.

Between 60-90% of patients with **bladder injuries** caused by blunt trauma have associated pelvic fractures, and 44% of patients with bladder injuries have at least one other intra-abdominal injury.

Bladder damage is characterized by pain in the lower abdomen, which is especially pronounced in fractures of the pelvic bones. Signs of external iatrogenic bladder trauma are extravasation of urine, visible laceration, clear fluid in the surgical field, appearance of the bladder catheter, and blood and/or gas in the urine bag during laparoscopy.

Diagnostics

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected iatrogenic bladder trauma in the post-operative setting.

Cystoscopy is the preferred method for detection of intra-operative bladder injuries, as it may directly visualise the laceration.

Treatment

Conservative treatment comprises clinical observation, continuous bladder drainage and antibiotics prophylaxis.

Blunt non-iatrogenic trauma. Although most extraperitoneal ruptures can be treated conservatively, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal injury or entrapment of the bladder wall will necessitate surgical intervention.

Penetrating non-iatrogenic trauma. This requires emergency exploration, debridement of devitalised bladder muscle and primary bladder repair. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters.

Non-iatrogenic bladder trauma with avulsion of lower abdominal wall or perineum and/or bladder tissue loss. A pedicled vastus lateralis myocutaneous flap has been proposed for this.

For **intraperitoneal injuries**, the standard of care is surgical exploration with repair.

The most common type of **urethral trauma** seen in urological practice is iatrogenic, due to catheterisation, instrumentation, or surgery. New treatment methods and applied energy sources can also injure the urethra. Blood at the meatus is the cardinal sign of urethral injury. The absence of it, however, does not rule out a urethral injury.

Diagnostics

Retrograde urethrography is the standard diagnostic investigation for the acute evaluation of a male urethral injury.

Treatment

Blunt anterior urethral injuries are associated with spongiosal contusion. The therapeutic options are suprapubic diversion or (a trial of) early endoscopic realignment with transurethral catheterisation.

Penile fracture-related anterior urethral injuries. The strategy consists of closing the tear in the cavernosal tunica albuginea, while the concomitant tear in the urethra is repaired at the same time.

Penetrating anterior urethral injuries. Immediate exploration is advised, except when this is precluded by other life-threatening injuries.

Blunt posterior urethral injuries. In posterior injuries, it is important to distinguish between complete and partial ruptures prior to treatment.

Theme # 11: Urogenital anomalies: renal anomalies, anomalies of ureter, anomalies of urinary bladder, anomalies of male urethra and testicular anomalies.

Anomaly (from Greek anomalia - a deviation, roughness) - the structural and/or functional deviation caused by violation of an embryonal development. Urogenital anomalies are widespread and are about 40% of all congenital defects. According to data of autopsy, about 10% of people have various anomalies of development of urogenital system.

11.1 Renal anomalies

Congenital renal anomalies comprise of vast spectrum of pathologies and include:

- **Anomalies of quantity:**
  - Supernumerary kidneys;
  - Renal agenesis;
- **Anomalies in position:**
  - Anomalies of rotation;
  - Anomalies of location (ectopia):
    - Ipsilateral ectopia;
    - Crossed renal ectopia;
    - Anomalies of renal fusion;
    - Anomalies of renal fusion U-shaped and L-shaped;
    - Disc kidney;
    - Unilateral fused kidney or crossed fused renal ectopia;
- **Anomalies of the size:**
  - Renal hypoplasia;
- **Anomalies of structure of a kidney:**
  - Renal Dysplasia;
  - Congenital megacalyectasis;
  - Congenital cystic renal disease:
    - Infantile polycystic renal disease: autosomal recessive polycystic kidney disease (ARPKD): Potter type I;
    - Multicystic dysplastic kidneys: Potter type II;
    - Early onset autosomal dominant polycystic kidney disease (ADPKD): Potter type III;
    - Obstructive cystic renal dysplasia: Potter type IV;
- **Anomalies of kidney vessels:**
  - Accessory renal arteries;
  - Renal vein anomalies:
    - Retroaortic or circumaortic left renal vein;
    - Supernumerary renal veins.

Anomalies of quantity. Anomalies in number can be in the form of supernumerary kidneys or renal agenesis.

Supernumerary kidneys (Fig. 39). Supernumerary kidney is an additional kidney to the number normally present. This can refer to more than two separate or an extra kidney coexisting with a horseshoe kidney.

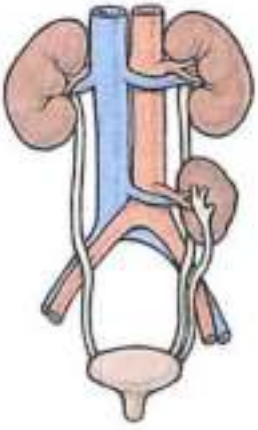

Fig. 39 - Supernumerary kidney
(Illustration from https://uroshemakey.com/wp-content/uploads/2016/09/C52-FF5.gif

Supernumerary kidney needs to be differentiated from a duplex kidney. Supernumerary kidney has a completely separate renal parenchyma and a renal capsule with a greater number of calyces as compared to duplex kidney in which both poles are attached with a single renal capsule and the number of calyces does not exceed from that of the opposite kidney. [47]

Two types of supernumerary kidney exist: drained by a bifid ureter and drained by a separate ureter. When a bifid system is present, supernumerary kidney lies caudally and when a separate ureter is seen then the supernumerary kidney is located cranially in relation to the normal kidney. In such a case the ureter enters the bladder ectopically and according to the Weigert-R Meyer rule the ureter may insert medially and inferiorly into the bladder. If both horseshoe kidney and a supernumerary kidney coexist then the half of the horseshoe kidney on the side of the body containing the supernumerary kidney is always small. Complications include renal malignancy, stones and hydronephrosis. For the diagnosis of supernumerary kidney, intravenous pyelography, ultrasonography, nuclear scintigraphy, CT, and MRI can be used. On imaging, an additional kidney is seen which is nearly always smaller than the normal kidneys with normal or impaired renal function.

Renal agenesis (Fig. 40). Absence of development of kidney may be due to the absence of the metanephric blastema, maldevelopment of the ureteral bud or lack of induction of the metanephric blastema by the ureteral bud. Occasionally, post-natal involution of multicystic dysplastic kidney and hydronephrotic kidney can result in a solitary kidney. It is important to look for additional associated ipsilateral urogenital anomalies which may include absence of the vas deferens, unicornuate uterus,

absence or cysts of the seminal vesicle, skeletal abnormalities, anorectal malformations, cryptorchidism, cardiovascular abnormalities. Renal agenesis can be unilateral or bilateral. Bilateral renal agenesis is incompatible with postnatal life and is usually diagnosed antenatally because it causes maternal oligohydramnios. On imaging, unilateral renal agenesis can be diagnosed on plain film by the absence of a renal outline and medial displacement of the colonic flexure into the renal bed. The contralateral kidney, when normal, shows compensatory hypertrophy and this may be visible on the plain film.

Anomalies in position. Anomalies in position include anomalies of rotation and location.

Anomalies of rotation. Normally, the kidneys lie at an angle of 30 degrees from the horizontal making the renal pelvis to face medially and slightly anteriorly.

Anomalies of renal location (renal ectopia). Congenital abnormal location of a kidney is described as renal ectopia. It is important to differentiate this entity from renal ptosis which is defined as renal descent by 5 cm or more (2 lumbar vertebrae) in upright position. In renal ectopia, the arterial blood supply arises ectopically and the length of the ureter may be short or long depending on the location of the ectopic kidney whereas in ptotic kidney the ureter is of normal length (may be redundant when the patient stands) and the renal arteries arise from the normal sites

Ipsilateral ectopia. Kidney is on the same side of the body as the orifice of its attendant ureter. It is further divided into cranial or caudal ectopia in reference to relationship with its normal position.

Caudal ectopia are further divided into – abdominal (above the iliac crest but below L2 vertebra), iliac (at the level of iliac crest) and pelvic (located in true pelvis).

Crossed renal ectopia. Kidney is located on the side of the body opposite the orifice of its attendant ureter. McDonald and McClellan classified crossed ectopic kidney into four types: crossed renal ectopia with fusion (85%), crossed renal ectopia without fusion (10%), solitary crossed renal ectopia, and bilaterally crossed renal ectopia.

Anomalies of renal fusion. Renal fusion anomalies are classified into horseshoe, disc and unilateral fused kidney or crossed fused renal ectopia. Embryological basis of renal fusion anomalies is related to their respective nephrogenic blastemas which squeeze together between the umbilical arteries at the beginning of the cranial migration of the ureteral buds leading to their fusion.

Fused kidneys are usually ectopic in position. In all fused kidneys, the arterial supply and venous drainage are grossly abnormal.

Horseshoe kidney (Fig. 41). Horseshoe kidney is the most common renal fusion anomaly, with an incidence of approximately 0.25% in the general population.

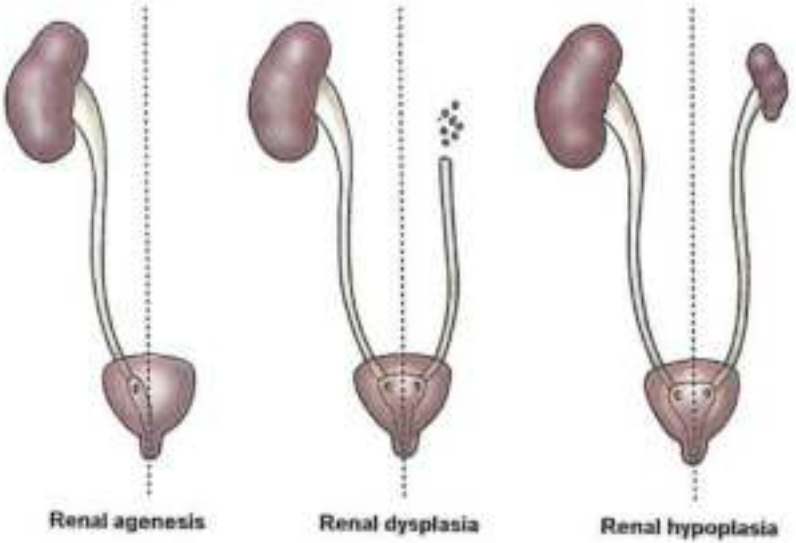

Fig. 40 - Renal agenesis, renal dysplasia, renal hypoplasia
(Illustration from https://illustrealgate.com/wp-content/uploads/2015/02/8978145574333986853?_fb53-481ac-9781455743339.jpg)

It usually lies in a lower position than the normal kidneys because the isthmus does not permit ascent beyond the inferior mesenteric artery (IMA).

Most cases are fused at the lower poles by an isthmus. Isthmus is comprised of either functioning renal parenchyma or fibrous tissue that crosses the midline of the body.

While most cases of horseshoe kidneys are asymptomatic and discovered upon autopsy, the condition may increase the risk for:

- kidney obstruction – abnormal placement of ureter may lead to obstruction and dilation of the kidney;
- kidney infections – associated with vesicoureteral reflux;
- kidney stones – deviant orientation of kidneys combined with slow urine flow and kidney obstruction may lead to kidney stones;
- kidney cancer – increased risk of renal cancer, especially Wilms' tumor, transitional cell carcinoma, and an occasional case report of carcinoid tumor. Despite increased risk, the overall risk is still relatively low.

Disc kidney. It is also known as cake or lump kidney.

First identified and defined by Glenn, disc kidney is an anomaly in which "the entire renal substance is fused into one mass, lying in the pelvis, and giving rise to two separate ureters which enter the bladder in normal relationship".

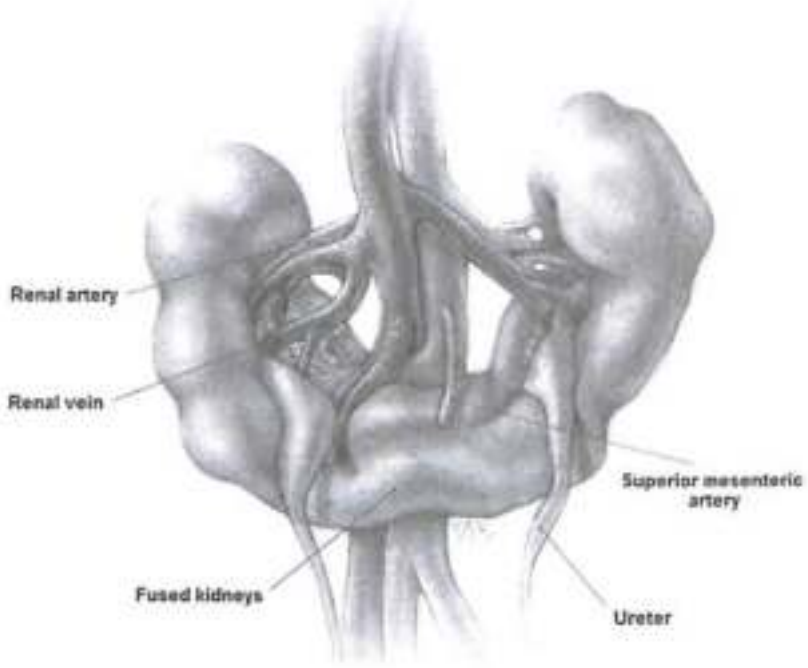

Fig. 41 - Horseshoe kidney
(Illustration from
https://static1.squarespace.com/static/538d4ce3e4b088a209446e29/t/589cd566cd0fd820a50b159a/1486673255000/horseshoe-kidney.jpg)

In rare instances, such kidneys possess one ureter. The fused kidney occupies prevertebral or presacral space.

Unilateral fused kidney or crossed fused renal ectopia: Crossed fused renal ectopia is the second mostcommon fusion abnormality of the kidney.

In crossed fused ectopia, one kidney crosses over to opposite side, and the parenchyma of the two kidneys fuse. Usually, the upper pole of the inferiorly positioned crossed ectopic kidney is fused to the lower pole of the superior, normally positioned kidney.

The ureter of the ectopic kidney crosses the midline and enters the bladder on the opposite side.

Types of crossed fused ectopia (Fig. 42):

- **Superior ectopia** – ectopic kidney crosses the midline and lies superior to the orthotopic kidney with fusion of the poles of kidney;
- **Sigmoid or S-shaped ectopia** – ectopic kidney lies inferiorly with pelvis directed laterally and

the pelvis of orthotopic kidney facing medially;

- **Unilateral lump kidney** – two kidneys completely fused forming lump on one side;
- **L-shaped kidney** – ectopic kidney lies inferiorly and transversely;
- **Unilateral disc kidney** – kidneys fused along the medial concave border;
- **Inferior ectopia** - ectopic kidney crosses the midline and lies inferior to the orthotopic kidney with fusion of the poles.

Blood supply to the ectopic kidney most frequently arises from the vessels on the ipsilateral side but occasionally arises from the contralateral side. [47]

Cross fused renal ectopia is typically asymptomatic and is diagnosed as an incidental finding when the patient is examined for other medical diseases. Complications are nephrolithiasis, ureteropelvic junction obstruction, hydronephrosis, reflux, ectopic ureteroceles and tumors.

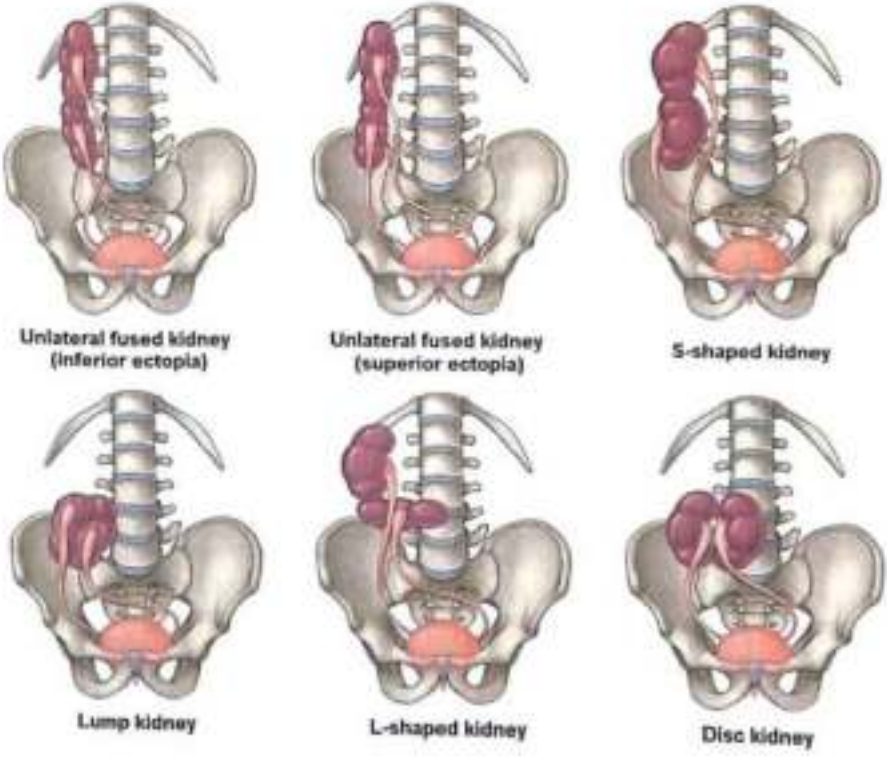

Fig. 42 - Renal anomalies

(Illustration from https://clinicalgate.com/wp-content/uploads/2015/03/B9780443066849500823_gr2.jpg)

On imaging, diagnosis of crossed renal ectopia may be suggested from abdominal radiograph if one renal outline is not visualised and the opposite renal outline is enlarged or when stones are seen at unusual positions.

Excretory urography shows the absence of a kidney in its normal position with evidence of two kidneys on the same side of the abdomen vertically oriented one above the other. Ultrasound can determine if the kidney is in its normal renal fossa.

The presence of the two kidneys on one side and the absence of a kidney in the contralateral side are suggestive of crossed ectopia

Anomalies of the size

Renal hypoplasia. Renal hypoplasia is a common, yet poorly understood and misused term describing congenital renal anomalies. Renal hypoplasia is defined as abnormally small kidneys (<2 SD below the expected mean when correlated with age or parameters of somatic growth) with normal morphology and reduced nephron number.

This definition predicts that ~2.2% of the population exhibit renal hypoplasia, whereas epidemiologic studies suggest an estimated incidence of 1 in 400 births.

Renal dysplasia is an aberrant developmental disease usually diagnosed during the perinatal and childhood years. Prevalence is estimated at 0.1% of infants (via ultrasound screening) and 4% of fetuses and infants (via autopsy study). Occurrences may be combined with abnormalities in the collecting system or associated with complex syndromes. Histopathology shows primitive tubules surrounded by a fibromuscular collar.

It is important to differentiate hypoplastic kidneys from dysplastic kidneys. On imaging, a hypoplastic kidney is small but otherwise normal whereas a dysplastic kidney is also small but it is poorly defined with presence of cortical cysts.

Anomalies of structure

Congenital cystic renal disease. The Potter classification of renal cystic diseases has been replaced by a classification based on the genetic or nongenetic origin of the renal cystic diseases. Genetic diseases include classic diseases such as autosomal recessive (ARPKD) and dominant (ADPKD) polycystic kidney diseases and more recently recognized diseases, such as glomerulocystic kidney disease (GCKD), medullary cystic dysplasia associated with syndromes, and nephronophthisis–medullary cystic dysplasia complex. The Potter classification of renal cystic disease separates cystic kidneys into the following four types: type 1, so-called infantile polycystic kidney disease (ARPKD in the genetic-nongenetic classification); type 2, cystic dysplastic kidney disease (multicystic dysplastic kidney disease [MCDK] in the genetic-nongenetic classification); type 3, adult polycystic kidney disease (ADPKD); and type 4, partial or intermittent

urinary outflow obstruction (obstructive dysplasia).

Among the nongenetic cystic diseases, obstructive dysplasia and MCDK are the most common. Obstructive dysplasia is associated with urinary tract dilatation and various congenital uropathies. MCDK results from an early defect in the connection between the ureteral bud and blastema. The result is a nonfunctioning kidney. Some cases of MCDK are genetically transmitted (discussed later). The differential diagnosis of obstructive dysplasia and MCDK includes complex renal cysts and cystic tumors.

Autosomal recessive polycystic kidney disease (ARPKD). This condition is inherited in an autosomal recessive pattern, giving a 25% recurrence risk for parents having subsequent children. The kidneys are affected bilaterally, so that in utero, there is typically oligohydramnios because of poor renal function and failure to form significant amounts of fetal urine. The most significant result from oligohydramnios is pulmonary hypoplasia, so that newborns do not have sufficient lung capacity to survive, irrespective of any attempt to treat renal failure. Grossly, the kidneys are markedly enlarged and tend to fill the retroperitoneum and displace abdominal contents. The kidneys tend to be symmetrically enlarged. The cysts are quite small and uniform, perhaps 1 to 2 mm on average. Microscopically, the characteristic finding in the later third trimester is cystic change with the cysts elongated and radially arranged. The few remaining glomeruli are not involved by the cysts, and the intervening parenchyma is not increased. In the second trimester, the cysts may not be as well-developed.

Multicystic renal dysplasia. This condition has a sporadic inheritance pattern. It is perhaps the most common form of inherited cystic renal disease. It results from abnormal differentiation of the metanephric parenchyma during embryologic development of the kidney. However, in many cases it can be unilateral, so the affected person survives, because one kidney is more than sufficient to sustain life. In fact, with absence of one functional kidney from birth, the other kidney undergoes compensatory hyperplasia and may reach a size similar to the combined weight of two kidneys (400 to 500 gm). Multicystic renal dysplasia was termed "Type II" in the Potter classification. There are two main subgroups. If the affected kidney is large, then it is termed "Type IIa". If the affected kidney is quite small, it can be termed "hypodysplasia" or "Type IIb". Different combinations are possible, so that only one kidney or part of one kidney can be affected and be either larger or small; both affected kidneys can be large or both can be small, or one can be larger and the other small. It is quite common for asymmetry to be present.

Grossly, the cysts are variably sized, from 1 mm to 1 cm in size, and filled with clear fluid. There are few recognizable glomeruli and tubules microscopically, and the remaining glomeruli are not affected by the cystic change. The hallmark of renal dysplasia is the presence of "primitive ducts" lined by cuboidal to columnar

epithelium and surrounded by a collagenous stroma. This increased stroma may contain small islands of cartilage. The liver will not show congenital hepatic fibrosis. [47]

Multicystic renal dysplasia is often the only finding, but it may occur in combination with other anomalies and be part of a syndrome (e.g., Meckel-Gruber syndrome), in which case the recurrence risk will be defined by the syndrome. If this disease is bilateral, the problems associated with oligohydramnios are present, with pulmonary hypoplasia the rate limiting step for survival.

Autosomal dominant polycystic kidney disease (ADPKD). This condition is inherited in an autosomal dominant pattern, so the recurrence risk in affected families is 50% (Fig. 43).

Fig. 43 - Autosomal dominant kidney disease

(illustration from https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcO-1C3BIoN-...)

It is one of the most common genetic diseases, with an incidence of 1:400 to 1:1000 persons. However, this disease rarely manifests itself before middle age. It may begin in middle aged to older adults to cause progressive renal failure as the cysts become larger and the functioning renal parencyma smaller in volume. This form of cystic disease is rarely manifested prenatally or in children.

ADPKD has been linked with defects in the PKD1 gene, encoding for polycystin-1, and the PKD2 gene, encoding for polycystin-2. The former is more common. The polycystins function in Ca2+ channels and disruption of normal intracellular Ca2+ homeostasis may underlie cyst formation. There are many alleles, explaining variations in onset and severity of ADPKD.

Grossly, ADPKD results in very large kidneys, perhaps up to 3 or 4 kg or more. The affected kidneys are just a mass of large fluid-filled cysts. There is often hemorrhage into the cysts, so that some can be filled with grumous brown organizing hemorrhage. There may be intervening normal renal parenchyma earlier in the disease, or just fibrotic stroma late in the course. If ADPKD is manifested in fetuses and infants, the cysts may involve the gomeruli (so-called "glomerular cysts"). In adults, it is common for all or part of the liver to also demonstrate polycystic disease, and it is possible in some cases for the liver to be more severely affected, so that hepatic failure results. Patients with ADPKD are also prone to have berry aneurysms of the cerebral arteries.

Cystic change with obstruction. In the fetus and newborn with urinary tract obstruction, it is possible for cystic change to occur in the kidneys, in addition to hydroureter, hydronephrosis, and bladder dilation. Depending upon the point of obstruction, either or both kidneys may be involved. For example, posterior urethral valves in a male fetus, or urethral atresia in a male or female fetus, will cause bladder outlet obstruction so that both kidneys are involved. With bladder outlet obstruction, there will be oligohydramnios and the appearance of pulmonary hypoplasia.

Grossly, this form of cystic disease may not be apparent. The cysts may be no more than 1 mm in size. Microscopically, the cysts form in association with the more sensitive developing glomeruli in the nephrogenic zone so that the cysts tend to be in a cortical location. Thus, "cortical microcysts" are the hallmark of this form of cystic disease, which is "Type IV" in the Potter's classification. There are no accompanying cystic changes in other organs in association with this disease. However, if the obstruction is at the bladder outlet, oligohydramnios with pulmonary hypoplasia can result.

Miscellaneous cystic renal changes in adults. Perhaps the most common cystic change of all is the appearance of one or more "simple renal cysts" in adults. These cysts may be only a few millimeters in size, or may reach 10 cm or more. They are rarely numerous enough so that intervening normal parenchyma is not recognizable, and they are very unlikely to be the cause for renal failure. These cysts are lined by a flattened cuboidal epithelium and filled with clear fluid. On occasion, there may be hemorrhage into a larger cyst, and it may appear as a mass lesion that can be difficult to differentiate from a renal cell carcinoma (which may undergo necrosis with hemorrhage). However, the finding of clear cells in the cyst is consistent with renal cell carcinoma.

Persons with renal failure who are on long-term dialysis may develop cystic changes in the kidneys. These cysts may be numerous, but never as large as with DPKD, and the kidneys are still generally small, because most diseases leading to renal failure produce small, shrunken kidneys with end-stage renal disease.

Medullary sponge kidney (MSK) is a congenital condition that most often occurs sporadically, without a defined inheritance pattern. It is often bilateral, but incidental and found only on radiologic imaging studies, with an incidence of 0.5 to 1% in adults. MSK may become symptomatic in young adults, with onset of recurrent hematuria and/or urinary tract infection as a consequence of formation of calculi, which develop in 60% of cases. Renal failure is unlikely to occur, but may result from severe pyelonephritis.

11.2 Anomalies of ureter

Congenital anomalies of ureter are:

- Megaureter (primary, secondary);
- Ureterocele;
- Duplex systems;
- Retrocaval ureter;
- Vesicoureteral reflux;
- Ectopic ureter.

Megaureter (Fig. 44) is defined as presence of an enlarged ureter with or without concomitant dilatation of the upper collecting system. A ureteric diameter of 7 mm or more should be considered a megaureter.

There are two types of this pathology: primary and secondary.

Primary megaureter includes all cases of megaureter due to an idiopathic congenital alteration at the vesicoureteral junction.

There are three subtypes - obstructed primary megaureter, refluxing primary megaureter, and nonrefluxing unobstructed primary megaureter.

In obstructed primary megaureter, there is dilatation above a short (0.5 - 4 cm), aperistaltic, normal-caliber juxtavesical section of a normally inserted ureter.

Refluxing primary megaureter is caused by a short or absent intravesical ureter, congenital paraureteric diverticulum, or other derangement of the vesicoureteral junction.

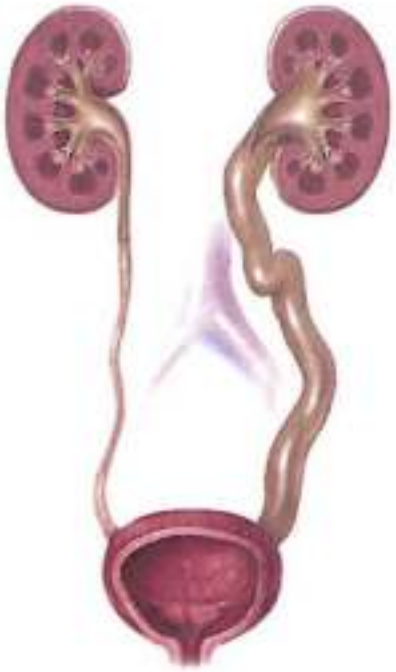

Fig. 44 - Megaureter
(illustration from https://www.urologyhealth.org/Images/Conditions/Megaureter/M-1.jpg)

Secondary megaureter occurs as a result of some abnormality involving the bladder or urethra (eg, urethral valves, neuropathic bladder dysfunction, urethral strictures, ureteroceles, and acquired causes of obstruction).

On imaging, first voiding cystourethrography is performed to exclude vesicoureteral reflux. In obstructed primary megaureter, it is not revealed. Ultrasound shows hydronephrosis and ureteral dilatation above the persistently narrowed distal aperistaltic segment. Real-time

ultrasound reveals active peristaltic waves passing to and fro in the dilated ureter above the narrowed segment and disproportionate dilatation of the lower ureter relative to the upper ureter and renal pelvis.

Ureterocele (Fig. 45). A ureterocele is a cystic out-pouching of the distal ureter into the urinary bladder. It is one of the more challenging urologic anomalies facing pediatric and adult urologists. Ureteroceles may pose a diagnostic and therapeutic dilemma with perplexing clinical symptoms resulting from a spectrum of abnormal embryogenesis associate with anomalous development from the intravesical ureter, the kidney, and the collecting system.

Ureteroceles may be asymptomatic or may produce a wide range of clinical signs and symptoms, from recurrent cystitis to bladder outlet obstruction to renal failure. Because of the obstructive nature of ureteroceles, the activity of the affected renal unit varies from a normal, well-functioning kidney to a nonfunctioning, dysplastic renal segment or kidney. However, with proper diagnosis and treatment, the outcome remains excellent.

The following are the different types of ureteroceles classified by their association with the renal unit:

- **Single-system ureteroceles** are those associated with a single kidney, collecting system, and ureter;
- **Duplex-system ureteroceles** are associated with kidneys that have completely duplicated ureters;
- **Orthotopic (intravesical) ureterocele** is a term used for a ureterocele contained within the bladder. An orthotopic ureterocele may prolapse into and beyond the bladder neck, but the origin of the walls of an orthotopic ureterocele are contained within the bladder. The orthotopic ureterocele usually arises from a single renal unit with one collecting system and is more commonly diagnosed in adults;
- **Ectopic (extravesical) ureterocele** refers to ureteroceles with tissue that originates at the bladder neck or beyond, into the urethra. They typically arise from the upper pole moiety of a duplicated collecting system and are more common in the pediatric population.

Retrocaval or circumcaval ureter results from anomalous development of the infra-renal portion of inferior vena cava (IVC) and not from anomalous development of the ureter.

There is anomalous development of the infrarenal IVC from the right posterior cardinal vein that is embryologically more medial.

- In type 2 there is mild hydronephrosis and less medial deviation of the ureter.

Fig. 45 - Ureterocele

(Illustration from http://radiologyassets.com/UPTODATE/contents/images/lb/16172.myrtf?title=Ureterocele+hydronephrosis)

Classically, the ureter crosses posterior to the IVC and then travel medially and anteriorly to partially circumscribe the IVC.

There are two types:

- Type 1, the more common form, has severe or moderate hydronephrosis with extreme medial deviation of the middle ureteral segment, usually medial to the pedicle or across the midline at the L3 level resulting in "S" or "fish hook" deformity at the point of obstruction;

The ureter is noted to be sickle shaped at the level of obstruction. On imaging, IVU shows characteristic reverse - J appearance due to medial deviation of the ureters with moderate proximal hydroureteronephrosis.

Vesicoureteral reflux (VUR) is characterized by the retrograde flow of urine from the bladder to the kidneys. VUR may be associated with urinary tract infection (UTI), hydronephrosis, and abnormal kidney development (renal dysplasia). [47]

Early diagnosis and vigilant monitoring of VUR are the cornerstones of management. Voiding

cystourethrography (VCUG) or radionuclear cystourethrography (RNC) is used to confirm the diagnosis of VUR. A dimercaptosuccinic acid (DMSA) renal scan is used to evaluate for any renal abnormalities. Until the reflux resolves or the reflux is surgically treated, the patient should undergo monitoring with cystography (RNC or VCUG) every 12-24 months. Serial ultrasonography can also be performed to evaluate renal growth, especially in patients with a history of renal abnormalities such as size discrepancy or hydronephrosis. Prophylactic antibiotics are prescribed to reduce the risk of bacterial infection of the bladder while reflux is present. Bladder management to ensure good lower urinary tract hygiene should be considered in children who have undergone toilet training.

The International Reflux Grading system classifies VUR into 5 grades, depending on the degree of retrograde filling and dilatation of the renal collecting system. This system is based on the radiographic appearance of the renal pelvis and calyces on a voiding cystogram, as follows (Fig. 46):

- Grade I: Urine backs up into the ureter only, and the renal pelvis appears healthy, with sharp calyces;
- Grade II: Urine backs up into the ureter, renal pelvis, and calyces. The renal pelvis appears healthy and has sharp calyces;
- Grade III: Urine backs up into the ureter and collecting system. The ureter and pelvis appear mildly dilated, and the calyces are mildly blunted;
- Grade IV: Urine backs up into the ureter and collecting system. The ureter and pelvis appear moderately dilated, and the calyces are moderately blunted;
- Grade V: Urine backs up into the ureter and collecting system. The pelvis is severely dilated, the ureter appears tortuous, and the calyces are severely blunted.

Ectopic ureter. An ectopic ureter is a congenital renal anomaly that occurs as a result of abnormal caudal migration of the ureteral bud during its insertion to the urinary bladder.

Normally the ureter drains via the internal ureteral orifice at the trigone of the urinary bladder.

In females, the most common site for ureter insertion is bladder neck and upper urethra (33%), vaginal vestibule between the urethra and introitus (33%), vagina (25%), and cervix and uterus (<5%).

In males, the ureter may insert into the lower urinary bladder, posterior urethra, seminal vesicle,

ductus deferens, ejaculatory duct and rarely the rectum.

In complete ureteral duplication with each segment having its own ureteral orifice in the bladder, the Weigert-Meyer rule applies.

In these cases, the ureter draining the upper pole moiety frequently ends in an ureterocele, whereas reflux into the lower moiety typically occurs.

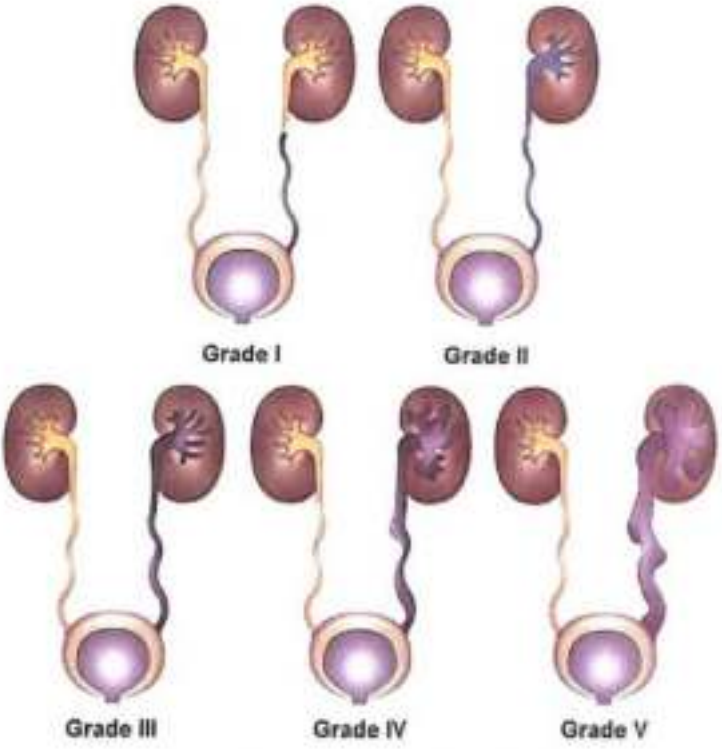

Fig. 46 - 5 grades of vesicoureteral reflux
(illustration from https://www.kidneyfit.com/wp-content/uploads/2012/07/Vesicoureteral-reflux-Picture.jpg)

11.3 Anomalies of urinary bladder

The most common anomalies of bladder are:

- Anomalies of urachus;
- Bladder agenesis (rare anomaly);
- Bladder duplication (rare anomaly);
- Congenital diverticulum of a bladder;
- Bladder exstrophy;

- Congenital contracture of bladder's neck.

The urachus is located behind the abdominal wall and anterior to the peritoneum in the space of Retzius.

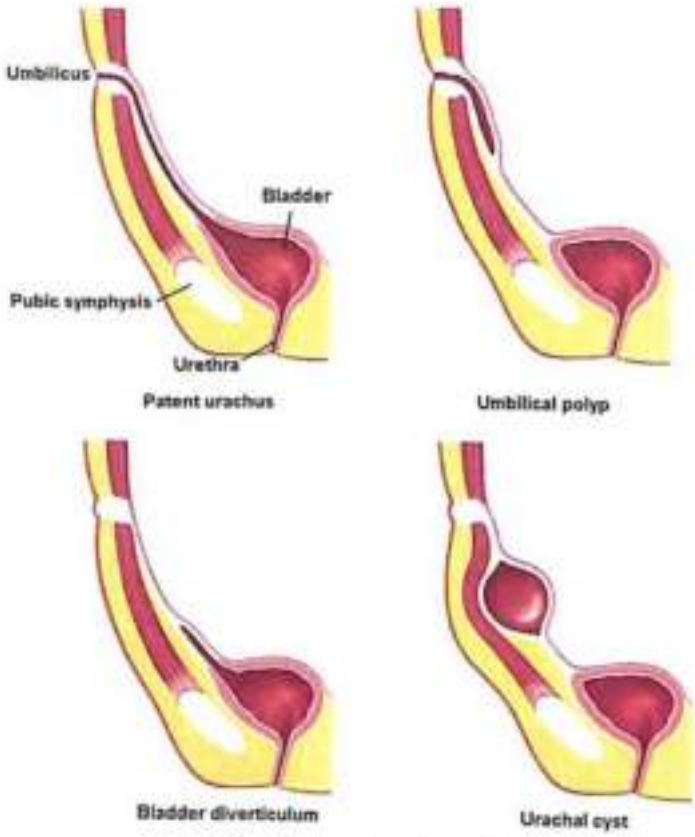

Fig. 47 - Anomalies of urachus
(Illustration from http://meddinfo.pcu.ac.th/pe/MedBoard/Img/20100321111617.jpg)

Anomalies of urachus (Fig. 47). The urachus develops from the superior portion of the urogenital sinus and connects the dome of the bladder to the allantoic duct during fetal life.

Before birth, the urachus is obliterated and becomes a vestigial structure known as the medial umbilical ligament.

In the absence of complete obliteration, the urachus persists as

either a patent urachus, urachal cyst, urachal sinus, or urachal diverticulum.

A persistent urachus frequently coexists with congenital lower urinary tract obstruction such as posterior urethral valves or prune-belly syndrome. It may also coexist with ventral abdominal wall defects such as omphalocele. Although adenocarcinoma of the urachus is rare, it has been reported in patients as young as 15 years of age. Patent urachus represents the failure of the entire course of the urachus to close, resulting in an open channel between the bladder and the umbilicus.

A patent urachus is usually diagnosed in the neonate when urine is noted leaking from the umbilicus.

This anomaly is demonstrated by retrograde injection of contrast material into the orifice of the channel at the umbilical end or during VCUG in the lateral projection. A patent urachus manifests at longitudinal US as a tubular connection between the anterosuperior aspect of the bladder and the umbilicus. Patency is better assessed with a linear high-frequency transducer due to the superficial location of the urachus. Occasionally, patency of the urachus can be demonstrated at CT. [47]

Bladder diverticulum. Congenital bladder diverticula that are not associated with posterior urethral valves or neuropathic bladder are unusual but not rare and occur almost exclusively in boys. Bladder diverticulum can be unilateral or bilateral and are caused by congenital bladder muscular anomalies.

A diverticulum that occurs at the ureterovesicular junction is usually called periureteric diverticulum, classically known as Hutch diverticulum, and is often associated with VUR. This is because the presence of the diverticulum alters the normal slanted insertion of the ureter into the bladder.

In male infants, bladder diverticula must be distinguished from protrusions of the urinary bladder bilaterally into the inguinal rings anteriorly.

These outpouchings, known as "bladder ears" are transient and usually disappear with age. Lateral VCUG usually helps differentiate between the two conditions. Most bladder diverticula are diagnosed during evaluation for urinary tract infection, incontinence, or urine retention. Diverticula are easy to diagnose at VCUG. At US, diverticula appear as round or oval anechoic fluid collections that arise from the base of the bladder or around the ureteric orifice.

Bladder exstrophy (also known as **ectopia vesicae**) (Fig. 48) refers to a herniation of the urinary bladder through an anterior abdominal wall defect. The severity of these defects is widely variable.

Bladder exstrophy is thought to be caused by a developmental defect of the cloacal membrane which results in a subsequent eversion of the bladder mucosa. This then protrudes out as a mass-like lesion.

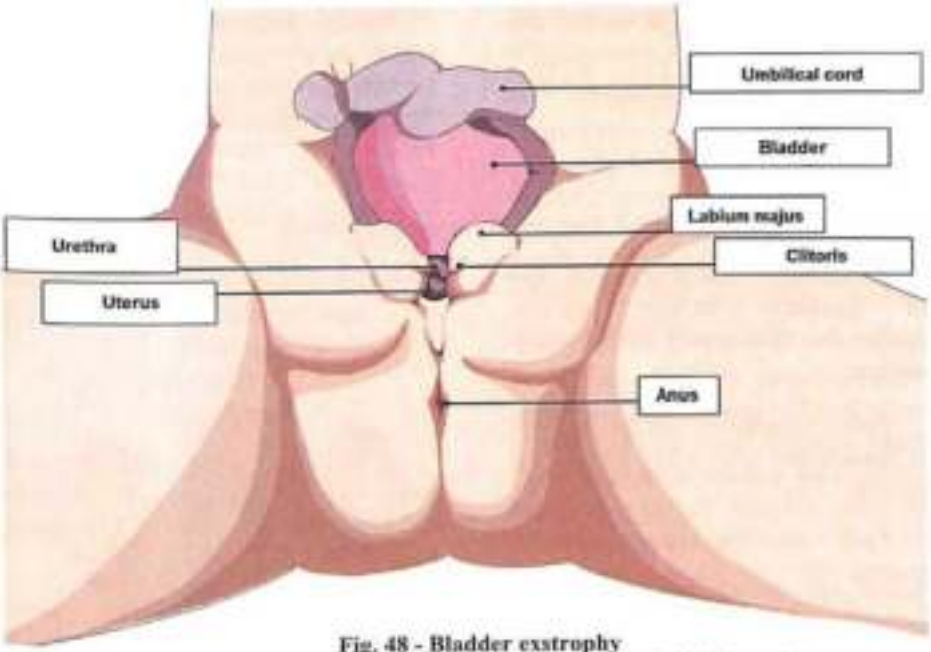

Fig. 48 - Bladder exstrophy

Illustration from http://www.childrenshospital.org/~/media/centers-and-services/programs/b_c/bladder-exstrophy-care-and-support-group/urs_14980_bladderexstrophy_girls.ashx?la=en

Modern therapy is aimed at surgical reconstruction of the bladder and genitalia. Both males and females are born with this anomaly. Treatment is similar. In males treatments have been: In the modern staged repair of exstrophy (MSRE) the initial step is closure of the abdominal wall, often requiring a pelvic osteotomy.

This leaves the patient with penile epispadias and urinary incontinence. At approximately 2–3 years of age the patient then undergoes repair of the epispadias after testosterone stimulation. Finally, bladder neck repair usually occurs around the age of 4–5 years, though this is dependent upon a bladder with adequate capacity and, most importantly, an indication that the child is interested in becoming continent. In the complete primary repair of exstrophy (CPRE) the bladder closure is combined with an epispadias repair, in an effort to decrease costs and morbidity. This technique has, however, led to significant loss of penile and corporal tissue, particularly in younger patients.

In females treatment has included:

- Surgical reconstruction of the clitoris which is separated into two distinct bodies;
- Surgical reconstruction to correct the split of the mons, redefine the structure of the bladder neck and urethra;

- Vaginoplasty will correct the anteriorly displaced vagina;
- If the anus is involved, it is also repaired.

Fertility remains and women who were born with bladder extrophy usually develop prolapse due to the weaker muscles of the pelvic floor.

11.4 Anomalies of male urethra

Congenital anomalies of the male urethra include various anomalies due to complex development of urethra.

These anomalies can be isolated or in association with other coexisting anomalies.

They can be categorised as following:

- Congenital valves:
  - Posterior urethral valve;
  - Anterior urethral valve;
- Diverticula and outpouchings:
  - Anterior urethral diverticulum;
  - Lacuna magna (sinus of Guérin);
  - Cowper's gland syringocele;
  - Enlarged prostatic utricle;
- Urethral dilatation:
  - Megalourethra;
  - Prune-belly syndrome - associated with dilated prostatic urethra;
- Congenital urethral stricture;
- Urethral duplication;
- Congenital urethral polyps;
- Congenital fistulas:
  - Congenital urethroperineal fistula;
  - Fistulas associated with anorectal malformation;
- Abnormal external opening(malformations of the urethral groove):
  - Hypospadias;
  - Epispadias.

In this part we will consider the most widespread anomalies of urethra (posterior urethral valves, hypospadias and epispadias).

Posterior urethral valves (PUVs), also referred as **congenital obstructing posterior urethral membranes (COPUM)**, are the most common congenital obstructive lesion of the urethra and a common cause of obstructive uropathy in infancy. Posterior urethral valves are congenital and only seen in male infants (Fig. 49).

Clinical presentation depends on the severity of obstruction. In severe obstruction, the diagnosis is usually made antenatally.

The fetus will be small for gestational age and ultrasound examination will demonstrate oligohydramnios. In less severe cases, the diagnosis is often not apparent until early infancy. Urinary tract infections are common in this group.

Antenatal treatment is possible, consisting of vesicoamniotic shunting (allowing urine to exit the bladder via the shunt, bypassing the obstructed

urethra). Essentially this procedure consists of a supra-pubic catheter performed under ultrasound guidance. The efficacy of this procedure is controversial, as often despite this significant renal and pulmonary morbidity exist.Postnatally, definitive treatment is simple and involves transurethral ablation of the offending valve.

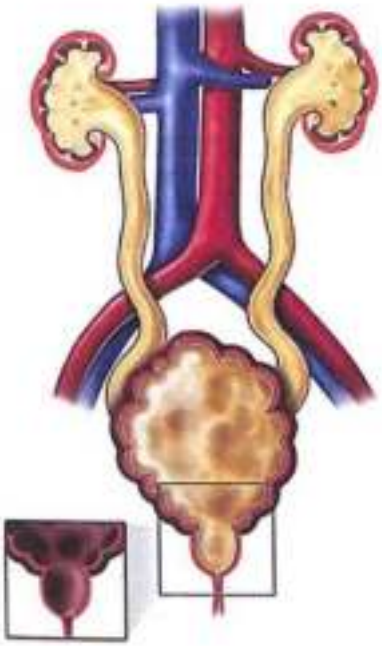

Fig. 49 - Posterior urethral valves
(Illustration from
http://www.chop.edu/sites/default/files/styles/1x_9_large/public/posterior-urethral-valves-illustration.png?itok=FkMdPTRm)

The overall prognosis is most affected by the degree and duration of obstruction. Severe cases with obstructive cystic renal dysplasia, oligohydramnios and pulmonary hypoplasia are often incompatible with life.

Hypospadias. Hypospadias is an abnormality of anterior urethral and penile development in which the urethral opening is ectopically located on the ventral aspect of the penis proximal to the tip of the glans penis, which, in this condition, is splayed open (Fig. 50).

The urethral opening may be located as far down as in the scrotum or perineum. The penis is more likely to have associated ventral shortening and curvature, called chordee, with more proximal urethral defects.

The location of the abnormal urethral meatus classifies the hypospadias. Although several different classifications have been described, most physicians use the one proposed by Barcat and modified by Duckett, which describes the location of the meatus after correction of any associated chordee.

Descriptive locations described include the following:

- Anterior (glanular and subcoronal);
- Middle (distal penile, midshaft, and proximal penile);
- Posterior (penoscrotal, scrotal, and perineal).

Surgery is usually recommended for hypospadias, with the goal to restore normal appearance and function to the penis. A urinary opening that is not surrounded by glans tissue is more likely to "spray" the urine, which can cause a man to sit to urinate because he

cannot reliably stand and hit the toilet. Downward curvature of the penis can impair sexual activity as an adult.

Surgery extends the urinary channel to the end of the penis, straightens bending, and corrects the foreskin abnormality by either circumcision or by repairing it to look normal ("prepucioplasty"), depending on the desire of care-givers.

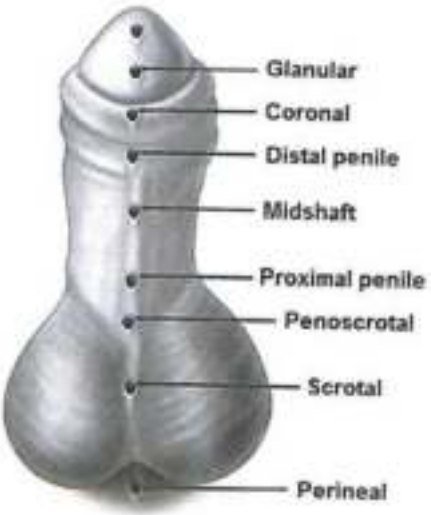

Fig. 50 - Forms of hypospadias
(illustration from http://www.chop.edu/sites/default/files/hypospadias-illustration-773px.jpeg)

When the hypospadias is third degree (penoscrotal), or has associated birth defects such as chordee or cryptorchidism, the best management can be a more complicated decision. A karyotype and endocrine evaluation should be performed to detect intersex conditions or hormone deficiencies. If the penis is small, testosterone or human chorionic gonadotropin (hCG) injections may be given to enlarge it before surgery.

Surgical repair of severe hypospadias may require multiple procedures and mucosal grafting. Preputial skin is often used for grafting and circumcision should be avoided before repair. In a minority of patients with severe hypospadias, surgery produces unsatisfactory results, such as scarring, curvature, or formation of urethral fistulas, diverticula, or strictures. A fistula is an unwanted opening through the skin along the course of the urethra, and can result in urinary leakage or an abnormal stream. A diverticulum is an "outpocketing" of the lining of the urethra which interferes with urinary flow and may result in posturination leakage. A stricture is a narrowing of the urethra severe enough to obstruct flow. Reduced complication rates even for third-degree repair (e.g., fistula rates below 5%) have been reported in recent years from centers with the most experience, and surgical repair is now performed for the vast majority of infants with hypospadias.

Epispadias. Epispadias is a rare congenital malformation of the male or female urogenital apparatus that consists of a defect of the dorsal wall of the urethra (Fig. 51). The extent of the defect can vary from a mild glandular defect to complete defects as are observed in bladder exstrophy, diastasis of the pubic bones, or both.

Simple epispadias occurs less commonly than the more severe form

associated with exstrophy of the bladder.

Epispadias is an uncommon and partial form of a spectrum of failures of abdominal and pelvic fusion in the first months of embryogenesis known as the exstrophy - epispadias complex. While epispadias is inherent in all cases of exstrophy it can also, much less frequently, appear in isolation as the least severe form of the complex spectrum. It occurs as a result of defective migration of the genital tubercle primordii to the cloacal membrane, and so malformation of the genital tubercle, at about the 5th week of gestation.

glandular, penile, or complete (ie, penopubic).

With the glandular type, the malformation affects the distal part of the urethra. With the penile type, the entire penile urethra is affected, with an external meatus on the dorsal shaft of the penis.

With the complete or penopubic type, a total deficiency of the dorsal wall of the urethra and the anterior wall of the bladder is present. The glans is often spatulated, and the prepuce is clefted dorsally with ventral transposition. [52]

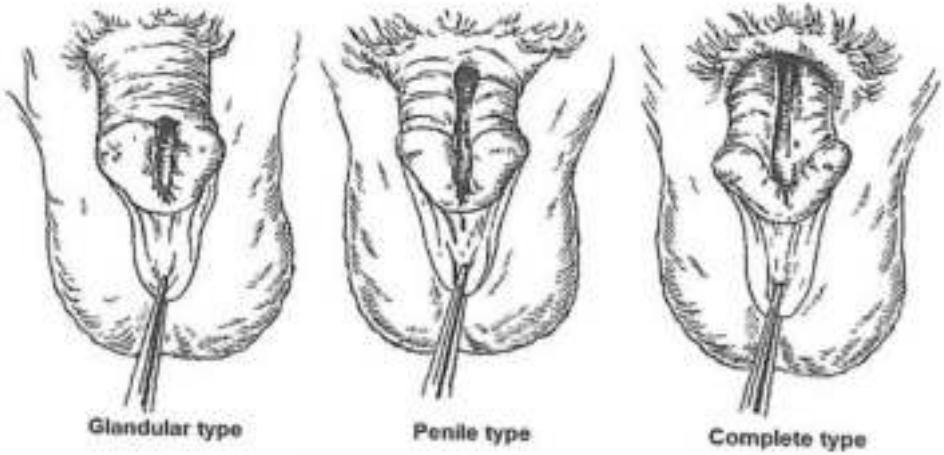

Fig. 51 - Forms of epispadias
(Illustration from https://lh3.googleusercontent.com/JS_xxN2qVIFOyVERaZ93LqdSqvaOzqbmyDc9HDd4Nc-z5cMdtpNPpS-_6N7gbrwE421NTw=s417)

Epispadias vary in severity according to the time of the pathognomic insult during embryologic development and can be classified as

All forms of epispadias are associated with chordee. The extent of chordee varies.

In females, epispadias consists of bifid clitoris with diastases of the corpora cavernosa, flattening of the mons, and separation of the labia.

Associated defects are usually limited to the genital tract and diastases of the pubic bones. In exstrophy of the bladder, the lower abdominal wall is absent, with diastasis of the rectus abdominis muscle. Reflux develops in approximately 40% of patients.

The main treatment for isolated epispadias is a comprehensive surgical repair of the genito-urinary area usually during the first 7 years of life, including reconstruction of the urethra, closure of the penile shaft and mobilisation of the corpora. The most popular and successful technique is known as the modified Cantwell-Ransley approach. In recent decades however increasing success has been achieved with the complete penile disassembly technique despite its association with greater and more serious risk of damage.

11.5 Anomalies of testicles

The most common testicular anomalies are cryptorchidism, anorchia and monorchidism.

Cryptorchidism (Fig. 52) is the most common abnormality of male sexual development.

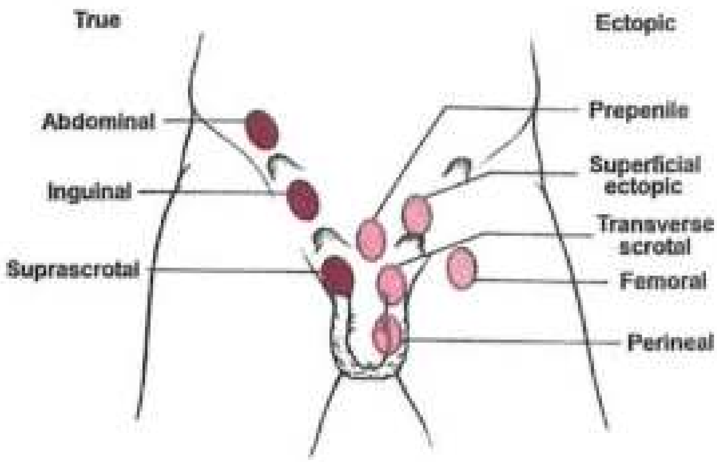

Fig. 52 - Types of cryptorchidism

(illustration from http://tophealthnews.net/wp-content/uploads/2017/02/Cryptorchidism-The-Origin-the-Cure.jpg)

In this condition, the testis is not located in the scrotum. It can be ectopic, incompletely descended, retractile, and absent or atrophic.

The most common diagnostic dilemma in otherwise normal boys is distinguishing a retractile testis from a testis that will not descend spontaneously into the scrotum.

Retractile testes are more common than truly undescended testes and do not need to be operated on.

In normal males, as the cremaster muscle relaxes or contracts, the testis moves lower or higher ("retracts") in the scrotum.

This cremasteric reflex is much more active in infant boys than older men. A retractile testis high in the scrotum can be difficult to distinguish from a position in the lower inguinal canal. Though there are various maneuvers used to do so, such as using a cross-legged position, soaping the examiner's fingers, or examining in a warm bath, the benefit of surgery in these cases can be a matter of clinical judgment.

In the minority of cases with bilaterally non-palpable testes, further testing to locate the testes, assess their function, and exclude additional problems is often useful.

Pelvic ultrasound or magnetic resonance imaging performed and interpreted by a radiologist can often, but not invariably, locate the testes while confirming absence of a uterus.

A karyotype can confirm or exclude forms of dysgenetic primary hypogonadism, such as Klinefelter syndrome or mixed gonadal dysgenesis.

Hormone levels (especially gonadotropins and AMH) can help confirm that there are hormonally functional testes worth attempting to rescue, as can stimulation with a few injections of human chorionic gonadotropin to elicit a rise of the testosterone level.

Occasionally these tests reveal an unsuspected and more complicated intersex condition.

In the even smaller minority of cryptorchid infants who have other obvious birth defects of the genitalia, further testing is crucial and has a high likelihood of detecting an intersex condition or other anatomic anomalies. Ambiguity can indicate either impaired androgen synthesis or reduced sensitivity. The presence of a uterus by pelvic ultrasound suggests either persistent Müllerian duct syndrome (AMH deficiency or insensitivity) or a severely virilized genetic female with congenital adrenal hyperplasia. An unambiguous micropenis, especially accompanied by hypoglycemia or jaundice, suggests congenital hypopituitarism.

The primary management of cryptorchidism is watchful waiting, due to the high likelihood of self-resolution. Where this fails, a surgery, called orchiopexy, is effective if inguinal testes have not descended after 4–6 months. Surgery is often performed by

a pediatric urologist or pediatric surgeon, but in many communities still by a general urologist or surgeon.

When the undescended testis is in the inguinal canal, hormonal therapy is sometimes attempted and very occasionally successful. The most commonly used hormone therapy is human chorionic gonadotropin (HCG). A series of hCG injections (10 injections over 5 weeks is common) is given and the status of the testis/testes is reassessed at the end. [52]

In cases where the testes are identified preoperatively in the inguinal canal, orchiopexy is often performed as an outpatient and has a very low complication rate. An incision is made over the inguinal canal. The testis with accompanying cord structure and blood supply is exposed, partially separated from the surrounding tissues ("mobilized"), and brought into the scrotum. It is sutured to the scrotal tissue or enclosed in a "subdartos pouch." The associated passage back into the inguinal canal, an inguinal hernia, is closed to prevent re-ascent. In patients with intraabdominal maldescended testis, laparoscopy is useful to see for oneself the pelvic structures, position of the testis and decide upon surgery (single or staged procedure).

Surgery becomes more complicated if the blood supply is not ample and elastic enough to be stretched into the scrotum. In these cases, the supply may be divided, some vessels sacrificed with expectation of adequate collateral circulation. In the worst case, the testis must be "auto-transplanted" into the scrotum, with all connecting blood vessels cut and reconnected ("anastomosed").

When the testis is in the abdomen, the first stage of surgery is exploration to locate it, assess its viability, and determine the safest way to maintain or establish the blood supply. Multi-stage surgeries, or autotransplantation and anastomosis, are more often necessary in these situations. Just as often, intra-abdominal exploration discovers that the testis is non-existent ("vanished"), or dysplastic and not salvageable.

The principal major complication of all types of orchiopexy is a loss of the blood supply to the testis, resulting in loss of the testis due to ischemic atrophy or fibrosis.

Monorchism (also monorchidism) is the state of having only one testicle within the scrotum.

This can be due to:

- One testicle not descending into the scrotum during normal embryonic or fetal development (3–4% of 'normal' live births), also known as undescended testis or cryptorchidism. In this case the testis is within the abdominal cavity, somewhere along the normal route of descent – most commonly, within the inguinal canal. Such a testis has an increased risk of malignancy.
- One testicle may disappear during development (the so-called vanishing testis) due to some intrauterine insult. This is

thought to be most likely vascular, such as testicular torsion.

- One testicle may have been surgically removed through orchiectomy.
- One testicle may be injured.

Anorchia (or anorchism) is an XY disorder of sex development in which individuals have both testes absent at birth. Within a few weeks of fertilization, the embryo develops rudimentary gonads (testes), which produce hormones responsible for the development of the reproductive system. If the testes fail to develop within eight weeks, the baby will develop female genitalia (see Swyer syndrome). If the testes begin to develop but are lost or cease to function between eight and 10 weeks, the baby will have ambiguous genitalia when it is born. However, if the testes are lost after 14 weeks, the baby will have partial male genitalia with the notable absence of gonads.

Tests include observable lack of testes, low testosterone levels (typical female levels), elevated follicle stimulating hormone and luteinizing hormone levels, XY karyotype, ultrasound or magnetic resonance imaging showing absent gonadal tissue, low bone density, low anti-Müllerian hormone levels, and surgical exploration for evidence of male gonadal tissue.

Treatment includes androgen (testosterone) supplementation to artificially initiate puberty, testicular prosthetic implantation, and psychological support. Gender Dysphoria may result in anorchic individuals who are assigned male at birth and raised as male despite lacking the necessary masculinizing hormones during prenatal, childhood, and adolescent development. Anorchic individuals who have a female identity may be administered estrogen alone in place of testosterone as no androgen blockers are necessary due to the lack of gonads.

Urogenital anomalies

Anomaly (from Greek anomalia - a deviation, roughness) - the structural and/or functional deviation caused by violation of an embryonal development. Urogenital anomalies are widespread and are about 40% of all congenital defects. According to data of autopsy, about 10% of people have various anomalies of development of urogenital system.

Renal anomalies

Anomalies of quantity. Anomalies in number can be in the form of supernumerary kidneys or renal agenesis.

Anomalies in position. Anomalies in position include anomalies of rotation and location.

Anomalies of renal fusion. Renal fusion anomalies are classified into horseshoe, disc and unilateral fused kidney or crossed fused renal ectopia.

Anomalies of the size. Anomalies of the size include renal hypoplasia.

Anomalies of structure. Anomalies of structure include congenital cystic renal disease, autosomal recessive polycystic kidney disease (ARPKD), multicystic renal dysplasia, autosomal dominant polycystic kidney disease (ADPKD), cystic change with obstruction, miscellaneous cystic renal changes in adults.

Congenital anomalies of ureter are:

1. Megaureter (primary, secondary);
2. Ureterocele;
3. Duplex systems;
4. Retrocaval ureter;
5. Vesicoureteral reflux;
6. Ectopic ureter.

The most common **anomalies of bladder** are:

1. Anomalies of urachus;
2. Bladder agenesis (rare anomaly);
3. Bladder duplication (rare anomaly);
4. Congenital diverticulum of a bladder;
5. Bladder exstrophy;
6. Congenital contracture of bladder's neck.

Congenital anomalies of the male urethra include:

1. Congenital valves:

- Posterior urethral valve;
- Anterior urethral valve;

2. Diverticula and outpouchings:

- Anterior urethral diverticulum;
- Lacuna magna (sinus of Guérin);
- Cowper's gland syringocele;
- Enlarged prostatic utricle;

3. Urethral dilatation:

- Megalourethra;
- Prune-belly syndrome - associated with dilated prostatic urethra;
- Congenital urethral stricture;
- Urethral duplication;
- Congenital urethral polyps;

4. Congenital fistulas:

- Congenital urethroperineal fistula;
- Fistulas associated with anorectal malformation;

5. Abnormal external opening(malformations of the urethral groove):

- Hypospadias;
- Epispadias.

The most common **testicular anomalies** are cryptorchidism, anorchia and monorchidism.

Theme # 12: Urinary incontinence. Overactive bladder.

12. 1 Urinary incontinence

Urinary incontinence is defined by the International Continence Society as the involuntary loss of urine that represents a hygienic or social problem to the individual. Urinary incontinence can be thought of as a symptom as reported by the patient, as a sign that is demonstrable on examination, and as a disorder.

Urinary incontinence should not be thought of as a disease, because no specific etiology exists; most individual cases are likely multifactorial in nature. The etiologies of urinary incontinence are diverse and, in many cases, incompletely understood.

Patients with urinary incontinence should undergo a basic evaluation that includes a history, physical examination, and urinalysis. Additional information from a patient's voiding diary, cotton-swab test, cough stress test, measurement of postvoid residual (PVR) urine volume, cystoscopy, and urodynamic studies may be needed in selected patients.

Videourodynamic studies are reserved to evaluate complex cases of stress urinary incontinence. Videourodynamic studies combine the radiographic findings of a voiding cystourethrogram and multichannel urodynamics.

Types of urinary incontinence

Four types of urinary incontinence are defined in the Clinical Practice Guideline issued by the Agency for Health Care Policy and Research: stress, urge, mixed, and overflow. Some authors include functional incontinence as a fifth type of incontinence.

Stress incontinence is characterized by urine leakage associated with increased abdominal pressure from laughing, sneezing, coughing, climbing stairs, or other physical stressors on the abdominal cavity and, thus, the bladder.

Urge urinary incontinence is involuntary leakage accompanied by or immediately preceded by urgency.

Mixed urinary incontinence is a combination of stress and urge incontinence; it is marked by involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.

Functional incontinence is the inability to hold urine due to reasons other than neuro-urologic and lower urinary tract dysfunction.

Other terms describing urinary incontinence are as follows:

1. **Enuresis** – involuntary loss of urine;
2. **Nocturnal enuresis** - loss of urine occurring during sleep;
3. **Continuous urinary incontinence** - continuous leakage.

Successful treatment of urinary incontinence must be tailored to the specific type of incontinence and its cause. The usual approaches are as follows:

Stress incontinence – pelvic floor physiotherapy, anti-incontinence devices, and surgery;

Urge incontinence – changes in diet, behavioral modification, pelvic-floor exercises, and/or medications and new forms of surgical intervention;

Mixed incontinence – pelvic floor physical therapy, anticholinergic drugs, and surgery;

Overflow incontinence – catheterization regimen or diversion;

Functional incontinence – treatment of the underlying cause.

Historical context

Urinary incontinence in women is not a recent medical and social phenomenon, but the relative importance attributed to urinary incontinence as a medical problem is increasing. Several factors responsible for the increased attention to incontinence can be cited. [61, 62]

First, women are more willing to talk openly about this disorder. Women are realizing that, in most cases, urinary incontinence is a treatable condition. Consequently, less embarrassment and fewer social stigmas are associated with the diagnosis.

Second, as the population ages, incontinence becomes a more frequent concern. Urinary incontinence often is the chief reason for institutionalization of elderly people.

Third, interest in urinary incontinence disorders within the medical community is surging. This increased interest is arising among basic scientists, clinical researchers, and clinicians. The subspecialties of urogynecology and female urology are emerging, and structured fellowships are in the credentialing process. A Female Pelvic Medicine and Reconstructive Surgery fellowship is now accredited as a subspecialty by the American Board of Obstetrics and Gynecology (ABOG) and the American Board of Urology (ABU).

As a direct result of this increased interest, the public is becoming more aware of the problem and more active and educated about incontinence. Patient advocacy groups provide patients access to information, incontinence products, and physicians who have interest or special expertise in these disorders. In the last decade, funding opportunities for incontinence research have increased vastly. Subspecialty professional organizations and journals are now active.

Important contributions to the understanding of the structure and functioning of the lower urinary tract include an improved understanding of the anatomy and dynamic functioning of the pelvic floor and its contribution to continence. In addition, much study has been conducted to bolster the understanding of the neurophysiology of the bladder, urethra, and pelvic floor. Finally, interest in the diagnosis

and treatment of incontinence is ongoing.

An estimated 50-70% of women with urinary incontinence fail to seek medical evaluation and treatment because of social stigma. Only 5% of individuals who are incontinent and 2% of nursing home residents who are incontinent receive appropriate medical evaluation and treatment. Patients who are incontinent often cope with this condition for 6-9 years before seeking medical therapy.

In a 1997 survey of primary care physicians, about 40% reported that they sometimes, rarely, or never ask patients about incontinence. More than 40% of internists and family practitioners routinely recommended absorbent pads to their patients as a solution to incontinence disorders. Continued education of the public and medical professionals is needed to improve the care rendered to individuals with urinary incontinence.

In 1989, the National Institutes of Health Consensus Development Conference estimated the annual cost of urinary incontinence in the United States to be $12.4 billion. Some experts believe that this is a conservative estimate. True costs can be difficult to estimate because many individuals do not come to the attention of medical specialists.

A 2009 survey of women in a managed care population found that the prevalence of undiagnosed urinary incontinence was 53% in the preceding year. Some individuals pay out of pocket for adult incontinence undergarments, absorbable pads, skin care products, deodorants, and increased laundry expenses.

The psychosocial costs and morbidities are even more difficult to quantify. Embarrassment and depression are common. The affected individual may experience a decrease in social interactions, excursions out of the home, and sexual activity.

The psychosocial impact on at-home caregivers, spouses, or family members rarely is considered. Kelleher et al. developed a questionnaire to assess the quality of life of women with incontinence. This questionnaire has proven to be easy to use, valid, and reliable. This tool may be a valuable adjunct to pretherapy and posttherapy assessment, as well as valuable in comparing the quality of life impact of different urodynamic diagnoses.

Several other questionnaires are available for urge incontinence, stress incontinence, and quality of life. Many have been validated in many languages, presurgery and postsurgery. The questionnaires most often used are the Urinary Distress Inventory (UDI)–6, Incontinence Quality of Life (IQoL) Questionnaire, Incontinence Impact Questionnaire (IIQ)–7, UDI, Overactive Bladder Symptom and Health-Related Questionnaire (OAB-Q), and King's Health Questionnaire KHQ).

Pathophysiology

Micturition requires coordination of several physiological processes. Somatic and autonomic nerves carry bladder volume input to the spinal

cord, and motor output innervating the detrusor, sphincter, and bladder musculature is adjusted accordingly. The cerebral cortex exerts a predominantly inhibitory influence, whereas the brainstem facilitates urination by coordinating urethral sphincter relaxation and detrusor muscle contraction.

As the bladder fills, sympathetic tone contributes to closure of the bladder neck and relaxation of the dome of the bladder and inhibits parasympathetic tone. At the same time, somatic innervation maintains tone in the pelvic floor musculature as well as the striated periurethral muscles. [63]

When urination occurs, sympathetic and somatic tones in the bladder and periurethral muscles diminish, resulting in decreased urethral resistance. Cholinergic parasympathetic tone increases, resulting in bladder contraction. Urine flow results when bladder pressure exceeds urethral resistance. Normal bladder capacity is 300-500 mL, and the first urge to void generally occurs between bladder volumes of 150 and 300 mL.

Incontinence occurs when micturition physiology, functional toileting ability, or both have been disrupted. The underlying pathology varies among the different types of incontinence (ie, stress, urge, mixed, reflex, overflow, and functional incontinence).

Stress incontinence pathophysiology

During episodes of stress incontinence, an increase in intra-abdominal pressure (eg, from laughing, sneezing, coughing, climbing stairs) raises pressure within the bladder to the point where it exceeds the urethra's resistance to urinary flow. Leakage ceases when bladder pressure again falls below urethral pressure.

The major cause of stress incontinence is urethral hypermobility due to impaired support from pelvic floor. A less common cause is an intrinsic sphincter deficiency, usually secondary to pelvic surgeries. In either case, urethral sphincter function is impaired, resulting in urine loss at lower than usual abdominal pressures.

In women with stress urinary incontinence, either or both mechanisms may be present, although some authors hold that stress incontinence does not develop in patients with poor pelvic support unless intrinsic sphincter deficiency is also present. Intrinsic sphincter deficiency, resulting from loss of function of both the internal and the external sphincter mechanism, is the only cause of stress incontinence in males.

Urethral hypermobility is related to impaired neuromuscular functioning of the pelvic floor coupled with injury, both remote and ongoing, to the connective tissue supports of the urethra and bladder neck. When this occurs, the proximal urethra and the bladder neck descend to rotate away and out of the pelvis at times of increased intra-abdominal pressure.

Because the bladder neck and proximal urethra move out of the pelvis, more pressure is transmitted to the bladder. During this process, the posterior wall of the urethra shears off the anterior urethral wall to open the bladder neck when intrinsic sphincter deficiency is present.

In women without urethral hypermobility, the urethra is stabilized during stress by three interrelated mechanisms. One mechanism is reflex, or voluntary, closure of the pelvic floor. Contraction of the levator ani complex elevates the proximal urethra and bladder neck, tightens intact connective tissue supports, and elevates the perineal body, which may serve as a urethral backstop.

The second mechanism involves intact connective tissue support to the bladder neck and urethra. The pubocervicovesical or anterior endopelvic connective tissue in the area of the bladder neck is attached to the back of the pubic bone, the arcus tendineus fascia pelvis, and the perineal membrane. The pubourethral ligaments also suspend the middle portion of the urethra to the back of the pubic bone.

These connective-tissue components form the passive supports to the urethra and bladder neck. During times of increased intra-abdominal pressure, if these supports are intact, they augment the supportive effect of muscular closure of the pelvic floor.

The third mechanism involves 2 bundles of striated muscle, the urethrovaginal sphincter and the compressor urethrae, found at the distal aspect of the striated urethral sphincter. These muscles may aid in compressing the urethra shut during stress maneuvers. These muscles do not surround the urethra, as the striated sphincter does, but lie along the lateral and ventral aspects.

The exact function and importance of these muscles are controversial. Some authors suggest that the urethrovaginal sphincter and the compressor urethrae may provide compression and increased pressure in the distal urethra during times of stress.

Damage to the nerves, muscle, and connective tissue of the pelvic floor is important in the genesis of stress incontinence. Injury during childbirth probably is the most important mechanism. Aging, hypoestrogenism, chronic connective tissue strain due to primary loss of muscular support, activities or medical conditions resulting in long-term repetitive increases in intra-abdominal pressure, and other factors can contribute. [63]

During childbirth, 3 types of lesions can occur: levator ani muscle tears, connective tissue breaks, and pudendal/pelvic nerve denervation. Any of these injuries can occur in isolation but 2 or more in combination are more likely to occur. The long-term result may be the loss of active and passive urethral support and loss of intrinsic urethral tone.

The loss of urethral and bladder neck support may impair urethral closure mechanisms during times of increased intra-abdominal pressure.

This phenomenon can be viewed in several ways.

Some hypothesize that under normal circumstances, any increase in intra-abdominal pressure is transmitted equally to the bladder and proximal urethra. This is likely due to the retropubic location of the proximal and mid urethra within the sphere of intra-abdominal pressure. At rest, the urethra has a higher intrinsic pressure than the bladder. This pressure gradient relationship is preserved if acute increases in intra-abdominal pressure are transmitted equally to both organs.

When the urethra is hypermobile, pressure transmission to the walls of the urethra may be diminished as it descends and rotates under the pubic bone. Intraurethral pressure falls below bladder pressure, resulting in urine loss. [62, 63]

A related way of describing the mechanism of hypermobility-related stress incontinence is the hammock theory posited by DeLancey. Normally, an acute increase in intra-abdominal pressure applies a downward force to the urethra. The urethra is then compressed shut against the firm support provided by the anterior vaginal wall and associated endopelvic connective tissue sheath. If the endopelvic connective tissue is detached from its normal lateral fixation points at the arcus tendineus fascia pelvis, optimal urethral compression does not take place.

A simple analogy is that of a garden hose (urethra) running over a pavement surface (anterior endopelvic connective tissue). A force is applied in a downward direction using the foot (increased intra-abdominal pressure). This force compresses the hose shut, occluding flow. If the same hose is run through a soft area of mud (damaged connective tissue), then the downward force does not occlude the hose but, rather, pushes the hose deeper into the mud.

An alternative theory of the mechanism of stress incontinence stems from research involving ultrasound visualization of the bladder neck and proximal urethra during stress maneuvers. This research found that 93% of patients with stress incontinence displayed funneling of the proximal urethra with straining, and half of those individuals also showed funneling at rest. In addition, during stress maneuvers, the urethra did not rotate and descend as a single unit; rather, the posterior urethral wall moved farther than the anterior wall.

Although mobile, the anterior urethral wall has been observed to stop moving, as if tethered, while the posterior wall continued to rotate and descend. Possibly, the pubourethral ligaments arrest rotational movement of the anterior wall but not the posterior wall. The resulting separation of the anterior and posterior urethral walls might open the proximal urethral lumen, thus allowing or contributing to stress incontinence.

Intrinsic sphincter deficiency. Intrinsic sphincter deficiency is a condition in which the urethral sphincter is unable to coapt and generate enough resting urethral

closing pressure to retain urine in the bladder. The anatomic support of the urethra may be normal.

Intrinsic sphincter deficiency is due to devascularization and/or denervation of the bladder neck and proximal urethra. The urethral sphincter may become weak after pelvic surgery (eg, failed bladder suspension surgery) because of nearby nerve damage or excessive scarring of the urethra and surrounding tissues. Additional causes of urethral dysfunction include pelvic radiation or neurologic injury, including myelomeningocele.

Women with severe intrinsic sphincter deficiency do not always have the usual urethral hypermobility during a Valsalva maneuver. Paradoxically, the urethra appears well supported. This results in so-called lead pipe urethra, where the urethra remains open at rest. Whenever intra-abdominal pressure exceeds proximal urethral pressure, involuntary urine loss ensues. Because the urethra cannot remain closed, the patient experiences almost continuous urinary incontinence.

Female urethral function is influenced by estrogen. The lack of estrogen at menopause leads to atrophy and replacement of submucosa (ie, vascular plexus) by fibrous tissue. When estrogen is administered to postmenopausal women with atrophic vaginitis, the mucosa regains its turgor, with simultaneous up-regulation of alpha-receptors and angiogenesis of vascular plexus. Lack of estrogen is a risk factor for developing intrinsic sphincter deficiency, but estrogen replacement may reverse its effects.

Occult stress incontinence. Stress incontinence on prolapse reduction (previously termed latent stress incontinence) is a term used to describe stress incontinence observed only after reduction of pelvic prolapse. Some believe that kinking of the urethra caused by the prolapse itself provides for at least part of the continence mechanism. These patients may have a history of stress incontinence that improved and finally resolved as their prolapse worsened.

In diagnosing occult incontinence, the goal is to avoid new-onset incontinence following surgical correction of prolapse. This may be accomplished through the use of an incontinence procedure, such as a colposuspension or sling. The diagnosis can be made by stress testing with the prolapse reduced or by pessary placement and pad testing. No particular method of prolapse reduction has been proved superior.

In a study of continent women with severe pelvic organ prolapse, reduction of the prolapse with a pessary revealed occult incontinence in 58% of cases. These patients were treated with a pubovaginal sling, anterior colporrhaphy, and other appropriate reparative operations. Eighty-six percent of the patients with potential incontinence so treated had no postoperative stress-related urine loss.

The group of patients with no demonstrable occult incontinence underwent anterior colporrhaphy and

additional individualized procedures. Incontinence procedures, per se, were not performed in this group. No patients had postoperative stress incontinence. Mean follow-up was 40-50 months.

This study points out that bladder neck procedures need not be performed if potential incontinence has been ruled out, even if bladder neck hypermobility is present. Indeed, incontinence procedures are not without their own morbidities and should not be performed unless necessary.

Urge incontinence pathophysiology

Urge incontinence is involuntary urine loss associated with a feeling of urgency. The corresponding urodynamic term is detrusor overactivity, which is the observation of involuntary detrusor contractions during filling cystometry. These contractions may be voluntary or spontaneous and may or may not cause symptoms of urgency and/or urgency incontinence.

However, a study using a quality of life assessment of women with incontinence showed that women with urge incontinence from detrusor overactivity consistently had a worse quality of life than did women with other urodynamic diagnoses.

Urge incontinence may be a result of detrusor myopathy, neuropathy, or a combination of both. When the identifiable cause is unknown, it is termed idiopathic urge incontinence. When a definable causative neuropathic disorder exists, the coexisting urinary incontinence disorder is termed neurogenic detrusor overactivity. Symptoms of overactive bladder or urge incontinence in the absence of neurologic causes are known as detrusor instability.

The term overactive bladder describes a syndrome of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology. Overactive bladder in adults is a disorder of unclear etiology and incompletely understood pathophysiology. For discussion of this topic, see the article Overactive Bladder.

Some researchers believe that detrusor overactivity represents the premature initiation of a normal micturition reflex. In vitro studies of bladder muscle strips from patients with detrusor overactivity have demonstrated an increase in response to electrical stimulation and an increased sensitivity to stimulation with acetylcholine. These findings may indicate a higher sensitivity to efferent neurologic activity or a lower threshold of acetylcholine release needed to initiate a detrusor contraction.

A relative cholinergic denervation may explain some of these findings. This proposed mechanism is most plausible in cases of de novo detrusor overactivity, which follow hysterectomy or other pelvic surgery. The mechanism of denervation in idiopathic detrusor overactivity is less certain. Subtle obstruction and the effects of aging on smooth muscle and

the autonomic nervous system are 2 possible contributors.

Another finding described in bladder muscle specimens from patients with detrusor overactivity is local loss of inhibitory medullary neurologic activity. Vasoactive intestinal peptide, a smooth muscle relaxant, is decreased markedly in the bladders of patients with detrusor overactivity. In addition, bladders of individuals with detrusor overactivity have been found deficient in smooth muscle–relaxing prostaglandins.

Mills and colleagues conducted a comparison study of bladder muscle strips from patients with severe idiopathic detrusor overactivity and from organ donors with no known urologic problems. The following are some of the findings:

1. Patchy partial denervation of the detrusor with areas of normal innervation and areas of reduced innervation by fibers staining for acetylcholinesterase;
2. A reduced force of contraction in response to electrical field stimulation: This finding is in contrast to a previous study showing an increased sensitivity to electrical field stimulation, but the authors believe that the muscle strips may have had increased sensitivity to direct electrical stimulation (non–nerve mediated);
3. Supersensitivity to potassium;
4. Increased electrical coupling of cells via cell-to-cell junctions;
5. Variability in the activity of muscle strips from the same bladder.

The authors believe that the primary abnormality in detrusor overactivity is at the detrusor muscle level with an increased capacity for spontaneous myogenic contractile activity and spread of electrical activity from cell to cell, resulting in tetanic contractions. Epidemiological studies have shown an association between detrusor overactivity and irritable bowel syndrome. Some authorities have proposed that a syndrome of smooth muscle dysfunction may underlie this association. [64]

Another study demonstrated the presence of an increased ratio of abnormal-to-normal cell junctions in patients with bladder dysfunction. The increased ratio was demonstrated most markedly in patients with detrusor overactivity. To a lesser degree, these changes also were observed in patients with outlet obstruction combined with detrusor overactivity and with idiopathic sensory urgency alone.

These authors concluded that idiopathic sensory urgency might represent a milder or less overt variant of detrusor overactivity. They suggested that, in the future, bladder biopsy with structural evaluation of cell junctions might become a useful clinical tool in the diagnostic evaluation of bladder dysfunction.

One study proposed that urge incontinence, regardless of the triggering mechanism, may share a final common pathway of myogenic dysfunction of the detrusor. Spread of contractile signals via cell-to-cell coupling was proposed as the likely mechanism.

Another possible explanation for detrusor overactivity in a subgroup of patients involves the triggering of the micturition reflex by leakage of urine into a funneled and partially incompetent proximal urethra. This theory is consistent with the findings of detrusor overactivity caused by coughing or changing position.

In males, early obstruction due to benign prostatic hyperplasia (BPH) may result in urge incontinence. The pathophysiology of BPH is poorly understood. Relative obstruction develops because of mechanical factors, dynamic factors, and detrusor alterations.

Androgen-induced enlargement of nodules of glandular tissue comprises the mechanical portion of the disorder. The dynamic component is related to increased alpha tone in prostatic and urethral smooth muscle. Detrusor dysfunction may consist of impaired contractility, detrusor overactivity, or both. In severe cases of obstruction, retention and overflow incontinence may develop, and the upper urinary tract can become damaged.

The presence of inflammation in the bladder is believed to result in bladder muscle irritability and urge incontinence in some instances, as depicted in the image below. One study showed that approximately 8% of patients with bacterial urinary tract infections had nonneuropathic bladder instability. If bacterial infection and detrusor overactivity coexist, successful treatment of the infection results in resolution of the detrusor overactivity in about one half of the patients.

Nonbacterial inflammatory conditions of the bladder, including interstitial cystitis, have been associated with detrusor overactivity. Foreign bodies, including permanent sutures, bladder stones, and neoplasms, also have been linked to bladder irritability and instability. [63, 64]

Mixed incontinence pathophysiology

Mixed incontinence is urinary incontinence resulting from a combination of stress and urge incontinence. Approximately 40-60% of females with incontinence have this combination. Although it is generally defined as detrusor overactivity and impaired urethral function, the actual pathophysiology of mixed urinary incontinence is still being investigated. While generally thought of as separate etiologies for incontinence, some indirect evidence may link these disorders in some instances.

In mixed incontinence, the bladder outlet is weak and the detrusor is overactive. A classic example of mixed incontinence is a patient with meningomyelocele and an incompetent bladder neck with a hyperreflexic

detrusor; however, a combination of urethral hypermobility and detrusor instability is a more common scenario.

Mixed incontinence is a common finding in older patients with urinary incontinence disorders. Often, stress incontinence symptoms precede urge incontinence symptoms in these individuals. Urgency without actual urge-related urine loss also is a common complaint of patients with stress incontinence.

Some patients with stress incontinence have urine leakage into the proximal urethra that may, at first, trigger sensory urgency and/or bladder contractions, which initially are suppressible. Later, in a subgroup of these individuals, myopathic changes may occur in the bladder that make the spread of abnormally generated contractile signals more efficient and more difficult to suppress voluntarily.

Reflex incontinence pathophysiology

Reflex incontinence is due to neurologic impairment of the central nervous system. Common neurologic disorders associated with reflex incontinence include stroke, Parkinson disease, and brain tumors. Reflex incontinence also occurs in patients with spinal cord injuries and multiple sclerosis. When patients with suprapontine or suprasacral spinal cord lesions present with symptoms of urge incontinence, this is known as detrusor hyperreflexia.

Spinal cord injuries interrupt the sacral reflex arc from the suprasacral spinal cord, cerebral cortex, and higher centers. These pathways are crucial for voluntary and involuntary inhibition. In the initial phase of spinal cord injury, the bladder is areflexic and overflow incontinence results. Later, detrusor hyperreflexia usually is found upon urodynamic evaluation.

In multiple sclerosis (MS), demyelinating plaques in the frontal lobe or lateral columns can produce lower urinary tract disorders. Incontinence may be the presenting symptom of MS in about 5% of cases. Approximately 90% of individuals with MS experience urinary tract dysfunction during the course of the disease.

A summary of the published series of urodynamic findings in MS demonstrated that in patients with lower urinary tract dysfunction, the most common urodynamic diagnosis is detrusor hyperreflexia (62%). Detrusor-sphincter dyssynergia (25%) and detrusor hyporeflexia (20%) also are common. Obstructive findings are much more common in males. Of note, the urodynamic diagnosis may change over time as the disease progresses.

Hemorrhage, infarction, or vascular compromise to certain areas of the brain can result in lower urinary tract dysfunction. The frontal lobe, internal capsule, brainstem, and cerebellum commonly are involved sites. Initially, urinary retention due to detrusor areflexia is observed. This may be followed by detrusor hyperreflexia.

Approximately 40-70% of patients with Parkinson disease have

lower urinary tract dysfunction. Controversy exists as to whether specific neurologic problems in patients with Parkinson disease lead to bladder dysfunction or if bladder symptoms simply are related to aging. The extrapyramidal system is believed to have an inhibitory effect on the micturition center; theoretically, loss of dopaminergic activity in this area could result in loss of detrusor inhibition.

In patients with dementia, incontinence and urinary tract dysfunction may be due to specific involvement of the areas of the cerebral cortex involved in bladder control. Alternatively, incontinence may be related to global deterioration of memory, intellectual capacity, and behavior. Urodynamically, both detrusor hyperreflexia and areflexia have been found.

CNS neoplasms may result in incontinence. Tumors of the superior medial frontal lobe, spinal cord tumors above the conus medullaris, and cervical spondylosis can cause detrusor hyperreflexia.

Overflow incontinence pathophysiology

The major contributing factor to overflow incontinence is incomplete bladder emptying secondary to impaired detrusor contractility or bladder outlet obstruction. [2, 9] Impaired detrusor contractility is typically neurogenic in nature; causes include diabetes mellitus, lumbosacral nerve disease from tumors, meningomyelocele, MS, prolapsed intravertebral disks, and high spinal cord injuries. Less common causes of overflow incontinence include AIDS, genital herpes affecting the perineal area, and neurosyphilis.

In most cases, both sensory and motor neuropathies are present. The maximal storage capacity of the bladder is reached, oftentimes without the individual realizing that this has occurred. Incontinence occurs off the top of a chronically over-filled bladder. Effective emptying is not possible because of an acontractile detrusor muscle.

Common causes of bladder outlet obstruction in men include benign prostatic hyperplasia (BPH), vesical neck contracture, and urethral strictures. In women, urethral obstruction after anti-incontinence surgery such as a sling or bladder neck suspension can result in iatrogenically induced overflow incontinence. [61, 62]

Functional incontinence

Functional incontinence is seen in patients with normal voiding systems but who have difficulty reaching the toilet because of physical or psychological impediments. In some cases, the cause is transient or reversible. In others, a permanent problem can be identified. The etiology of the incontinence may be iatrogenic, environmental, situational, or disease related. The following common mnemonic, DIAPPERS, is helpful in remembering the functional contributors to incontinence:

D - Delirium

I - Infection, urinary

A - Atrophic urethritis or vaginitis

P - Pharmacologic agents

P - Psychiatric illness

E - Endocrine disorders

R - Reduced mobility or dexterity

S - Stool impaction

Integral theory

A unifying theory of the etiology of stress incontinence, urge incontinence, voiding dysfunction, and fecal incontinence in women has been proposed. The basis of the theory is that these disorders are the result of overstretching of the vaginal connective tissue and supporting ligaments, which usually occurs during childbirth.

Laxity of the pubourethral ligaments (ie, anterior zone of damage), mid vagina (ie, middle zone), and uterosacral ligaments (ie, posterior zone) make the usual tridirectional support of the vagina ineffective. With the vagina no longer properly tethered to the pelvic girdle, the usual neuromuscular actions that occur during increases in intra-abdominal pressure or pelvic floor relaxation during voiding are not translated as effectively into urethral closure and opening, respectively.

Detrusor overactivity, according to this theory, occurs because of the premature firing of stretch receptors in the bladder base secondary to poor endopelvic connective tissue support to the filling bladder.

The integral theory is attractive from the standpoint of parsimony but is complex. The theory is best appreciated and understood with the help of illustrations and diagrams showing directional force vectors.

Continuous incontinence

This severe type of incontinence is characterized by constant or near constant leakage with no symptoms other than wetness. Generally, this represents a significant breech in the storage capabilities of the bladder or urethra. Urogenital fistulas are a classic example.

A nonfunctioning urethra can result in continuous leakage. Scarring and fibrosis from previous surgery, partial urethral resection for vulvar cancer, and urethral sphincter paralysis due to lower motor neuron disease can cause the urethra to fail.

Pelvic irradiation may not only cause urogenital fistula but in rare cases causes bladder noncompliance that results in continuous incontinence. Congenital malformations of the genitourinary tract, such as bladder exstrophy, epispadias, and ectopic ureters, can result in total incontinence.

Pediatric urinary incontinence

Pediatric incontinence disorders are classified according to cause. Primary incontinence disorders generally are due to congenital structural disorders, including ectopic ureter, exstrophy, epispadias, and

patent urachus. Secondary structural causes can result from obstruction from urethral valves, congenital urethral strictures, and large ectopic ureteroceles. In addition, trauma can result in secondary structural incontinence.

Neurogenic lesions make up the next category of pediatric incontinence disorders. These include spinal dysraphism, tethered spinal cord, and spinal cord tumors.

Nonstructural causes account for most cases of pediatric incontinence. Infection and inflammation may be the source. Dysfunctional voiding habits can develop even at a young age. Some children may become so preoccupied with activities that voiding is delayed until capacity is reached and accidents result. [63]

Some believe that certain children develop a pattern of not relaxing the pelvic floor while voiding. In some cases, this can be traced back to an infection or some other noxious stimuli. A vicious cycle of pelvic floor spasm, constipation, and urinary retention can develop.

So-called giggle incontinence has been thought to represent an underlying temporal lobe seizure. Other studies do not support this theory, however.

Vaginal voiding is a pseudoincontinence disorder, which may result from voiding with the legs held too tightly together. The impeded flow of urine may fill the vagina. The vagina empties when the child stands.

Actiology

Even in an individual patient, urinary incontinence may have multiple etiologies, with varying degrees of contribution to the overall disorder. Structural and functional disorders involving the bladder, urethra, ureters, and surrounding connective tissue can contribute. In addition, a disorder of the spinal cord or central nervous system (CNS) may be the major etiologic factor in some cases. Medical comorbidities also can be important. Finally, some cases of urinary incontinence may be pharmacologically induced.

The most common cause of stress incontinence in women is urethral hypermobility secondary to poor anatomic pelvic support. Women may lose this pelvic support with postmenopausal estrogen loss, childbirth, surgery, or certain disease states that affect tissue strength. A less common cause of stress incontinence is intrinsic sphincter deficiency, which can result from the aging process, pelvic trauma, surgery (eg, hysterectomy, urethropexy, pubovaginal sling), or neurologic dysfunction.

The most common cause of intrinsic sphincter deficiency in men is radical prostatectomy for prostate cancer or transurethral resection of the prostate for benign prostatic hyperplasia. A less common cause of intrinsic sphincter deficiency is trauma to the bladder neck or prostate, resulting from pelvic fracture due to high-impact deceleration injuries. [62]

Contributing factors with aging-related urinary incontinence include a weakening of connective tissue, genitourinary atrophy due to hypoestrogenism, increased incidence of contributing medical disorders, increased nocturnal diuresis, and impairments in mobility and cognitive functioning.

Other factors that may increase the risk of developing incontinence include obesity, straining at stool as a child or young adult, heavy manual labor, chronic obstructive pulmonary disease, and smoking. In many cases of incontinence that are due to detrusor overactivity, the problem is idiopathic in nature.

In a prospective cohort study of 5,391 young women from the Australian Longitudinal Study on Women's Health, depressive symptoms were associated with 37% higher odds of having urinary incontinence after adjustment for sociodemographic factors, body mass index, health behaviors, and reproductive factors. Having physician-diagnosed depression was associated with 42% higher odds.

A review of women with type 1 diabetes mellitus who participated in the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), found that incident urinary incontinence was associated with higher hemoglobin A1c levels, independent of other recognized risk factors. Thus, improved glycemic control might reduce the risk of urinary incontinence in such patients.

Less frequent causes of urinary incontinence include complications of urologic procedures or pelvic radiation therapy. In the pediatric population, it includes enuresis and congenital abnormalities of the genitourinary system.

Transient causes

Transient urinary incontinence is often seen in both elderly and hospitalized patients. The mnemonic DIAPPERS is a good way to remember most of the reversible causes of incontinence, as follows:

D: Delirium or acute confusion

I: Infection (symptomatic UTI)

A: Atrophic vaginitis or urethritis

P: Pharmaceutical agents

P: Psychological disorders (depression, behavioral disturbances)

E: Excess urine output (due to excess fluid intake, alcoholic or caffeinated beverages, diuretics, peripheral edema, congestive heart failure, or metabolic disorders such as hyperglycemia or hypercalcemia)

R: Restricted mobility (limits ability to reach a bathroom in time)

S: Stool impaction

In addition to urinary tract infection, conditions such as bladder cancer, bladder stones, and foreign bodies can irritate the bladder, resulting

in involuntary bladder contractions and incontinence. Less common infectious causes of overflow incontinence include AIDS, genital herpes affecting the perineal area, and neurosyphilis. Stones or neoplasms may also result in incontinence due to obstruction.

Neurological causes

Cortical lesions (eg, from strokes, tumors, aneurysms, or hemorrhages) can lead to inappropriate voiding secondary to depressed social awareness, decreased sensation, and/or inappropriate urethral sphincter relaxation. Cerebrovascular disease doubles the risk for urinary incontinence in older women.

Spinal cord lesions can alter sympathetic and parasympathetic tone, resulting in urinary incontinence. Peripheral nerve disease such as diabetic peripheral neuropathy can cause urinary incontinence through a contractile dysfunction of the bladder.

Metastatic carcinoma can cause epidural spinal cord compression. Back pain is the initial symptom in most cases. Almost 20% of cases involve the lumbosacral spine. If the sacral cord is involved, urinary incontinence or retention can be expected. Urinary incontinence symptoms represent an unfavorable prognostic indicator in this patient population. Early diagnosis and treatment of spinal cord compression is extremely important. Paraplegia or quadriplegia can develop within hours or days after the first neurologic deficit appears.

S2-S5 nerve root injury (herniation) can cause bladder dysfunction. Cauda equina syndrome can develop in patients with a large centrally protruding disk. Symptoms include bilateral leg pain and weakness, saddle anesthesia, urinary retention or incontinence, and fecal retention or incontinence. It is important to recognize this syndrome early because there is a high risk for chronic neurologic deficits if treatment is delayed.

Hemi–cauda equina syndrome (from a herniated lumbar disk) can also manifest as urinary incontinence. It presents as unilateral leg pain, unilateral sensory deficit in the S1-S5 dermatomes, and urinary incontinence or urinary retention. These patients require urgent neurosurgical consultation for emergency surgery.

Multiple sclerosis should be considered in any patient without evidence of urinary tract infection who has episodic or rapid onset of urinary symptoms. Urinary incontinence may occur by itself or may be accompanied by other vague neurological symptoms.

Patients with a neurogenic disorder such as myelomeningocele may have an open bladder neck that results in severe intrinsic sphincter deficiency and urinary loss.

Pharmacologic causes

Many medications contribute to urinary incontinence, directly or indirectly. Medications must always be considered as the cause of new-onset urinary incontinence – especially in elderly persons, in whom polypharmacy is often encountered.

Medication may result in incontinence through the following mechanisms:

1. Drugs with anticholinergic properties or side effects (eg, antipsychotics, antidepressants) - Urinary retention and thus overflow incontinence
2. Alpha-adrenergic agonists - Urinary retention and thus overflow urinary incontinence
3. Alpha-antagonist - Urethral relaxation
4. Diuretics – Overwhelming of bladder capacity in elderly persons
5. Calcium channel blockers - Decreased smooth muscle contractility in the bladder, causing urinary retention with overflow incontinence
6. Sedative-hypnotics - Immobility secondary to sedation, leading to functional incontinence
7. Angiotensin-converting enzyme (ACE) inhibitors – Diuretic effect, as well as side effect of cough with relaxation of pelvic floor musculature, can exacerbate incontinence
8. Antiparkinson medications - Urinary urgency and constipation

Epidemiology

The precise prevalence of urinary incontinence is difficult to estimate. Part of the difficulty has been in defining the degree, quantity, and frequency of urine loss necessary to qualify as pathologic, with varying definitions among studies. Consequently, the prevalence of urinary incontinence reported in the literature is varied.

In addition, urinary incontinence is underdiagnosed and underreported. An estimated 50-70% of women with urinary incontinence fail to seek medical evaluation and treatment because of social stigma. Only 5% of incontinent individuals in the community and 2% in nursing homes receive appropriate medical evaluation and treatment. People with incontinence often live with this condition for 6-9 years before seeking medical therapy.

In a Swedish study of 9197 nulliparous women aged 25-64 years, the rate of urinary incontinence increased from 9.7% in the youngest women with a body mass index <25 kg/m2 to 48.4% among the oldest women with a body mass index ≥35 kg/m2. In a Dutch study of 1257 adults, the prevalence of urinary incontinence was 49.0% in women versus 22.6% in men. In both men and women, the prevalence of urinary incontinence increased with aging.

Urinary incontinence has been estimated to affect 10-13 million people in the United States and 200 million people worldwide. The cost of treating urinary incontinence in United States alone is $16.3 billion, 75% of which is spent on treatment of women. Urinary incontinence can result in prolonged hospital admission, urinary tract infections, contact dermatitis, and falls. Urinary incontinence is a leading

cause of admission to a nursing home when families find it too difficult to care for a relative with incontinence.

Sex- and age-related patterns

Age is the single largest risk factor for urinary incontinence, although at any age, urinary incontinence is more than 2 times more common in females than in males. Urinary incontinence affects up to 7% of children older than 5 years, 10-35% of adults, and 50-84% of the elderly persons in long-term care facilities. The incidence of urinary incontinence is 1.4% of adults aged 15-24 years and 2.9% of those aged 55-64 years.

In a cross-sectional analysis of women who participated in the 2005-2006 National Health and Nutrition Examination Survey (NHANES), Nygaard et al demonstrated that the prevalence of urinary incontinence increased with age, but reported a lower overall prevalence than other researchers. The prevalence was 6.9% in women aged 20-39 years, 17.2% in those aged 40-59 years, 23.3% in those aged 60-79 years, and 31.7% in women older than 80 years. [53]

An age-related pattern also appears in the predominant type of urinary incontinence experienced. In general, studies have shown that stress urinary incontinence tends to be more common in women younger than 65 years, while urge urinary incontinence and mixed urinary incontinence is more common in women older than 65 years.

Stress incontinence affects 15-60% of women—both young and old individuals. More than 25% of nulliparous young college athletes experience stress incontinence when participating in sports. [53]

12.2 Overactive bladder

A normal bladder functions through a complex coordination of musculoskeletal, neurologic, and psychological functions that allow it to fill and empty. The prime effector of continence is the synergic relaxation of detrusor muscles and contraction of bladder neck and pelvic floor muscles.

Various efferent and afferent neural pathways and neurotransmitters are involved. Central neurotransmitters (eg, glutamate, serotonin, and dopamine) are thought to have a role in urination. Glutamate is an excitatory neurotransmitter in pathways that control the lower urinary tract. Serotonergic pathways facilitate urine storage. Dopaminergic pathways may have both inhibitory and excitatory effects on urination. Dopamine D1 receptors appear to have a role in suppressing bladder activity, whereas dopamine D2 receptors appear to facilitate voiding.

In bladder filling, sympathetic nerve fibers that originate from the T11 to L2 segments of the spinal cord, which innervate smooth-muscle fibers around the bladder neck and proximal urethra, cause these fibers to contract, allowing the bladder to fill. As the bladder fills, sensory stretch receptors

in the bladder wall trigger a central nervous system (CNS) response. During bladder filling, the intravesical pressure remains low as a result of the viscoelastic properties of the bladder and antagonism of the parasympathetic nervous system.

The parasympathetic nervous system (PNS) causes contraction of the detrusor, while the muscles of the pelvic floor and external sphincter relax. The PNS fibers, as well as those responsible for somatic (voluntary) control of micturition (urination), originate from the S2 to S4 segments of the spinal cord in the sacral plexus. The somatic fibers innervate the external sphincter and are responsible for the voluntary control of continence in the face of a pressing desire to void.

The normal adult bladder accommodates 300-600 mL of urine; a CNS response is usually triggered when the volume reaches 400 mL. However, urination can be prevented by cortical suppression of the PNS or by voluntary contraction of the external sphincter.

Pathophysiology

OAB appears to be multifactorial in both etiology and pathophysiology. Symptoms of OAB are suggestive of underlying detrusor overactivity. Overactivity of the detrusor muscle—neurogenic, myogenic, or idiopathic in origin—may result in urinary urgency and urgency incontinence.

The role of the M2 receptor in the human bladder is not well established. Data from small studies demonstrating up-regulation of the M2 receptor in certain pathologic states suggest that it may have a role in detrusor overactivity related to obstruction and spinal cord injury.

Binding of acetylcholine to the M3 receptor activates phospholipase C via coupling with G proteins. This action causes the release of calcium from the sarcoplasmic reticulum and contraction of the bladder smooth muscle. Increased sensitivity to stimulation by muscarinic receptors may lead to OAB. Leakage of acetylcholine from the parasympathetic nerve terminal may lead to micromotion of the detrusor, which may activate sensory afferent fibers, leading to the sensation of urgency.

Sensory afferent nerves may also play a role in OAB. Activation of normally quiescent C sensory fibers may help produce symptoms of OAB in individuals with neurologic and other disorders. Several types of receptors identified on sensory nerves may have a role in OAB symptoms. These include vanilloid, purinergic, neurokinin A, and nerve growth factor receptors. Substances such as nitric oxide, calcitonin gene-related protein, and brain-derived neurotropic factor may also have a role in modulating sensory afferent fibers in the human bladder.

Once thought to be biologically inert, the urothelium may also have a role in OAB (see the image below). The urothelium communicates directly with suburothelial afferents acting as luminal sensors. Low pH, high potassium concentration, and increased osmolality in the urine can influence

sensory nerves. Activation of suburothelial afferent fibers without changes in the smooth muscle may lead to urgency. Activation of the suburothelial afferents in the presence of enhanced smooth-muscle coupling may lead to urgency and unstable detrusor contractions.

Aetiology

OAB is primarily a neuromuscular problem in which the detrusor muscle contracts inappropriately during bladder filling (ie, storage phase). These contractions often occur regardless of the amount of urine in the bladder. OAB may result from a number of different causes, both neurogenic and nonneurogenic.

Neurologic injuries that may cause OAB include the following:

1. Spinal cord injury
2. Stroke

Neurologic diseases that may cause OAB include the following:

3. Multiple sclerosis
4. Dementia
5. Parkinson disease
6. Medullary lesions
7. Diabetic neuropathy

Detrusor overactivity can also occur in the absence of a neurogenic etiology. Contractions can be spontaneous or induced by rapid filling of the bladder, postural changes, or even walking or coughing. Because these causes are nonneurogenic, the pressing need to urinate can be contained for a few minutes from when it is first sensed. [58, 60]

Idiopathic OAB is OAB in the absence of any underlying neurologic, metabolic, or other causes of OAB, or conditions that may mimic OAB, such as urinary tract infection, bladder cancer, bladder stones, bladder inflammation, or bladder outlet obstruction.

Certain medications may lead to symptoms of OAB. Diuretics can cause urge incontinence because of increased bladder filling, stimulating the detrusor. Bethanechol can also cause urge incontinence through its stimulation of bladder smooth-muscle contraction.

Heart failure or peripheral venous and vascular disease can also contribute to symptoms of OAB. During the day, such individuals have excess fluid collect in dependent positions (feet and ankles). When they recline to go to sleep, much of this fluid becomes mobilized and increases renal output, thereby increasing urine output. Many of these patients describe increased nocturia that manifests as OAB.

Only in rare cases does it prove impossible to identify a specific cause (idiopathic OAB).

Risk factors

Several risk factors are associated with OAB. White people, persons with insulin-dependent diabetes, and individuals with depression are 3 times as likely to develop OAB. Other risk factors include the following:

1. Age >75 years
2. Arthritis

3. Use of oral hormone replacement therapy
4. High body mass index (BMI)

The physiologic changes associated with aging, such as decreased bladder capacity and changes in muscle tone, favor the development of OAB when precipitating factors intervene. In postmenopausal women, many of these changes are related to estrogen deficiency. Estrogen deprivation therapy in younger women with breast cancer has also been associated with increased risk for OAB. Perhaps the most important age-related change in bladder function that leads to incontinence is the increased number of involuntary bladder contractions (detrusor instability).

Any disruption in the integration of musculoskeletal and neurologic responses can lead to loss of control of normal bladder function and to urge incontinence.

Epidemiology

In the National Overactive Bladder Evaluation (NOBLE) study, which evaluated 5204 adults 18 years of age and older who were representative of the US population by sex, age, and geographical region, 16.5% of the study participants met the criteria for OAB. Of these, 6.1% met the criteria for OAB with urgency incontinence, and 10.4% met criteria for OAB without urgency incontinence. Among individuals with OAB with urgency incontinence, 45% had mixed incontinence symptoms (urgency incontinence plus stress incontinence). Data in the study were gathered with the use of a computer-assisted telephone interview questionnaire. OAB affects millions of people worldwide, regardless of race. The frequency data on OAB found in Europe are similar to that found in the United States.

The prevalence of OAB increases with age. However, OAB should not be considered a normal part of aging. Twenty percent of the population aged 70 years or older report symptoms of OAB; 30% of those aged 75 years or older report symptoms. Men tend to develop OAB slightly later in life than women do.

In the NOBLE study, the prevalence of OAB was similar in women and men (16.9% and 16%, respectively). However, the prevalence of incontinence associated with OAB differed. Among women, 9.3% reported having OAB with incontinence; 7.6% reported having OAB without incontinence. In contrast, more men reported having OAB without incontinence (13.4%) than with incontinence (2.6%). In women, the prevalence of OAB with urgency urinary incontinence increased with increasing body mass index (BMI), whereas in men, no difference was found.

Milsom et al, in a population-based survey (conducted by telephone or direct interview) of 16,776 men and women aged 40 years or older from the general population in Europe, found the overall prevalence of OAB symptoms to be 16.6%. The main outcome measures included the prevalence of urinary frequency (>8 micturitions per

day), urinary urgency, and urgency incontinence.

Frequency was the most common symptom (85%), followed by urgency (54%) and urgency incontinence (36%). The prevalence of OAB increased with age, and rates in men and women were similar. Symptoms of urinary urgency and frequency were similar between both sexes, but urgency incontinence was more prevalent in women than in men.

OAB in men is often related to obstruction; therefore, it may be important to differentiate between obstruction and irritative symptoms before the initiation of treatment.

Treatment

If a specific cause of overactive bladder (OAB) symptoms is identified, it should be treated appropriately; for example, urinary tract infection (UTI) should be treated with antibiotics, while atrophic urethritis can be treated with topical application of estrogen vaginal cream. For idiopathic OAB, the three main treatment approaches are behavioral therapy, pharmacotherapy, and surgery. The choice of a particular treatment depends on the severity of the symptoms and the extent that the symptoms interfere with the patient's lifestyle.

Guidelines for the treatment of OAB by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) include the following recommendations:

First-line therapy: Behavioral therapies and education should be offered first; behavioral therapies may be combined with pharmacologic management. [53]

Second-line therapy: Antimuscarinics (extended-release preparations should be used instead of immediate-release preparations when possible) or beta-3 adrenoceptor agonists should be offered; transdermal oxybutynin may be offered. If an antimuscarinic provides inadequate symptom relief or produces unacceptable adverse effects, thendose modification, a different antimuscarinic medication, or a beta3-adrenoceptor agonist may be tried.

Third-line therapy: Intradetrusor injection of onabotulinumtoxinA is an option for carefully selected and thoroughly counseled patients with severe refractory OAB symptoms or those who are not candidates for second-line therapy. Other third-line options are peripheral tibial nerve stimulation (PTNS), which may be offered to carefully selected patients, and sacral neuromodulation (SNS), which is an option for carefully selected patients who are not candidates for second-line therapy or who have severe refractory OAB symptoms despite such therapy, and who are willing to undergo a surgical procedure.

A combined treatment approach using behavioral and pharmaceutical interventions is effective in most patients with OAB. Several drugs that have been proven safe and efficacious in clinical trials have been approved for

the treatment of OAB. Behavioral interventions, such as the following, should be part of every treatment plan:

1. Limiting bladder irritants (eg, caffeine, alcohol);

2. Bladder training;

3. Urgency suppression techniques, including pelvic floor muscle exercises (consultation with a pelvic floor physical therapist may be helpful). [59]

Surgery is rarely used to treat OAB and is reserved for patients in whom pharmacologic and behavioral therapy fail. Various surgical options are available, including sacral nerve neuromodulation and, rarely, bladder augmentation. Percutaneous tibial nerve stimulation is a minimally invasive option for patients in whom pharmacologic therapy fails or is contraindicated.

Anticholinergics

Anticholinergic agents are currently the first-line pharmacologic therapy for OAB. These agents are thought to act primarily by inhibiting involuntary detrusor muscle contractions (at the level of the efferent pathway), but identification of muscarinic receptors in the urothelium/suburothelium suggests that they may also affect the afferent sensory pathway. The goals of therapy with anticholinergic agents are to prevent inappropriate detrusor contractions and to maintain normal bladder function, while minimizing adverse effects.

A meta-analysis of 50 randomized controlled trials involving more than 27,000 women with OAB found only modest improvement in symptoms with anticholinergic treatment. Daily treatment reduced urge incontinence by 1.73 episodes per day and voids by 2.06 per day, while placebo reduced urge incontinence episodes by 1.06 and voids by 1.2 per day. No individual agent was shown to be superior to the others.

The duration of treatment is controversial, although many physicians would argue that OAB is a chronic condition with symptom severity that may vary over time. In a prospective randomized, open-label, multicenter trial of symptom change and retreatment rate after discontinuation of the antimuscarinic tolterodine (extended-release, 4 mg) in known responders, 65% of patients requested retreatment and 62% experienced symptom relapse.

Symptom duration and baseline health-related quality of life (HRQol) were risk factors for retreatment according to univariate analysis. However, HRQol was the only independent risk factor. This article serves to highlight both the importance of patient education when managing those with OAB and the significant potential need for long-term anticholinergic therapy. [54]

Oxybutynin and tolterodine are the more commonly used anticholinergics in OAB treatment. Oxybutynin (Ditropan) was among the first anticholinergic agents to be used to treat detrusor overactivity; its

efficacy in treating OAB is well documented. However, the effects of oxybutynin are not tissue-specific, and studies have shown that oxybutynin has a greater inhibitory effect on salivation than on bladder contraction, resulting in a high incidence of dry mouth.

Tolterodine (Detrol, Detrol LA) is the first major drug to address the problems of treatment tolerability. Unlike oxybutynin, tolterodine has a greater inhibitory effect on bladder contraction than on salivation. Therefore, it has fewer side effects (eg, dryness of mouth), but with comparable efficacy.

A long-acting, extended-release formulation of oxybutynin (Ditropan XL), which is associated with fewer adverse effects than its immediate-release predecessor, and efficacy that is comparable to the agents above, is also currently available.

A study of 148 men aged 42-88 years with persistent OAB symptoms while receiving alpha-blocker therapy for bladder outlet obstruction found that behavioral and antimuscarinic therapy are effective in reducing these symptoms when added to alpha-blocker treatment. The study concluded that behavioral therapy is at least as effective as antimuscarinic therapy.

Other anticholinergic agents used to treat OAB include the following:

1. Trospium chloride (Sanctura);

2. Propiverine hydrochloride (approved in Europe, not in the United States);

3. Solifenacin (Vesicare);

4. Darifenacin (Enablex);

5. Oxybutynin patch (Oxytrol);

6. Fesoterodine (Toviaz).

The first over-the-counter (OTC) treatment for OAB in women aged 18 or older, Oxytrol for Women, was approved by the U.S. Food and Drug Administration (FDA) in January 2013. The drug is available only by prescription for men.

No head-to-head trials of these agents have assessed efficacy and side effects. The available literature suggests that these agents are clinically similar and that none appears to offer a major distinct advantage over the others. However, slight differences in these agents may be clinically useful in drug selection.

In two placebo-controlled studies that compared tolterodine (Detrol LA) 4 mg and fesoterodine 8 mg, a statistically significant greater reduction in urge urinary incontinence episodes was found with fesoterodine 8 mg.

In a 16-week randomized, double-blind, placebo-controlled study, increasing the solifenacin dose from 5 to 10 mg in OAB patients with more severe symptoms improved outcomes. Patients who had their dose increased experienced greater reductions in the mean number of severe urgency episodes from week 8 through the end of the study and significant reductions in mean total urgency score, mean maximum Patient

Perception of Intensity of Urgency Scale urgency rating, and mean micturition frequency.

Darifenacin has the most selective M3 activity and has shown the greatest degree of safety with respect to lack of impact on cognitive function, which suggests that it may offer a slight advantage in elderly patients. It is available in 2 formulations.

Trospium is a large-molecule quaternary amine with minimal central nervous system (CNS) penetration. It has a unique liver metabolic pathway, making it the most suitable for patients receiving multiple drugs with cytochrome P-450 (CYP-450) utilization.

The patch version of oxybutynin has minimal dry mouth or constipation adverse effects but is available in only a single, relatively small dosage and may irritate the skin. A gel formulation of oxybutynin is available that delivers 5 mg of oxybutynin and is not associated with the skin irritation of the patch.

Fesoterodine is the newest anticholinergic available for OAB. It shares the same active metabolite as tolterodine, 5-HMT; however, fesoterodine is efficiently and extensively metabolized to 5-HMT via ubiquitous esterases and thus does not have the pharmacokinetic variability associated with tolterodine. Furthermore, head-to-head studies have demonstrated superiority of the 8-mg dose of fesoterodine compared with tolterodine (Detrol LA) 4 mg in the reduction of UUI episodes.

Although efficacious, anticholinergic agents cause frequent adverse effects such as dry mouth, constipation, blurred vision, and drowsiness. These effects are dose-related and can severely limit tolerability, especially in elderly patients. Anticholinergics may also produce confusion, especially in elderly patients with pre-existing dementia.

A meta-analysis of antimuscarinic therapy for OAB in adults aged 65 years and older found higher rates of treatment discontinuation due to adverse events and dry mouth, compared with placebo. Adverse events that occurred at rates significantly higher than with placebo were dizziness, dyspepsia, and urinary retention with fesoterodine; headache with darifenacin; and urinary tract infections with solifenacin.

Anticholinergics are contraindicated in patients with urinary retention, gastric retention, and untreated narrow-angle glaucoma. They should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, treated narrow angle glaucoma, and myasthenia gravis. Cases of angioedema of the face, lips, tongue and/or pharynx have been reported with several of these agents, and patients should be counseled to seek care immediately if they experience swelling.

Various attempts have been made to improve the organ selectivity of these drugs to overcome their adverse effects. These include the development of new antimuscarinic agents with structural modifications and the use of innovative drug-delivery methods. The benefits of improved drug-delivery systems extends to the long-term therapeutic efficacy, with improved tolerability and patient compliance. [59]

Prospective therapies aimed at novel targets with novel mechanisms of action are currently at different stages of clinical development. These include beta3-adrenoceptor agonists, K+ channel openers, and 5-HT modulators.

Beta3-receptor agonists

In June 2012, the FDA approved the first beta3-receptor agonist, mirabegron (Myrbetriq), for symptoms of urge urinary incontinence, urgency, and urinary frequency associated with OAB.

Beta3-receptor agonists act directly to inhibit afferent nerve firing independent of the relaxing effects on the bladder smooth muscle. In one trial, mirabegron was shown to be safe and efficacious over a 1-year period. In another multicenter, randomized, double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial, mirabegron significantly improved the number of incontinence episodes and the number of micturitions per 24 hours compared with placebo and was well tolerated. Benefits of mirabegron have been demonstrated in men, the elderly, and Asian patients.

Combination therapy

Ongoing studies are evaluating the use of combination therapy with an anticholinergic agent plus a beta3-adrenoceptor agonist. The goal is to achieve improvement in OAB symptoms with a decreased incidence of side effects.

A dose-ranging study by Abrams et al that explored six doses of combination therapy with solifenacin plus mirabegron, five doses of monotherapy with either agent, or placebo, concluded that mirabegron 25/50 mg plus solifenacin 5/10 mg improves objective and subjective efficacy outcomes compared with placebo or solifenacin 5 mg. Micturition frequency normalization was approximately twofold greater with solifenacin 10 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg versus solifenacin 5 mg.

In a 12-week study by Drake et al of patients who remained incontinent despite treatment with solifenacin at a dose of 5 mg, the addition of mirabegron (50 mg) significantly improved incontinence and frequent urination, and was superior to monotherapy with solifenacin at a dose of 10 mg. Combination therapy was well tolerated.

In a prospective study in 26 elderly Japanese men with OAB who had been taking tamsulosin, the addition of mirabegron significantly improved OAB symptoms and

significantly increased voided volume without impairing bladder contractility during voiding. In a multinational phase II 12-week trial, the combination of mirabegron (25/50 mg) with solifenacin (5/10 mg) resulted in improved objective and subjective efficacy outcomes compared with placebo or solifenacin (5 mg) alone.

Botulinum toxins

Detrusor injections of onabotulinumtoxinA are approved by the FDA for the treatment of adults with OAB who cannot use, or do not adequately respond to, anticholinergic medication. Most of the effects of botulinum toxin are thought to be the result of inhibition of the release of acetylcholine from the presynaptic nerve terminal, which prevents stimulation of the detrusor muscle. Review of the clinical data shows a profound effect of botulinum toxin on involuntary detrusor contractions and elevated detrusor pressures. Botulinum neurotoxin type A may also affect other neurotransmitters, such as sensory/afferent neurotransmitters.

Approval was based on safety and efficacy data from two double-blind, randomized, multi-center, placebo-controlled 24-week clinical studies. By week 12 in both clinical trials, patients treated with onabotulinumtoxinA had a reduction of at least 50% in frequency of daily urinary incontinence episodes from baseline compared to placebo. Duration for efficacy with onabotulinumtoxinA at reducing urinary leakage and other symptoms of OAB was 135-168 days compared to 88-92 days with placebo.

OnabotulinumtoxinA is also FDA approved for treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication. [59]

The benefits of repeated detrusor injections of botulinum neurotoxin type A were demonstrated in a prospective study by Khan et al in 137 patients with multiple sclerosis–neurogenic OAB. Before treatment, 83% of the patients were incontinent; 4 weeks after the first treatment, 76% were completely dry. The efficacy was sustained with repeat injections. The median interval between retreatments remained constant at 12-13 months. Furthermore, considerable improvement was noted in the mean urogenital distress inventory and incontinence impact questionnaire 7 scores initially and after subsequent treatments.

A network meta-analysis concluded that after 12 weeks, onabotulinumtoxinA 100 U provides greater relief of OAB symptoms than mirabegron or anticholinergics in adults with idiopathic OAB. However, a long-term follow-up study of 128 women who received intravesical onabotulinumtoxinA for idiopathic OAB found that 70% had discontinued treatment—27% because of insufficient effect and 43% of intolerance. Most patients discontinued treatment after the first (79%) and second (19%) injections. Only 2% of patients had discontinued treatment after more than two injections.

Tricyclic antidepressants

Tricyclic antidepressants such as imipramine and doxepin have also been used to treat OAB. These block the reuptake of noradrenaline and serotonin. However, whether this mechanism mediates the beneficial effects on bladder hyperactivity is unclear. These agents have been associated with cardiac dysrhythmias and mental status changes and thus should be used with caution in elderly patients. Tricyclic antidepressants are not recognized as first-line therapy for the treatment of OAB.

Pelvic floor muscle therapy (PFMT)

PFMT involves exercises designed to improve the function of the pelvic floor muscles. The rationale for use of PFMT in urgency urinary incontinence and OAB is that contraction of the muscles can reflexively or voluntarily inhibit contraction of the detrusor muscle. PFMT is defined as any program of repeated voluntary pelvic floor muscle contractions taught by a healthcare professional.

Regular daily exercising of pelvic muscles can improve, and even prevent, urinary incontinence. This is particularly helpful in younger women. PFM exercises should be performed 30-80 times daily for at least 8 weeks. The principle behind PFM exercises is to strengthen the muscles of the pelvic floor, thereby improving function of the urethral sphincter. The success of PFM exercises depends on proper technique and adherence to a regular exercise program. These exercises have limited value in elderly patients and in patients with poor mobility.

Another approach is to use vaginal cones to strengthen the muscles of the pelvic floor. A vaginal cone is a weighted device that is inserted into the vagina. The woman contracts the pelvic floor muscles in an effort to hold the device in place. The contraction should be held for up to 15 minutes and should be performed twice daily. Within 4-6 weeks, symptoms improve in about 70% of women who try this method.

Biofeedback-assisted therapy

Biofeedback is a method of positive reinforcement in which electrodes are placed on patient's abdomen and the anal area. Biofeedback-assisted behavioral therapy uses biofeedback to teach patients how to control normal physiologic responses of the bladder and pelvic floor muscles that mediate incontinence. Used in conjunction with PFM exercises, biofeedback helps patients gain awareness and control of the pelvic muscles.

Early biofeedback for OAB consisted of bladder-pressure biofeedback. Feedback of pelvic floor muscular activity was subsequently added. Bladder-pressure biofeedback was not widely adopted because of the need for catheterization during each training session. Biofeedback is most commonly used to teach individuals to identify and contract their pelvic floor muscles.

Some therapists place a sensor in the vagina (in women) or in the anus

(in men) to assess contraction of the pelvic floor muscles. A monitor displays a graph that shows which muscles are contracting and which are at rest. The therapist can help the patient identify the correct muscles for performing Kegel exercises. About 75% of people who use biofeedback to enhance performance of Kegel exercises report symptom improvement, with 15% considered cured.

Electrical stimulation

Pelvic floor electrical stimulation involves the use of mild electrical pulses to elicit contractions in a specific group of muscles. The current may be delivered using an anal or vaginal probe. Pelvic floor electrical stimulation should be performed in conjunction with PFM exercises. The electrical stimulation therapy may be performed at the clinic or at home. Treatment sessions usually last 20 minutes and may be performed every 1-4 days. Some clinical studies have shown promising results in treating urge incontinence with electrical stimulation.

Urgent PC (Cogentix Medical, Minnetonka, MN) is an office-based method of neuromodulation that uses percutaneous tibial nerve stimulation via needle electrodes to deliver retrograde access to the sacral nerve. Typically, twelve 30-minute sessions are performed, followed by a maintenance regimen. Urgent PC is approved by the FDA for treatment of OAB symptoms such as urinary urgency, urinary frequency, and urge incontinence.

Surgical Therapy

Guidelines for the management of OAB by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) suggest that surgical treatment may be offered as a third-line option for carefully selected patients. Procedures include neuromodulation and, rarely, augmentation cystopasty or urinary diversion. Neuromodulation (sacral nerve stimulation; InterStim, Medtronic, Minneapolis, Minn) is a new technique that is FDA approved for the management of OAB and urge urinary incontinence. It requires the surgical implantation of a small device at the S3 level. Typically, an external stimulator is placed initially, and if the patient experiences a 50% or greater reduction in symptoms, a permanent internalized stimulator is placed.

A prospective study in 272 patients undergoing neuromodulation reported an adverse event rate of 30%. Most were minor, but 13% of patients required surgical intervention, typically revision or replacement. For more information, go to Sacral Nerve Stimulation.

Augmentation cystoplasty is rarely necessary in idiopathic OAB. However, it may be used in individuals with refractory neurogenic OAB, particularly in those with poor compliance. In this reconstructive procedure, a segment of the bowel is removed and used to replace a portion of the bladder. For more information, go to Augmentation Cystoplasty.

Urinary incontinence

Urinary incontinence is an underdiagnosed and underreported problem that increases with age – affecting 50-84% of the elderly in long-term care facilities – and at any age is more than twice as common in females than in males.

Types of urinary incontinence

Stress. Urine leakage associated with increased abdominal pressure from laughing, sneezing, coughing, climbing stairs, or other physical stressors on the abdominal cavity and, thus, the bladder.

Urge. Involuntary leakage accompanied by or immediately preceded by urgency.

Mixed. A combination of stress and urge incontinence, marked by involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.

Functional. The inability to hold urine due to reasons other than neuro-urologic and lower urinary tract dysfunction (eg, delirium, psychiatric disorders, urinary infection, impaired mobility)

Diagnostics

Patients with urinary incontinence should undergo a basic evaluation that includes a history, physical examination, and urinalysis. In selected patients, the following may also be needed:

1. Voiding diary;

2. Cotton swab test;

3. Cough stress test;

4. Measurement of postvoid residual (PVR) urine volume;

5. Cystoscopy.

The following points regarding the clinical presentation should be sought when obtaining the history:

1. Severity and quantity of urine lost and frequency of incontinence episodes;

2. Duration of the complaint and whether problems have been worsening;

3. Triggering factors or events (eg, cough, sneeze, lifting, bending, feeling of urgency, sound of running water, sexual activity/orgasm);

4. Constant versus intermittent urine loss;

5. Associated frequency, urgency, dysuria, pain with a full bladder;

6. History of urinary tract infections (UTIs);

7. Concomitant fecal incontinence or pelvic organ prolapsed;

8. Coexistent complicating or exacerbating medical problems;

9. Obstetrical history, including difficult deliveries, grand multiparity, forceps use, obstetrical lacerations, and large babies;

10. History of pelvic surgery, especially prior incontinence procedures, hysterectomy, or pelvic floor reconstructive procedures;

11. Other urologic procedures;

12. Spinal and central nervous system surgery;

13. Lifestyle issues, such as smoking, alcohol or caffeine abuse, and occupational and recreational factors causing severe or repetitive increases in intra-abdominal pressure.

Medications that may be associated with urinary incontinence include the following:

1. Cholinergic or anticholinergic drugs;

2. Alpha-blockers;

3. Over-the-counter allergy medications;

4. Estrogen replacement;

5. Beta-mimetics;

6. Sedatives;

7. Muscle relaxants;

8. Diuretics;

9. Angiotensin-converting enzyme (ACE) inhibitors.

Treatment

Successful treatment of urinary incontinence must be tailored to the specific type of incontinence and its cause. The usual approaches are as follows:

Stress incontinence: Pelvic floor physiotherapy, anti-incontinence devices, and surgery.

Urge incontinence: Changes in diet, behavioral modification, pelvic-floor exercises, and/or medications and new forms of surgical intervention.

Mixed incontinence: Pelvic floor physical therapy, anticholinergic drugs, and surgery.

Overflow incontinence: Catheterization regimen or diversion.

Functional incontinence: Treatment of the underlying cause.

Absorbent products may be used temporarily until a definitive treatment has a chance to work, in patients awaiting surgery, or long-term under the following circumstances:

1. Persistent incontinence despite all appropriate treatments;
2. Inability to participate in behavioral programs, due to illness or disability;
3. Presence of an incontinence disorder that cannot be helped by medications;
4. Presence of an incontinence disorder that cannot be corrected by surgery.

In stress and urge urinary incontinence, the following medications may provide some benefit:

1. Alpha-adrenergic agonists;
2. Anticholinergic agents;
3. Antispasmodic drugs;
4. Tricyclic antidepressants;
5. Estrogen;
6. Alpha-adrenergic blockers;
7. Botulinum toxin.

Surgical care for stress incontinence involves procedures that increase urethral outlet resistance, including the following:

1. Bladder neck suspension;
2. Periurethral bulking therapy;
3. Midurethral slings;
4. Artificial urinary sphincter.

The transobturator male sling may be of particular benefit to men who experience stress incontinence after prostatectomy. Transobturator vaginal tape (TVT-O) is widely used for stress incontinence in women.

Surgical care for urge incontinence involves procedures that improve bladder compliance or bladder capacity, including the following:

1. Sacral nerve modulation;

2. Injection of neurotoxins such as botulinum toxin;

3. Bladder augmentation.

Overactive bladder

The International Continence Society (ICS) defines overactive bladder (OAB) as a syndrome consisting of urinary urgency, with or without urgency urinary incontinence, usually with urinary frequency and nocturia, in the absence of causative infection or pathologic conditions and suggestive of underlying detrusor overactivity (phasic increases in detrusor pressure).

Urgency, the hallmark of OAB, is defined as the sudden compelling desire to urinate, a sensation that is difficult to defer. Urgency urinary incontinence (UUI) is urinary leakage associated with urgency. UUI is one of the most common types of urinary incontinence. Some women may have both stress urinary incontinence and UUI, and this is called mixed urinary incontinence.

Urinary frequency is defined as voiding 8 or more times in a 24-hour period. Nocturia is defined as the need to wake 1 or more times per night to void.

The term OAB has been adopted by the US Food and Drug Administration (FDA) to expand the number and types of patients eligible for clinical trials. As noted, OAB may include not only urgency urinary incontinence but also urgency, frequency, dysuria, and nocturia. Other terms used include detrusor overactivity, detrusor instability, detrusor hyperreflexia, and involuntary bladder contractions.

A preliminary diagnosis of OAB can be made on the basis of the history and physical examination, in conjunction with a few simple office and laboratory tests.

Treatment of OAB is aimed at reducing the debilitating symptoms in order to improve the overall the quality of life in affected patients. Anticholinergic agents that target the muscarinic receptors in the bladder (antimuscarinic agents) are the pharmacologic treatment of choice because they reduce the contractility of the detrusor muscle. However, the use of antimuscarinic drugs is limited by certain adverse effects, particularly dry mouth and constipation.

Behavioral therapy focusing on dietary and lifestyle modification, voiding regimens, and pelvic floor muscle exercises is also helpful in the management of OAB and may be used by itself or in conjunction with antimuscarinic therapy.

Various attempts have been made to improve the bladder selectivity of these drugs, and thereby overcome the systemic adverse effects, as well as to come up with different formulations to lower peak levels of agents and avoid first-pass liver metabolism, which is often associated with an increased risk of adverse effects in some of these agents. These include the development of new antimuscarinic agents with structural modifications and the use of innovative drug-delivery methods.

The advancement in the drug-delivery systems extends to the long-term therapeutic efficacy, with improved tolerability and patient compliance; however, future prospective therapies are aimed at novel targets with novel mechanisms of action, including beta3-adrenoceptor agonists, K+ channel openers, and 5-HT modulators. These prospective therapies are currently at different stages of clinical development.

Among other investigational therapies, neurokinin receptor antagonists, alpha-adrenoceptor antagonists, nerve growth factor inhibitors, gene therapy, and stem cell–based therapies are of considerable interest. The future development of new modalities in OAB treatment appears promising.

Theme # 13: Erectile dysfunction. Premature ejaculation. Delayed ejaculation.

13.1 Erectile dysfunction

Erectile dysfunction (ED) affects 50% of men older than 40 years, exerting substantial effects on quality of life. This common problem is complex and involves multiple pathways. Penile erections are produced by an integration of physiologic processes involving the central nervous, peripheral nervous, hormonal, and vascular systems. Any abnormality in these systems, whether from medication or disease, has a significant impact on the ability to develop and sustain an erection, ejaculate, and experience orgasm.

A common and important cause of ED is vasculogenic. Many men with ED have comorbid conditions such as hyperlipidemia, hypercholesterolemia, tobacco abuse, diabetes mellitus, or coronary artery disease (CAD). The Princeton III Consensus recommends screening men who present with ED for cardiovascular risk factors; ED may be the earliest presentation of atherosclerosis and vascular disease.

Additionally, the physiologic processes involving erections begin at the genetic level. Certain genes become activated at critical times to produce proteins vital to sustaining this pathway. Some researchers have focused on identifying particular genes that place men at risk for ED. At present, these studies are limited to animal models, and little success has been reported to date. Nevertheless, this research has given rise to many new treatment targets and a better understanding of the entire process.

The first step in treating the patient with ED is to take a thorough sexual, medical, and psychosocial history. Questionnaires are available to assist clinicians in obtaining important patient data. Successful treatment of sexual dysfunction has been demonstrated to improve sexual intimacy and satisfaction, improve sexual aspects of quality of life, improve overall quality of life, and relieve symptoms of depression. [68]

The availability of phosphodiesterase-5 (PDE5) inhibitors—sildenafil, vardenafil, tadalafil, and avanafil—has fundamentally altered the medical management of ED. In addition, direct-to-consumer marketing of these agents over the last 15 years has increased the general public's awareness of ED as a medical condition with underlying causes and effective treatments.

Unfortunately, some patients may have an overly simplified understanding of the role of PDE5 inhibitors in ED management. Such patients may not expect or be willing to undergo a long evaluation and testing process to obtain a better understanding of their sexual problem, and they may be less likely to involve their partner in discussing their sexual relationship with the physician. They may expect to obtain medications through a phone call to their doctor or even over the

Internet, with minimal or no physician contact at all.

In such cases, the physician's role may have to include efforts to educate patients about realistic sexual expectations. These efforts can help prevent the misuse or overuse of these remarkable medications.

Although this article focuses primarily on the male with ED, it is essential to remember that the sexual partner plays an integral role in treatment. If successful and effective management is to be achieved, evaluation and discussion of any intervention must include both partners.

Diagnostic criteria for erectile disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), classifies erectile disorder as belonging to a group of sexual dysfunction disorders typically characterized by a clinically significant inability to respond sexually or to experience sexual pleasure.

Sexual functioning involves a complex interaction among biologic, sociocultural, and psychological factors, and the complexity of this interaction makes it difficult to ascertain the clinical etiology of sexual dysfunction. Before any diagnosis of sexual dysfunction is made, problems that are explained by a nonsexual mental disorder or other stressors must first be addressed. Thus, in addition to the criteria for erectile disorder, the following must be considered:

1. Partner factors (eg, partner sexual problems or health issues)

2. Relationship factors (eg, communication problems, differing levels of desire for sexual activity, or partner violence)

3. Individual vulnerability factors (eg, history of sexual or emotional abuse, existing psychiatric conditions such as depression, or stressors such as job loss)

4. Cultural or religious factors (eg, inhibitions or conflicted attitudes regarding sexuality)

5. Medical factors (eg, an existing medical condition or the effects of drugs or medications)

The specific DSM-5 criteria for erectile disorder are as follows:

1. In almost all or all (75-100%) sexual activity, the experience of at least one of the following three3 symptoms: (1) marked difficulty in obtaining an erection during sexual activity, (2) marked difficulty in maintaining an erection until the completion of sexual activity, or (3) marked decrease in erectile rigidity. [68]

2. The symptoms above have persisted for approximately 6 months

3. The symptoms above cause significant distress to the individual

4. The dysfunction cannot be better explained by nonsexual mental disorder, a medical condition, the effects of a drug or medication, or

severe relationship distress or other significant stressors

The severity of delayed ejaculation is classified as mild, moderate or severe on the basis of the level of distress the patient exhibits over the symptoms. The duration of the dysfunction is specified as follows:

1. Lifelong (present since first sexual experience)

2. Acquired (developing after a period of relative normal sexual functioning)

In addition, the context in which the dysfunction occurs is specified as follows:

1. Generalized (not limited to certain types of stimulation, situations, or partners)

2. Situational (limited to specific types of stimulation, situations, or partners)

Lifelong erectile disorder is associated with psychological factors, whereas acquired erectile disorder is more often related to biologic factors. Distress associated with erectile disorder is lower among older men than among younger men.

Anatomy

An understanding of penile anatomy is fundamental to management of ED. The common penile artery, which derives from the internal pudendal artery, branches into the dorsal, bulbourethral, and cavernous arteries (Fig. 53).

The dorsal artery provides for engorgement of the glans during erection, whereas the bulbourethral artery supplies the bulb and the corpus spongiosum. The cavernous artery effects tumescence of the corpus cavernosum and thus is principally responsible for erection. The cavernous artery gives off many helicine arteries, which supply the trabecular erectile tissue and the sinusoids. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection.

Venous drainage of the corpora originates in tiny venules that lead from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel in the trabeculae between the tunica and the peripheral sinusoids to form the subtunical venous plexus before exiting as the emissary veins.

Sexual behavior involves the participation of autonomic and somatic nerves and the integration of numerous spinal and supraspinal sites in the central nervous system (CNS). The penile portion of the process that leads to erections represents only a single component.

The hypothalamic and limbic pathways play an important role in the integration and control of reproductive and sexual functions. The medial preoptic center, paraventricular nucleus, and anterior hypothalamic regions modulate erections and coordinate autonomic events associated with sexual responses.

Afferent information is assessed in the forebrain and relayed to the hypothalamus. The efferent pathways from the hypothalamus enter the medial forebrain bundle and project caudally near the lateral part of the substantia nigra into the midbrain tegmental region.

Several pathways have been described to explain how information travels from the hypothalamus to the sacral autonomic centers. One pathway travels from the dorsomedial hypothalamus through the dorsal and central gray matter, descends to the locus ceruleus, and projects ventrally in the mesencephalic reticular formation. Input from the brain is conveyed through the dorsal spinal columns to the thoracolumbar and sacral autonomic nuclei.

The primary nerve fibers to the penis are from the dorsal nerve of the penis, a branch of the pudendal nerve. The cavernosal nerves are a part of the autonomic nervous system and incorporate both sympathetic and parasympathetic fibers. [68, 69]

They travel posterolaterally along the prostate and enter the corpora cavernosa and corpus spongiosum to regulate blood flow during erection and detumescence.

The dorsal somatic nerves are also branches of the pudendal nerves. They are primarily responsible for penile sensation.

Pathophysiology

Factors mediating contraction and relaxation. The degree of contraction of cavernosal smooth muscle determines the functional state of the penis. The balance between contraction and relaxation is controlled by central and peripheral factors that involve many transmitters and transmitter systems.

The nerves and endothelium of sinusoids and vessels in the penis produce and release transmitters and modulators that control the contractile state of corporal smooth muscles.

Although the membrane receptors play an important role, downstream signaling pathways are also important. The RhoA–Rho kinase pathway is involved in the regulation of cavernosal smooth muscle contraction.

Factors that mediate contraction in the penis include noradrenaline, endothelin-1, neuropeptide Y, prostanoids, angiotensin II, and others not yet identified. Factors that mediate relaxation include acetylcholine, nitric oxide (NO), vasoactive intestinal polypeptide, pituitary adenylyl cyclase–activating peptide, calcitonin gene–related peptide, adrenomedullin, adenosine triphosphate, and adenosine prostanoids.

Nitric oxide pathway. The NO pathway is of critical importance in the physiologic induction of erections. The drugs currently used to treat ED were developed as a result of experimental and clinical work showing that NO released from nerve endings relaxes the vascular and corporal smooth muscle cells of the penile arteries and trabeculae, resulting in an erection.

NO is produced by the enzyme NO synthase (NOS). NOS plays many roles, ranging from homeostasis to immune system regulation. To date, 3 subtypes have been identified: nNOS, iNOS, and eNOS, which are produced by the genes NOS1, NOS2, and NOS3, respectively. This nomenclature is derived from the sources of the original isolates: neuronal tissue (nNOS), immunoactivated macrophage cell lines (iNOS), and vascular endothelium (eNOS).

The subtypes are not, however, limited to the tissues from which they were first isolated.

All NOS subtypes produce NO, but each may play a different biologic role in various tissues. nNOS and eNOS are considered constitutive forms because they share biochemical features: They are calcium-dependent, they require calmodulin and reduced nicotinamide adenine dinucleotide phosphate for catalytic activity, and they are competitively inhibited by arginine derivatives.

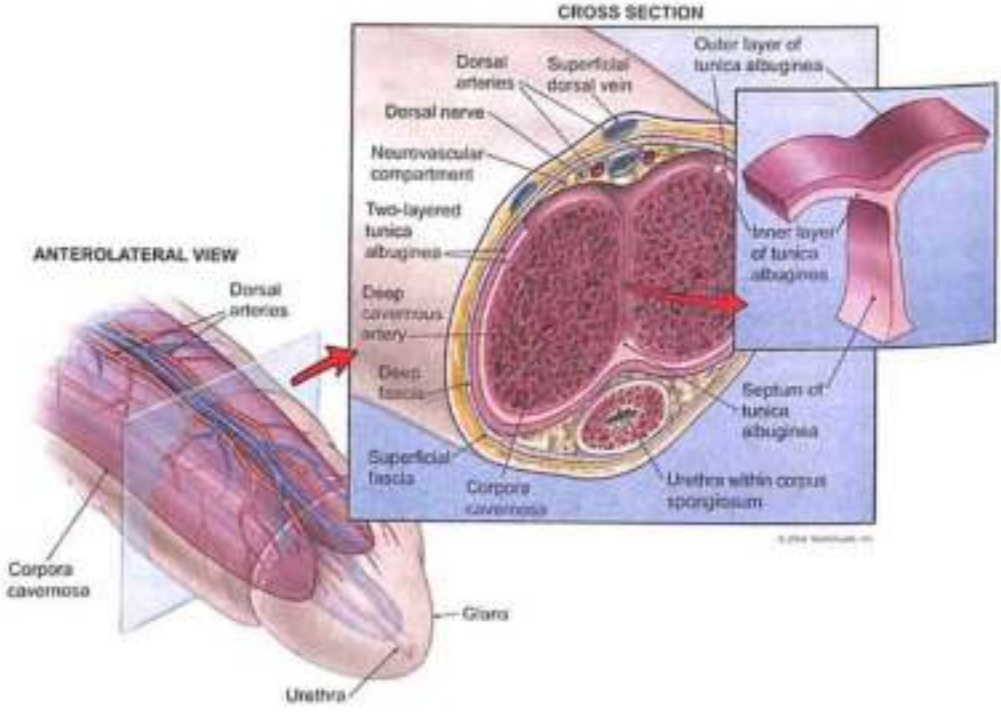

Fig. 53 - Anatomy of the penis

illustration from http://www.pcyrosler.org/wp-content/uploads/2011/11/anatomy-1.jpg)

nNOS is involved in the regulation of neurotransmission, and eNOS is involved in the regulation of blood flow.

iNOS is considered an inducible form because it is calcium-independent. iNOS is induced by the inflammatory process, in which it participates in the production of nitrogenous amines. This subtype has been shown to be involved in carcinogenesis, leading to transitional cell carcinoma.

Inside the cell, NOS catalyzes the oxidation of L-arginine to NO and L-citrulline. Endogenous blockers of this pathway have been identified. The gaseous NO that is produced acts as a neurotransmitter or paracrine messenger. Its biologic half-life is only 5 seconds. NO may act within the cell or diffuse and interact with nearby target cells.

In the corpora cavernosa, NO activates guanylate cyclase, which in turn increases cyclic guanosine monophosphate (cGMP). Relaxation of vascular smooth muscles by cGMP leads to vasodilation and increased blood flow. [68, 69]

Alteration of NO levels is the focus of several approaches to the treatment of ED. Inhibitors of phosphodiesterase, which primarily hydrolyze cGMP type 5, provided the basis for the development of the PDE5 inhibitors. Chen et al administered oral L-arginine and reported subjective improvement in 50 men with ED. These supplements are readily available commercially. Reported adverse effects include nausea, diarrhea, headache, flushing, numbness, and hypotension.

Increasing evidence indicates that NO acts centrally to modulate sexual behavior and to exert its effects on the penis. NO is thought to act in the medial preoptic area and the paraventricular nucleus. Injection of NOS inhibitors prevents the erectile response in rats that have been given erectogenic agents.

Normal erectile process

Erections occur in response to tactile, olfactory, and visual stimuli. The ability to achieve and maintain a full erection depends not only on the penile portion of the process but also on the status of the peripheral nerves, the integrity of the vascular supply, and biochemical events within the corpora. The autonomic nervous system is involved in erection, orgasm, and tumescence. The parasympathetic nervous system is primarily involved in sustaining and maintaining an erection, which is derived from S2-S4 nerve roots. [70]

Sexual stimulation causes the release of neurotransmitters from cavernosal nerve endings and relaxation factors from endothelial cells lining the sinusoids. NOS produces NO from L-arginine, and this, in turn, produces other muscle-relaxing chemicals, such as cGMP and cyclic adenosine monophosphate (cAMP), which work via calcium channel and protein kinase mechanisms (see the image below). This results in the relaxation of smooth muscle in the

arteries and arterioles that supply the erectile tissue, producing a dramatic increase in penile blood flow.

Relaxation of the sinusoidal smooth muscle increases its compliance, facilitating rapid filling and expansion. The venules beneath the rigid tunica albuginea are compressed, resulting in near-total occlusion of venous outflow. These events produce an erection with an intracavernosal pressure of 100 mm Hg.

Additional sexual stimulation initiates the bulbocavernous reflex. The ischiocavernous muscles forcefully compress the base of the blood-filled corpora cavernosa, and the penis reaches full erection and hardness when intracavernosal pressure reaches 200 mm Hg or more. At this pressure, both inflow and outflow of blood temporarily cease.

Detumescence results from cessation of neurotransmitter release, breakdown of second messengers by phosphodiesterase, and sympathetic nerve excitation during ejaculation. Contraction of the trabecular smooth muscle reopens the venous channels, allowing the blood to be expelled and thereby resulting in flaccidity.

Role of testosterone

Both ED and low testosterone (hypogonadism) increase with age. The incidence of the latter is 40% in men aged 45 years and older. Testosterone is known to be important in mood, cognition, vitality, bone health, and muscle and fat composition. It also plays a key role in sexual dysfunction (eg, low libido, poor erection quality, ejaculatory or orgasmic dysfunction, reduced spontaneous erections, or reduced sexual activity).

The association between low testosterone and ED is not entirely clear. Although these 2 processes certainly overlap in some instances, they are distinct entities. Some 2-21% of men have both hypogonadism and ED; however, it is unclear to what degree treating the former will improve erectile function. About 35-40% of men with low testosterone see an improvement in their erections with testosterone replacement; however, almost 65% of these men see no improvement.

One study examined the role of testosterone supplementation in hypogonadal men with ED. These men were considered nonresponders to sildenafil, and their erections were monitored by assessing nocturnal penile tumescence (NPT). After these men were given testosterone transdermally for 6 months, the number of NPTs increased, as did the maximum rigidity with sildenafil. This study suggests that a certain level of testosterone may be necessary for PDE5 inhibitors to function properly.

In a randomized double-blind, parallel, placebo-controlled trial, sildenafil plus testosterone was not superior to sildenafil plus placebo in improving erectile function in men with ED and low testosterone levels. The objective of the study was to determine whether the addition of testosterone to sildenafil therapy improves erectile response in men with ED and low testosterone levels. [69]

However, in contrast, a recent systematic review of published studies, the authors concluded that overall, the addition of testosterone to PDE-5 inhibitors might benefit patients with ED associated with testosterone levels of less than 300 ng/dL (10.4 nmol/L) who failed monotherapy. A limitation of existing studies are their heterogeneous nature and methodological drawbacks.

The mechanisms by which testosterone plays a role in erectile function are not completely understood. A study evaluating the effect of testosterone on erections in surgically castrated rabbits and control animals, in which the rabbits' intracavernosal pressures were compared after cavernosal nerve stimulation, determined that castrated rabbits had much lower pressures after stimulation than control rabbits did. Notably, the pressures increased when castrated rabbits received exogenous testosterone replacement.

Another study compared the response of surgically and medically castrated rabbits to vardenafil with that of control rabbits. Castrated rabbits did not respond to vardenafil, whereas noncastrated rabbits did respond appropriately. This result suggests that a minimum amount of testosterone is necessary for PDE5 inhibitors to produce an erection. [65]

Another study found that castrated rats had erections if given testosterone alone or dihydrotestosterone (DHT) and 5-alpha reductase inhibitors but not if given testosterone and 5-alpha reductase inhibitors. This finding suggests that DHT is the active component and is necessary at a certain level for rats to have an erection.[67]

This study also measured intracavernosal pressure to monitor erections and NOS activity in the penile cytosol. NO levels correlated with intracavernosal pressure, which suggests that testosterone and DHT act through NOS. Testosterone and DHT may act at the genomic level to stimulate production of NOS.

It appears that testosterone has NOS-independent pathways as well. In one study, castrated rats were implanted with testosterone pellets and then divided into a group that received an NOS inhibitor (L-nitro-L-arginine methyl ester [L-NAME]) and a control group that received no enzyme. The castrated rats that were given testosterone pellets and L-NAME still had partial erections, a result suggesting the presence of a pathway independent of NOS activity.

Aetiology

ED usually has a multifactorial aetiology. Organic, physiologic, endocrine, and psychogenic factors are involved in the ability to obtain and maintain erections. In general, ED is divided into 2 broad categories, organic and psychogenic. Although most ED was once attributed to psychological factors, pure psychogenic ED is in fact uncommon; however, many men with organic etiologies may also have an associated psychogenic component.

Conditions that may be associated with ED include

diabetes, hypertension, and CAD, as well as neurologic disorders, endocrinopathies, benign prostatic hyperplasia, sleep apnea, COPD, and depression. In fact, almost any disease may affect erectile function by altering the nervous, vascular, or hormonal systems. Various diseases may produce changes in the smooth muscle tissue of the corpora cavernosa or influence the patient's psychological mood and behavior.

Conditions associated with reduced nerve and endothelium function (eg, aging, hypertension, smoking, hypercholesterolemia, and diabetes) alter the balance between contraction and relaxation factors. These conditions cause circulatory and structural changes in penile tissues, resulting in arterial insufficiency and defective smooth muscle relaxation. In some patients, sexual dysfunction may be the presenting symptom of these disorders.

Given the multiplicity of possible etiologic factors, it may be difficult to determine how much any given factor is contributing to the problem. A thorough evaluation is necessary for correct identification of the specific cause or causes in any given individual.

Vascular diseases. Vascular diseases account for nearly 50% of all cases of ED in men older than 50 years. These diseases include atherosclerosis, peripheral vascular disease, myocardial infarction (MI), and arterial hypertension.

Vascular damage may result from radiation therapy to the pelvis and prostate in the treatment of prostate cancer. Both the blood vessels and the nerves to the penis may be affected. Radiation damage to the crura of the penis, which are highly susceptible to radiation damage, can induce ED. Data indicate that 50% of men undergoing radiation therapy lose erectile function within 5 years after completing therapy; fortunately, some respond to one of the PDE5 inhibitors.

Trauma. Trauma to the pelvic blood vessels or nerves can also lead result in ED. Bicycle riding for long periods has been implicated as an etiologic factor; direct compression of the perineum by the bicycle seat may cause vascular and nerve injury. On the other hand, bicycling for less than 3 hours per week may be somewhat protective against ED. Some of the newer bicycle seats have been designed to diminish pressure on the perineum.

Diabetes mellitus. Diabetes is a well-recognized risk factor for ED. A systematic review and meta-analysis found that the prevalence of ED was 37.5% in type 1 diabetes, 66.3% in type 2 diabetes, and 52.5% in diabetes overall—a rate approximately 3.5 times higher than that in controls. The etiology of ED in diabetic men probably involves both vascular and neurogenic mechanisms. Evidence indicates that establishing good glycemic control can minimize this risk.

Abnormal cholesterol levels. The Massachusetts Male Aging Study (MMAS) documented an inverse

correlation between ED risk and high-density lipoprotein (HDL) cholesterol levels but did not identify any effect from elevated total cholesterol levels. Another study involving male subjects aged 45-54 years found a correlation with abnormal HDL cholesterol levels but also found a correlation with elevated total cholesterol levels. The MMAS included a preponderance of older men.

Respiratory diseases. Men with sleep disorders commonly experience ED. Heruti et al recommended that in adult male patients, ED should be considered when a sleep disorder—especially sleep apnea syndrome—is suspected, and vice versa.

Endocrine disorders. Hypogonadism that results in low testosterone levels adversely affects libido and erectile function. Hypothyroidism is a very rare cause of ED.

Penile conditions. Peyronie disease may result in fibrosis and curvature of the penis. Men with severe Peyronie disease may have enough scar tissue in the corpora to impede blood flow.

Mental health disorders. Mental health disorders, particularly depression, are likely to affect sexual performance. The MMAS data indicate an odds ratio of 1.82 for men with depression. Other associated factors, both cognitive and behavioral, may contribute. In addition, ED alone can induce depression.

Cosgrove et al reported a higher rate of sexual dysfunction in veterans with posttraumatic stress disorder (PTSD) than in veterans who did not develop this problem. The domains on the International Index of Erectile Function (IIEF) questionnaire that demonstrated the most change included overall sexual satisfaction and erectile function. Men with PTSD should be evaluated and treated if they have sexual dysfunction.

Prostate surgery. Prostate surgery for benign prostatic hyperplasia has been documented to be associated with ED in 10-20% of men. This association is thought to be related to nerve damage from cauterization. Newer procedures (eg, microwave, laser, or radiofrequency ablation) have rarely been associated with ED. [69]

Radical prostatectomy for the treatment of prostate cancer poses a significant risk of ED. A number of factors are associated with the chance of preserving erectile function. If both nerves that course on the lateral edges of the prostate can be saved, the chance of maintaining erectile function is reasonable. The odds depend on the age of the patient. Men younger than 60 years have a 75-80% chance of preserving potency, but men older than 70 years have only a 10-15% chance.

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study, designed to determine whether an individual man's sexual outcomes after most common treatments for early-stage prostate cancer could be accurately predicted on the basis of baseline characteristics and treatment plans, found that 2 years after treatment, 177 (35%) of 511 men who

underwent prostatectomy reported the ability to attain functional erections suitable for intercourse.

In comparison, 37% of men who had received external radiotherapy as their primary therapy reported the ability to attain functional erections suitable for intercourse, along with 43% of men who had received brachytherapy as primary treatment. Pretreatment sexual health-related quality of life score, age, serum prostate-specific antigen (PSA) level, race or ethnicity, body mass index, and intended treatment details were associated with functional erections 2 years after treatment.

After surgery, one of the oral PDE5 inhibitors (sildenafil, vardenafil, or tadalafil) is frequently used to assist in the recovery of erectile function. The benefit of penile rehabilitation therapy is under investigation, but results have been mixed.

Medications. ED is an adverse effect of many commonly prescribed medications. For example, some psychotropic drugs and antihypertensive agents are associated with ED. Persistent posttreatment ED is a listed adverse effect of the 5-alpha reductase inhibitors finasteride and dutasteride and of alpha blockers.

However, a review of a United Kingdom medical record database found no evidence that the use of 5-alpha reductase inhibitors independently increase the risk for ED. In 71,849 men with benign prostatic hyperplasia (BPH), the risk of ED was not increased with the use of finasteride or dutasteride only (odds ratio [OR] 0.94), or a 5-alpha reductase inhibitor plus an alpha blocker (OR 0.92) compared with an alpha blocker only. In addition, the risk of ED was not increase in 12 346 men prescribed finasteride 1 mg for alopecia, compared with unexposed men with alopecia (OR 0.95). The risk of ED did increase with longer duration of BPH, regardless of drug exposure. [71, 72]

Lifestyle. Exercise and lifestyle modifications may improve erectile function. Weight loss may help by decreasing inflammation, increasing testosterone, and improving self-esteem. Patients should be educated to increase activity, reduce weight, and stop smoking, as these efforts can improve or restore erectile function in men without comorbidities. Precise glycemic control in diabetic patients and pharmacologic treatment of hypertension may be important in preventing or reducing sexual dysfunction. Cigarette smoking has been shown to be an independent risk factor. In studies evaluating more than 6000 men, the risk of developing ED increased by a factor of 1.5.

Epidemiology

Sexual dysfunction is highly prevalent in men and women. In the MMAS, 52% of the respondents reported some degree of erectile difficulty. Complete ED, defined as (1) the total inability to obtain or maintain an erection during sexual stimulation and (2) the absence of nocturnal erections, occurred in 10% of the respondents. Mild and moderate ED occurred in 17% and 25% of

responders, respectively. Although the rate of mild ED in the MMAS remained constant (17%) in men aged 40-70 years, the number of men reporting moderate ED doubled (17-34%) and the number of men reporting complete ED tripled (5-15%). If the MMAS data are extrapolated to the US population, an estimated 18-30 million men are affected by ED.

In the National Health and Social Life Survey (NHSLS), a nationally representative probability sample of men and women aged 18-59 years, 10.4% of men reported being unable to achieve or maintain an erection during the past year. There is a striking correlation with the proportion of men in the MMAS who reported complete ED. [72]

All studies demonstrate a strong association with age, even when data are adjusted for the confounding effects of other risk factors. The independent association with aging suggests that vascular changes in the arteries and sinusoids of the corpora cavernosa, similar to those found elsewhere in the body, are contributing factors. Other risk factors associated with aging include depression, sleep apnea, and low HDL levels.

Long-term predictions based on an aging population and an increase in risk factors (eg, hypertension, diabetes, vascular disease, pelvic and prostate surgery, benign prostatic hyperplasia, and lower urinary tract symptoms) suggest a large increase in the number of men with ED.

In addition, the prevalence of ED is underestimated because physicians frequently do not question their patients about this disorder.

Prognosis

In a prospective population-based study of 1709 men aged 40-70 years, Araujo et al found that ED was significantly associated with increased all-cause mortality. The increase primarily resulted from cardiovascular mortality.

In a prospective study from the Prostate Cancer Prevention Trial database, Thompson et al reported that men presenting with ED had a significantly higher chance of developing a cardiovascular event over a 7-year follow-up period. The hazard ratio was 1.45, which is in the range of risk associated with current smoking or a family history of MI.

An analysis of 14 studies involving more than 90,000 patients with ED confirmed the relation between ED and an increased risk of cardiovascular events and mortality. Compared with patients without ED, those with ED had a 44% increased risk of cardiovascular events, a 25% increased risk of all-cause mortality, a 62% increased risk of MI, and a 39% increased risk of cerebrovascular events. Treatment of ED, either through lifestyle interventions or by pharmacologic means, may improve prognosis and reduce risk.

Associated morbidity may include various other male sexual dysfunctions, such as premature (early)

ejaculation and male hypoactive sexual desire disorder. The NHSLS found that 28.5% of men aged 18-59 years reported premature ejaculation, and 15.8% lacked sexual interest during the past year. An additional 17% reported anxiety about sexual performance, and 8.1% had a lack of pleasure in sex.

Men with ED may also experience anxiety or depression. Erectile disorder is common in men with lower urinary tract symptoms related to BPH. [72]

Patient Education

The laboratory results should be discussed with the patient and, if possible, with his sexual partner. This educational process allows a review of the basic aspects of the anatomy and physiology of the sexual response and an explanation of the possible etiology and associated risk factors (eg, smoking and the use of various medications). Treatment options and their benefits and risks should be discussed. This type of dialogue allows the patient and physician to cooperate in developing an optimal management strategy.

Patients with both ED and cardiovascular disease who receive treatment with an oral PDE5 inhibitor require education regarding what to do if anginal episodes develop while the drug is in their system. Such education includes stressing the importance of alerting emergency care providers to the presence of the drug so that nitrate treatment is avoided.

Patients receiving penile prostheses should be instructed in the operation of the prosthesis before surgery and again in the postoperative period. The prosthesis usually is not activated until approximately 6 weeks after surgery, so as to allow the edema and pain to subside. The prosthesis is checked in the office before the patient begins to use it.

History

In assessing a patient with erectile dysfunction (ED), the first step is to gather the following information:

1. Sexual history;

2. Medical and surgical history;

3. Medication and nonprescription drug history;

4. Psychological history.

ED is a sensitive topic, and the clinician must be aware of the patient's comfort level. Taking the history provides an opportunity for the physician to initiate patient and partner education about ED and its treatments and to facilitate communication. It also allows the physician to establish a rapport with the couple, which assists in treatment. Formal questionnaires may be valuable in this setting. [68]

Sexual history. Even clinicians who are not comfortable dealing with ED should inquire into the sexual aspect of the patient's health. A simple way to do this is simply to ask, "How's your sex life? Everything working all right?" This type of inquiry should elicit a clear, quick, direct "Everything's fine" from the patient. Any other response or even just a delay

in answering should suggest potential ED in that patient.

If ED is a possibility, questioning should be aimed at determining which part of the sexual response is abnormal. A clear description of the problem is vital. The following information should be elicited:

1. Whether the patient has difficulty obtaining an erection;

2. Whether the erection is suitable for penetration;

3. Whether the erection can be maintained until the partner has achieved orgasm;

4. Whether ejaculation occurs;

5. Whether both partners experience sexual satisfaction.

Taking the sexual history also allows the clinician to begin forming an objective opinion regarding the interpersonal relationship between the patient and his sexual partner.

Premature (early) ejaculation generally occurs in men younger than 40 years. This problem can place a great deal of stress on the couple's relationship. A history of premature ejaculation can be obtained from many men who present in later years with erectile difficulty. Effective treatments, including selective serotonin reuptake inhibitor (SSRI) medications and sex therapy, are available to remedy this condition.

The sexual history may include specific questions such as the following:

1. Are you ever able to obtain an erection suitable for penetration, even momentarily?

2. Is your ED getting worse or stable?

3. How long have you had trouble attaining or maintaining an erection?

4. How hard is the erection, on a scale of 0-100?

5. Is maintaining the erection a problem?

6. Have you ever had a traumatic sexual experience?

7. Are you able to achieve orgasm and ejaculation?

8. Approximately how long are able to have intercourse before ejaculating?

9. Do you use any type of contraceptives, such as condoms?

10. Do you experience nocturnal or morning erections?

11. Does pain or discomfort occur with ejaculation?

12. Do you have premature (early) ejaculation?

13. Is penile curvature (Peyronie disease) a problem?

14. How frequently do you have sexual activity? Is it typically spontaneous or planned?

15. If your erections were functional, what would be your preferred frequency of intercourse? Do you and your sexual partner agree on this issue?

16. Is adequate foreplay occurring? Is your sexual partner satisfied with the sexual experience?

17. Have you already tried any treatments? If so, what were they? Are you interested in trying a particular treatment first? Are you opposed to trying a particular type of therapy?

18. To what degree do you wish to proceed in determining the cause of the ED? How important is this to you?

Medical and surgical history

Information should be obtained about any previous surgical procedures or other medical disorders. In particular, in addition to general medical information, any history of pelvic surgery, trauma, previous prostate surgery, or irradiation of the prostate should be elicited.

Inquiries should be made regarding cardiovascular risk factors, such as hypertension, diabetes, obesity, dyslipidemia, and family history of cardiac disease. For example, there is an established link between obesity and ED in men.

The Princeton Consensus Conference is a multispecialty collaborative tradition dedicated to optimizing sexual function and preserving cardiovascular health. It has the following two primary objectives:

To focus on evaluating and managing cardiovascular risk in men with ED and no known cardiovascular disease (CVD), with a particular emphasis on identifying those who may require additional cardiologic workup

To focus is on reevaluating and modifying previous recommendations for evaluation of cardiac risk associated with sexual activity in men with known CVD

The Second Princeton Consensus suggests that men with ED and no obvious cause are at high risk for subclinical coronary artery disease (CAD) and should undergo, at the least, screening for blood glucose and lipids and blood pressure measurement.

The Third Princeton Consensus focuses on (1) emphasizing the use of exercise ability and stress testing to ensure that each man's cardiovascular health is consistent with the physical demands of sexual activity before prescribing treatment for ED and (2) highlighting the link between ED and CVD, which may be asymptomatic and may benefit from cardiovascular risk reduction.

ED has been demonstrated to be a harbinger of potential future cardiovascular events. The development of ED has proved to be a precursor to symptomatic CAD in men, with an average lead-time of 38.8 months. Since 2005, several observational studies have shown a strong correlation between ED and CAD, and subsequent large longitudinal studies have demonstrated

that men with ED have a 65-85% increased risk of subsequent CAD.

Medication and nonprescription drug history

It is important to obtain a detailed list of all medications taken during the past year, including all vitamins and other dietary supplements. (Patients often neglect to list dietary supplements they have tried in an effort to improve their sexual function.) Numerous prescription medications have been associated with ED, including the following:

1. Antihypertensive drugs;

2. Antiulcer drugs (eg, proton pump inhibitors [PPIs] and cimetidine);

3. Lipid-lowering (eg, statins and fibrates);

4. 5-Alpha reductase inhibitors (eg, finasteride and dutasteride);

5. Antidepressants;

6. Antipsychotic drugs (especially risperidone);

7. Testosterone and anabolic steroids.

In addition to prescription drug use, tobacco use, alcohol intake, caffeine intake, and illicit drug use should be documented. A smoking history is particularly important, in view of the contribution of smoking to vascular disease.

Psychological history

Factors that give rise to stress factors and tension, whether at work or at home, should be explored. The patient's psychological state should be assessed, with particular attention to the following:

1. Indications of depression;

2. Loss of libido;

3. Problems and tension in the sexual relationship;

4. Insomnia;

5. Lethargy;

6. Moodiness;

7. Stress from work or other sources.

It is especially important to have the patient explain his own interpretation of the problem. To this end, questions such as the following may be asked:

1. Did the onset of ED coincide with a specific event, such as a major operation or a divorce? Have you experienced the death of a spouse or family member?

2. Do you have diminished sexual desire? If so, how long have you had this? Is your diminished sexual desire a primary symptom, or is it a reaction to poor sexual performance?

3. Do you have any feelings of performance anxiety?

Pure psychogenic impotence is relatively uncommon. It is characterized objectively by the presence of good nocturnal and morning erections and negative findings on all other tests. However, a

psychogenic component often is present in men with organic ED. A history of highly variable erections that can be totally absent one day but virtually normal the next suggests a psychogenic cause. Virtually 100% of men with severe depression have ED.

Use of formal questionnaires

Various formal questionnaires have been developed to gather objective data regarding ED and to assist clinicians in the evaluation of their patients, including the following:

1. International Index of Erectile Function (IIEF);

2. Sexual Encounter Profile (SEP);

3. Global Assessment Question (GAQ);

4. Psychological and Interpersonal Relationship Scales (PAIRS);

5. Self-Esteem and Relationship (SEAR) questionnaire;

6. Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS).

The IIEF is a sensitive, specific, and standardized tool that has been validated in several languages. This 15-question instrument evaluates 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and global satisfaction. It is used to evaluate pharmacologic and other therapies for the treatment of ED.

A shorter version of the IIEF, termed the IIEF-5, has been developed as a sexual health inventory for men. This tool is helpful in screening patients for ED, a problem that many men are hesitant to discuss. In the IIEF-5, the patient is asked the following 5 questions with respect to the preceding 6 months:

1. How do you rate your confidence that you could achieve and maintain an erection?

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?

4. During sexual intercourse, how difficult was it to maintain your erection to the completion of intercourse?

5. When you attempted sexual intercourse, how often was it satisfactory for you?

The answers to these 5 questions are each scored on a scale of 0-5. A score of 25 is typical for a healthy man; scores of 11 or lower indicate moderate-to-severe ED. After completion of the IIEF or the IIEF-5 and a discussion with the patient, the physician should have a good understanding of the nature and scope of the patient's problem.

The SEP is commonly used in clinical trials involving pharmacologic therapies for ED. It is a diary maintained by men after each sexual

attempt, consisting of a series of yes/no questions regarding specific aspects of each encounter, as follows:

1. Were you able to insert your penis into your partner's vagina?

2. Did your erection last long enough for you to complete intercourse with ejaculation?

The GAQ has also been used in clinical trials. The questions are as follows:

1. Has the treatment you have been taking improved your erectile function?

2. If yes, has the treatment improved your ability to engage in sexual activity?

Psychosocial questionnaires have been developed, but they are infrequently used in clinical practice. They have been employed in clinical trials for product development.

The PAIRS is a self-administered questionnaire containing 3 domains (sexual self-confidence, time concerns, and spontaneity) related to the broader psychological and interpersonal outcomes associated with ED and its treatment. Patients rate their agreement or disagreement with a specific statement on a scale of 1 ("strongly disagree") to 4 ("strongly agree"). If more than 50% of data are missing from a domain for any patient at any given visit, then that domain is considered missing for that patient at that visit.

The SEAR questionnaire is a subject-reported measure of psychosocial outcomes in men with ED. It consists of 14 items assessing two domains, as follows:

1. Sexual relationship (items 1-8);

2. Confidence (items 9-14).

The confidence domain consists of two subscales, as follows:

1. Self-esteem (items 9-12);

2. Overall relationship (items 13 and 14).

The EDITS is a reliable and validated questionnaire used to assess patients' satisfaction with their ED treatment. For each question, satisfaction is rated on a scale of 0 ("extremely low treatment satisfaction") to 4 ("extremely high treatment satisfaction").

Physical Examination

A physical examination is necessary for every patient, with particular emphasis on the genitourinary, vascular, and neurologic systems. A focused physical examination entails evaluation of the following:

1. Blood pressure;

2. Peripheral pulses;

3. Sensation;

4. Status of the genitalia and prostate;

5. Size and texture of the testes;

6. Presence of the epididymis and vas deferens;

7. Any penile abnormalities, such as hypospadias and Peyronie plaques.

The physical examination may corroborate history findings or may reveal unsuspected physical findings, such as penile plaques, small testes, evidence of possible prostate cancer, prostate infections, or hypertension.

Several studies have found a strong correlation between hypertension and ED—not surprisingly, given that both are manifestations of a vascular disorder. In a large hypertension clinic, men who also demonstrated ED had a much higher prevalence of complications related to high blood pressure.

It has been suggested that hypertensive patients with ED and poor cavernosal artery blood flow as measured during duplex ultrasonography studies should proceed to a full cardiac evaluation because of the high prevalence of associated problems.

A number of studies have shown a correlation between benign prostatic hyperplasia and ED. The cause of this correlation is not yet clear.

In addition to the conditions listed in the differential diagnosis, the following conditions should be taken into consideration:

1. Cancer and cancer treatment;

2. Epilepsy;

3. Multiple sclerosis;

4. Guillain-Barré syndrome;

5. Alzheimer disease;

6. Epispadias;

7. Widower syndrome;

8. Performance anxiety;

9. Malnutrition;

10. Leukemias;

11. Medications (eg, antidepressants, antipsychotics, antihypertensives, antiulcer drugs, hyperlipidemia medications).

Excessive expectations on the part of men who actually have normal erectile function should also be considered in the differential diagnosis.

The Process of Care Model for the Evaluation and Treatment of Erectile Dysfunction was developed to advance new guidelines for the diagnosis and management of ED in primary care and multidisciplinary settings. The key components of this model are the following:

1. A rational approach to diagnosis and treatment;

2. Emphasis on clinical history taking and a focused examination;

3. Specialized testing and referral in predefined situations;

4. A stepwise management approach with ranking of treatment options;

5. Incorporation of patient and partner needs and preferences in the decision-making process.

An alternative model was developed that included algorithms and consensus guidelines. This approach is oriented toward patient goals and involves a minimum of testing. The patient and his partner express a preference for reasonable and appropriate treatment options and work with the physician to implement this plan. [72]

Laboratory Studies

Hormonal blood tests. According to an American College of Physicians (ACP) guideline, the evidence for the utility of hormonal blood tests in identifying and affecting therapeutic outcomes for treatable causes of ED is inconclusive. The ACP makes no recommendations either for or against routine use of hormonal blood tests or hormonal treatment in the management of patients with ED. Clinicians should make decisions to measure hormone levels on a case-by-case basis, in accordance with the patient's clinical presentation.

Patients who express a loss of libido, depression, or any signs of diminished secondary sexual characteristics should undergo an endocrine evaluation. At a minimum, this should consist of measuring morning serum testosterone levels.

The relative merits of measuring total, free, and bioavailable testosterone levels and serum hormone-binding globulin are controversial. In screening for hypogonadism, total and free testosterone levels should be measured to investigate the hypothalamic-pituitary-gonadal axis. Testosterone levels peak at about 8 AM; thus, a morning level should be checked whenever possible. Free or bioavailable testosterone is important because it is the testosterone that is usable; the rest is attached mainly to serum hormone–binding globulin.

Measurement of luteinizing hormone (LH) may be helpful. LH levels vary according to the body's need for testosterone. The hypothalamus regulates testosterone levels by releasing or inhibiting LH-releasing hormone (LHRH), which acts in the pituitary to produce LH. A high LH level associated with a low testosterone level implies primary testicular (Leydig cell) failure. Conversely, a low LH level associated with a low testosterone level suggests a central defect.

In some instances, prolactin levels may be helpful as well. A serum prolactin level is obtained if the patient has evidence of pituitary hyperfunction (eg, from a pituitary tumor) or if low serum testosterone levels have been documented.

A serum thyroid-stimulating hormone (TSH) evaluation is appropriate in selected patients.

Additional useful screening studies include the following:

1. Hemoglobin A 1c;

2. Serum chemistry panel;

3. Lipid profile.

These studies should be considered unless the patient has had

them performed recently and the results are available.

Measurement of prostate-specific antigen (PSA) levels may be appropriate if the patient is a candidate for prostate cancer screening. Such screening is controversial, however, and should be performed only after its risks and benefits have been reviewed with the patient.

Urinalysis. Performing a urinalysis is recommended. The presence of red blood cells (RBCs), white blood cells (WBCs), protein, or glucose can be important clues to a genitourinary disorder.

Injection of Prostaglandin E1. A test used to evaluate penile function is the direct injection of prostaglandin E1 (PGE1; alprostadil) into one of the corpora cavernosa. If the penile vasculature is normal or at least adequate, an erection should develop within several minutes. The patient and the clinician can judge the quality of the erection. If successful, this test also establishes penile injections as a possible therapy.

Biothesiometry. The sensitivity of the skin of the penis to detect vibrational stimuli (ie, biothesiometry) can be employed as a simple nerve function office screening test, but it is infrequently indicated. In this test, a small electromagnetic test probe is placed on the right and left sides of the penile shaft and on the glans. The vibrational amplitude is adjusted until the subjective sensory threshold is reached, which is determined by questioning the patient

A series of these tests determines the average vibrational sensory threshold in each location; these thresholds are then compared with reference range standards for the patient's age group. Although this test does not directly measure erectile nerve function, it serves as a reasonable means of screening for possible sensory deficit and is simple to perform. Formal nerve conduction studies (eg, bulbocavernosus reflex latency time) are reserved for very specific situations.

Ultrasonography. Vascular function within the penis can be evaluated by means of duplex ultrasonography. In this procedure, blood flow in the cavernosal arteries within the corpora cavernosa is measured before and after the intracavernosal injection of a test dose of a standard vasodilator (eg, 20 µg of PGE1).

Criteria for evaluating the study results vary to some degree. A peak systolic velocity lower than 25 cm/sec is generally agreed to indicate arterial insufficiency. The proposed value for the lower limit of normal ranges from 25-35 cm/sec, but a peak systolic velocity of 35 cm/sec or higher clearly rules out arterial insufficiency. End-diastolic velocity serves as a proxy for venous outflow; a velocity of 5 cm/sec or lower when the penis is at full rigidity indicates the absence of abnormal venous leakage.

Nocturnal Penile Tumescence Testing. Nocturnal penile tumescence testing involves placing several bands around the penis, connected to a device

such as the Rigiscan monitor, and instructing the patient to wear the assembly for 2 or 3 successive nights. If an erection occurs, which is expected during rapid eye movement sleep, its force and duration are measured on a graph (see the image below). Inadequate or absent nocturnal erections suggest organic dysfunction, whereas a normal result indicates a high likelihood of a psychogenic etiology.

Nocturnal penile tumescence testing was once frequently performed; it was thought to be useful in distinguishing psychogenic from organic impotence. Currently, other devices are available that provide similar information. Some are also able to measure rigidity (resistance to mild compression) and tumescence (size). Nocturnal penile tumescence testing is rarely used in current practice, but it can be helpful in situations where the diagnosis is in doubt.

Other Studies. Angiography is useful if the patient is a potential candidate for some type of vascular surgery. Young men with traumatic vascular injuries resulting in ED are candidates for this angiography because they may qualify for a vascular reconstruction.

In the vast majority of patients with ED, formal neurologic testing is unnecessary. However, those with a history of central nervous system (CNS) problems, peripheral neuropathy, diabetes, or penile sensory deficit may benefit from some level of neurologic testing.

After all the information regarding the patient's status has been gathered, the various options for management of erectile dysfunction (ED) can be discussed. It is best to include the patient's partner in this discussion.

The task of the physician is to identify which treatment would be most appropriate and most likely to have long-term success. To do that, the physician must take the time to understand the patient's problem and be knowledgeable about the available options.

Enough options are available that every man who wants to be sexually active can be, regardless of the etiology of the problem. These include sexual counseling if no organic causes can be found for the dysfunction, oral medications, external vacuum devices, or some type of invasive therapy. One of the most difficult aspects of treatment is teaching men that sex entails more than simply achieving an erection.

Where possible, drugs that may be contributing to ED should be discontinued. However, ED as a manifestation of hypogonadism from abuse of anabolic steroids can persist for months to years after cessation of steroid use.

Interim treatment for hypogonadism in such patients, while hypothalamic-pituitary-gonadal function recovers, has included judicious use of testosterone replacement therapy, human chorionic gonadotropin (hCG), and selective

estrogen receptor modulators (eg, clomiphene).

Hyperprolactinemia from antipsychotic medication, especially risperidone, has been associated with sexual dysfunction. Treatment has included dose reduction, drug holidays, adjunctive medication, and switching to another drug (eg, olanzapine); however, data to support any of those strategies are limited.

A small open-label study by Fujioi et al of adjunctive aripiprazole for patients with antipsychotic-induced hyperprolactinemia and sexual dysfunction reported a significant decrease in erectile dysfunction at week 24.

Treatment in men with cardiovascular disease

Many patients with ED also have cardiovascular disease—not surprisingly, given that the two disorders have a common etiology. Treatment of ED in these patients must take cardiovascular risks into account.

Sexual activity, in and of itself, increases the chances of ischemic events and myocardial infarction (MI) because of the exertion and sympathetic activation that may accompany it. The absolute risk of MI during sexual activity and for 2 hours afterward is only 20 chances per million per hour in post-MI patients and is even lower in men without a history of MI.

The Princeton Consensus Panel has produced guidelines for managing ED in patients with cardiovascular disease. The panel advises that a man with ED and no cardiac symptoms should be considered to have cardiac or vascular disease until proven otherwise. ED patients should be assessed and categorized as high-, intermediate-, or low-risk. This stratification can guide management.

Risk-factor modification, including lifestyle interventions (eg, exercise and weight loss) is strongly encouraged for ED patients with cardiovascular disease. A study by Gupta et al supports the view that for men with cardiovascular risk factors, modifications in lifestyle along with pharmacotherapy are helpful in improving sexual function.

Patients who have serious cardiac disease or exertional angina or are taking multiple antihypertensive medications should seek the advice of a cardiologist before beginning therapy with a phosphodiesterase type 5 (PDE5) inhibitor. Nevertheless, several studies examining the cardiac effects of sildenafil and tadalafil have demonstrated that there is no increased risk of cardiovascular events in comparison with placebo. No significant differences in the incidence of MI, myocardial ischemia, or postural hypotension has been reported.

Angioplasty. Balloon angioplasty has been studied as treatment for erectile dysfunction in men with focal atherosclerotic narrowing of the penile artery. In a prospective study in 22 men with 34 isolated penile artery stenoses, Wang et al reported achieving procedural success with balloon angioplasty in 31

cases. At 8 months, however, CT angiography showed binary restenosis in 14 of 34 lesions in 13 patients, and at 1 year, clinical success had been sustained in only 11 of the 22 patients.

Low-intensity shock wave therapy. Although not approved for this indication in the United States, low-intensity shock wave therapy has proved effective in European patients with severe ED that is unresponsive to treatment with phosphodiesterase type 5 (PDE-5) inhibitors. The mechanism of action is presumably promotion of revascularization in the penis.

Pharmacologic Therapy. An increasing array of medications is available to assist in the management of ED. New agents are still undergoing clinical testing, and more are in the early phases of development. Medications currently being developed include dopaminergic and melanocortin receptor agonists, second-generation phosphodiesterase 5-inhibitors, rho-kinase inhibitors, soluble guanylate cyclases, and maxi-k channel activators.

For any medication to be effective, the physiologic components involved in the erectile process must be functional. Serious impairments render the medication either completely or partially ineffective. [72]

Phosphodiesterase-5 inhibitors. In current practice, PDE5 inhibitors are the most commonly used treatment for ED. This drug class consists of sildenafil, vardenafil, tadalafil, and avanafil. Sildenafil was the first in this series of PDE inhibitors; avanafil is the newest, having been approved by the US Food and Drug Administration (FDA) in April 2012. In a study of 390 men with diabetes and erectile dysfunction, avanafil was found to be a safe and effective treatment as early as 15 minutes and more than 6 hours after dosing.

Guidelines from the American Urological Association (AUA) recommend offering PDE5 inhibitors as first-line therapy for ED unless the patient has contraindications to their use (eg, concurrent organic nitrate therapy). The AUA notes that insufficient evidence exists to support the superiority of any one of these agents over the others. European guidelines suggest that the choice of drug (short- versus long-acting) depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience.

The AUA warns that PDE5 inhibitors can cause mild transient systemic vasodilation, which may be aggravated by alpha-blocking agents. Consequently, the guidelines advise that vardenafil and tadalafil, at any dose, and sildenafil at 50 mg and 100 mg doses should be administered with caution in patients who are taking alpha blockers.

In patients with ED that is refractory to therapy with oral PDE5 inhibitors, one of these agents can be combined with an injection of prostaglandin E1 (PGE1; alprostadil). Gutierrez et al demonstrated that this combination was

more effective than either one alone. The combination of a PDE5 inhibitor with intraurethral PGE1 has also proved successful.

Androgens. Men who present with diminished libido and ED may be found to have low serum testosterone levels (hypogonadism). Hormone replacement may benefit men with severe hypogonadism and may be useful as adjunctive therapy when other treatments are unsuccessful by themselves. Libido and an overall sense of well-being are likely to improve when serum testosterone levels are restored to the reference range. However, a meta-analysis by Corona et al found that the positive effect of testosterone therapy on erectile function and libido was significance only in randomized controlled trials partially or completely supported by pharmaceutical companies.

Meta-analyses suggest that the combination of testosterone and PDE5 inhibitors yields more effective results, but in noncontrolled versus controlled studies. However, adverse effects, especially in older frail men, require consideration.

Replacement androgens are available in the following four forms:

1. Oral
2. Injectable
3. Gel
4. Transdermal

Oral therapy is rarely used; of the available approaches, it is the least effective and the most likely to be associated with hepatotoxicity, even though the risk is relatively small.

Parenteral therapy is the approach most likely to restore androgen levels to the reference range, but it requires periodic injections (usually every 2 weeks) to sustain an effective level. Measurement of peak and trough levels can help avoid symptomatic troughs and supernormal peak levels, though such measurement is rarely done in clinical practice. Typically, a level is obtained 1 week after an injection. Weekly injections using lower doses can be used to minimize the wide swings in blood levels noted with less frequent dosing.

Skin patches deliver a sustained dose and are generally accepted by patients. Testosterone gels are available for daily topical use to treat male hypogonadism and have the advantage of minimizing the peaks and troughs associated with the use of injectable agents. However, these gels require daily application and are relatively expensive.

Implantation of longer-acting testosterone pellets has become increasingly popular. The pellet is placed during an office visit. The advantage of this approach is the infrequency of pellet placement (only every 3-6 months).

The use of exogenous androgens suppresses natural androgen production. Elevation of serum androgen levels has the potential to stimulate prostate growth and may increase the risk of activating a latent

cancer. Periodic prostate examinations, including digital rectal examinations, prostate-specific antigen (PSA) determinations, and blood counts (ie, complete blood count [CBC]), are recommended in all patients receiving supplemental androgens. Obtaining a testosterone level during therapy is necessary for optimizing the dosage.

Intracavernosal injection of vasodilators. The modern age of pharmacotherapy for ED began in 1993, when papaverine, an alpha-receptor blocker that produces vasodilatation, was shown to produce erections when injected directly into the corpora cavernosa. Soon afterward, other vasodilators, such as alprostadil (ie, synthetic PGE1) and phentolamine, were demonstrated to be effective either as single agents or in combination.

Alprostadil is the single agent most commonly used for intracavernosal injections. In a study of 683 men, 94% reported having erections suitable for penetration after alprostadil injections. Self-injection of this and similar agents has been of enormous benefit because they represent an effective way to achieve adequately rigid erections for a wide variety of men who otherwise would be unable to do so.

If the vasculature within the corpora cavernosa is healthy, intracavernosal injection therapy is almost always effective. However, careful instruction in how to perform the injections is essential. The dosage is adjusted so as to achieve an erection with adequate rigidity for no more than 90 minutes. Alprostadil doses as high as 40 µg can be used. An abnormal finding after biothesiometry testing has been suggested as an indicator of possible heightened sensitivity to intracavernosal injections, but this suggestion remains unproven.

The main adverse effects of intracavernosal injection are as follows:

1. Painful erection

2. Priapism

3. Development of scarring at the injection site

4. Intraurethral prostaglandin E1 pellets

Another option for ED is the Medicated Urethral System for Erections (MUSE). MUSE involves the formulation of alprostadil (PGE1) into a small intraurethral suppository that can be inserted into the urethra (see the image below). In one study, the agent was effective in 65% of a selected group of men. Widespread application of MUSE has been limited by the system's cost and its inability to provide rigid erections consistently.

MUSE may be effective in men who have vascular disease or diabetes or have undergone prostate surgery. Intraurethral alprostadil is a useful agent for men who do not want to use self-injections or for men in whom oral medications have failed. It has been successfully used together with sildenafil in cases in which each agent alone failed.

Few adverse effects occur. The most common is a painful erection and

urethral burning, which occurs in fewer than 10% of patients.

A topical gel formulation of alprostadil for treatment of ED has been developed. However, it has not been approved for use by the FDA.

Vascular endothelial growth factor. One area of research has involved the use of vascular endothelial growth factor (VEGF), an angiogenic growth factor and endothelial cell mitogen. VEGF is produced by vascular smooth muscle, endothelial, and inflammatory cells. It increases production of nitric oxide (NO), which results in improves endothelial function and blood flow in chronic ischemic disorders.

Direct intracavernosal injection of recombinant VEGF protein or adenoviral VEGF that contains plasmids has shown dramatic results on cavernosography in animal models with arteriogenic, venogenic, and neural forms of ED. Burchardt et al identified VEGF 165 as the predominant isoform in the corpora cavernosa, as well as a novel splice variant.

Although VEGF is a potent and important vascular regulator, it probably acts in conjunction with other vascular factors. Although a single-agent VEGF is unlikely to ever be used as monotherapy for ED, the research done into its actions represents an important step in understanding the normal and abnormal vascular physiology associated with ED.

Other oral agents. Before the advent of oral PDE5 inhibitors, various other oral medications were investigated for treatment of ED, including the following:

1. Adrenergic receptor antagonists (eg, phentolamine, yohimbine, and delequamine)

2. Dopamine receptor antagonists (eg, apomorphine and bromocriptine)

3. Serotoninergic receptor activators (eg, trazodone)

4. Xanthine derivatives (eg, pentoxifylline)

5. Oxytocinergic receptor stimulators (eg, oxytocin)

Although the AUA does not recommend the use of any of these agents, several are worth reviewing briefly.

Yohimbine, a bark extract, has been available for many years. It has both a central and a peripheral effect. Even in properly conducted, well-controlled studies, it is only slightly more effective than placebo, and AUA guidelines do not recommend its use. Nevertheless, there has been a renewed interest in this agent, particularly when it is combined with an oral PDE5 inhibitor. Yohimbine is a safe agent with few known adverse effects. It is administered in a dosage of 5.4 mg (1 tablet) 3 times daily

Apomorphine. A sublingual formulation of apomorphine has demonstrated some benefit in ED. Apomorphine is not approved by the FDA for this indication.

Phentolamine is an alpha-receptor blocker that has not been approved by the FDA for the treatment of ED but has undergone limited clinical testing. Two placebo-controlled trials reported effectiveness in 42% and 32% of patients taking 50 mg, compared with 9% and 13% of control subjects, respectively. The erections occurred in 20-30 minutes. The drug was well tolerated, with mild-to-moderate adverse effects (usually headaches or light-headedness) occurring in less than 10% of patients.

External Erection-Facilitating Devices

Constriction devices. Men who have a vascular (venous) leak phenomenon may need a constriction device placed at the base of the penis to maintain their erection. Such a device may be effective by itself or in combination with a PDE5 inhibitor. In selected cases, combination therapy with one of the PDE5 inhibitors plus an intraurethral or intracavernosal agent may be tried.

Vacuum devices. Vacuum devices for drawing blood into the penis are a relatively inexpensive method for producing an erection that has been used for many years. These devices are plastic cylinders that are placed over the penis. Air is pumped out, causing a partial vacuum. Releasing the vacuum after a few minutes and then reapplying the vacuum sometimes gives a better result. After an erection is obtained, a constricting band is placed at the base of the penis.

This technique is effective in 60-90% of patients and maintains the erection for up to 30 minutes. (In fact, the erection would last until the constricting band is released, but keeping the band in place for longer than 30 minutes is not recommended.) The devices are very reliable and seem to work better with increased use and practice. They can be operated and used quickly with experience but still tend to be less "romantic" than other therapeutic options.

Although vacuum devices are generally safe, hematomas, petechia, and ecchymosis have been reported. Other adverse effects include pain, lower penile temperature, numbness, absent or painful ejaculation, and pulling of scrotal tissue into the cylinder, where it becomes trapped under the ring. Many of these problems can be alleviated by proper selection of the tension rings and cylinders.

Drawbacks to the use of external vacuum devices include the need to assemble the equipment and the difficulty of transporting it. Many patients lose interest in using the device because of the preparations that are necessary, the lack of easy transportability, the inability to hide the tension ring, and the relative lack of spontaneity. Approximately half the men who use a vacuum device obtain very good erections, but only half of these men consistently use the device for a prolonged period.

Surgical Care

Surgical revascularization. A small number of healthy young men

have developed ED as a result of trauma to the pelvic arteries. Revascularization procedures such as rotating the epigastric artery (or even smaller vessels) into the corpora have been attempted. Long-term results have been marginal. AUA guidelines recommend arterial reconstructive surgery as a treatment option only in healthy patients who have recently acquired ED as the result of a focal arterial occlusion and who have no evidence of generalized vascular disease.

Surgical elimination of venous outflow. On occasion, men who have difficulty maintaining erections as a result of venous leaks may benefit from undergoing a surgical procedure designed to eliminate much of the venous outflow. Although there was considerable initial enthusiasm for this and other surgical approaches was significant, this type of surgery has become rare because of a lack of long-term efficacy. AUA guidelines recommend against the use of such procedures.

Placement of penile implant. In the past, the placement of prosthetic devices within the corpora was the only effective therapy for men with organic ED.

At present, however, it is the last option considered, even though more than 90% of men with an implant would recommend the procedure to their friends and relatives.

Before selecting this form of management, the patient and his sexual partner should be counseled regarding the benefits and risks of this procedure.

Tab. 18 - Advantages and disadvantages of types of surgical treatment

Treatment	Advantages	Disadvantages
Semirigid or malleable rod implants	Simple surgery Relatively few complications No moving parts Least expensive implant Success rate of 70-80% Highly effective	Constant erection at all times May be difficult to conceal Does not increase width of penis Risk of infection Permanently alters or may injure erection bodies Most likely implant to cause pain or erode through skin If unsuccessful, interferes with other treatments

Fully inflatable implants	Mimics natural process of rigidity-flaccidity Patient controls state of erection Natural appearance No concealment problems Increases width of penis when activated Success rate of 70-80% Highly effective	Relatively high rate of mechanical failure Risk of infection Most expensive implant Permanently alters or may injure erection bodies If unsuccessful, interferes with other treatments
Self-contained inflatable unitary implants	Mimics natural process of rigidity-flaccidity Patient controls state of erection Natural appearance No concealment problems Simpler surgical procedure than that required for fully inflatable prosthesis Success rate of 70-80% Highly effective	Sometimes difficult to activate the inflatable device Does not increase width of penis Mechanical breakdowns possible Long-term results not available Risk of infection Relatively expensive Permanently alters or may injure erection bodies If unsuccessful, interferes with other treatments

Implants are usually used for men who have not experienced success with other therapies or who require penile reconstructions. Men who have undergone a radical prostatectomy for prostate cancer and in whom a nerve-sparing procedure was not performed or was not successful often do not respond to oral PDE5 inhibitors, and these men are good candidates for a penile implant. The same is true for men treated with radiation therapy, though more of these men tend to respond to oral agents.

Daily use of a vacuum erection device for a month before implantation of a penile prosthesis may prove beneficial. A randomized controlled trial by Canguven et al found that this strategy was associated with a significantly greater mean stretched penile length on the day of surgery; in addition, surgeons reported easier corporal dilatation intraoperatively.

There is some evidence to suggest that an additional benefit may be gained by some men who have an implant but also take an oral PDE5 inhibitor. Sexual stimulation and sensation are enhanced.

Penile prostheses can be divided into the following 2 broad categories (Tab. 18):

1. Semirigid;
2. Inflatable.

With the semirigid prosthesis, 2 matching cylinders are implanted into the corpora cavernosa. These devices provide enough rigidity for penetration and rarely break. The major drawbacks are the cosmetic appearance of the penis (which remains semierect at all times), the need for surgery, and the destruction of the natural erectile mechanism when the prosthesis is implanted.

The inflatable devices consist of 2 Silastic or Bioflex cylinders inserted into the corpora cavernosa, a pump placed in the scrotum to inflate the cylinders, and a reservoir that is contained either within the cylinders or in a separate reservoir placed beneath the fascia of the lower abdomen (see the images below). The inflatable prosthesis generally remains functional for 7-10 years before a replacement may be necessary. Improvements in these devices have resulted in a failure rate lower than 10%.

Patient acceptance of these devices is very high, with nearly 100% of recipients expressing satisfaction. Part of this enthusiasm is related to the failure of other therapies and the highly motivated patient population.

Rajpurkar and Dhabuwala reported significantly better erectile function and satisfaction with a penile implant than with sildenafil or intracavernosal alprostadil (PGE1). This was a nonrandomized study in which all 138 subjects were initially offered sildenafil. The mean follow-up was 19.54 months, and questionnaires were used to obtain the data.

Complications include infections (occurring in 2% of patients), erosion of the device through the urethra or skin (2%), and painful erections (1%). The development of an antibiotic-coated device has further reduced the infection rate. Patients should also be counseled that the penis does not lengthen as much as with normal erections.

Counseling and Psychological Care

Sexual counseling is the most important part of treatment for patients with sexual problems. Many professional sexual counselors are skilled in working with patients, but the primary care physician, the urologist, and the gynecologist also serve in this capacity to some degree. These are usually the first professionals to learn about the problem, and they often have to extract the information about the sexual problem from the patient.

Men are frequently reluctant to discuss their sexual problems and must be specifically asked. Opening a dialogue allows the clinician to begin the investigation or to refer the patient to a consultant. Regardless of any subsequent therapy, the emotional aspects of the disorder must be addressed. Ideally, the patient's partner should be involved in counseling, but even if this is not possible, the time spent may help resolve or at least clarify the problem and certainly helps determine which of the other options would be most beneficial and appropriate.

Regardless of the etiology of ED, a psychological component is frequently associated with the disorder. The ability to achieve erection is intimately connected to a man's self-esteem and sense of worth. Pure psychogenic ED is generally evident when a man reports that he has normal erections some of the time but is unable to achieve or to maintain a full erection at other times. Once the man has doubt regarding sexual performance, he loses confidence; thus, future attempts to have sexual relations provoke anxiety.

In many instances, the couple must work together to resolve the problem, although in some cases, the relationship itself may be responsible for the problem. Referral to a sex therapist may be helpful.

A study of 31 newly diagnosed men with ED (aged 20-55 years) who were treated with either tadalafil (n = 12) or tadalafil plus 8 weeks of stress management (n = 19) found that both groups showed significant improvement in perceived stress and erectile function scores but that the reduction in perceived stress was greater in the latter group. This result suggests that stress reduction may be a useful component of ED treatment. Further research, involving randomized, controlled trials with larger samples and longer follow-up time, is needed.

Men with organic ED can be treated with one or more of the various available therapies. However, if they have lost confidence in their ability to obtain and maintain an erection suitable for penetration, a few words of encouragement from their physician can be of great help.

Prevention

The AUA observes that because diabetes, heart disease, and hypertension increase the risk of developing ED, optimal management of these diseases may prevent the development of ED. Similarly, because attaining and maintaining a firm erection requires good vascular function, it is reasonable to assume that lifestyle modifications to improve vascular function (eg, smoking cessation, maintenance of ideal body weight, and regular exercise) may prevent or reverse ED. At present, however, only minimal data support these suppositions.

In a clinical trial that included 106 men with newly diagnosed type 2 diabetes, Maiorino et al reported that men randomized to a Mediterranean diet demonstrated a significantly lesser decrease in erectile function, compared with men randomized to a low-fat diet (P=0.024). Total follow-up in the trial was 8.1 years.

13.2 Premature ejaculation

Premature (early) ejaculation—also referred to as rapid ejaculation—is the most common type of sexual dysfunction in men younger than 40 years. An occasional instance of premature ejaculation might not be cause for concern, but, if the problem occurs with more than 50% of attempted sexual relations, a dysfunctional pattern usually exists for which treatment may be appropriate. [70]

Most professionals who treat premature ejaculation define this condition as the occurrence of ejaculation earlier than both sexual partners wish. This broad definition thus avoids specifying a precise "normal" duration for sexual relations and reaching a climax. The duration of intimate relations is highly variable and depends on many factors specific to the individuals involved.

For example, a male may reach climax after 8 minutes of sexual intercourse, but if his partner regularly climaxes in 5 minutes and both are satisfied with the timing, this is not premature ejaculation. Alternatively, a male might delay his ejaculation for up to 20 minutes of sexual intercourse, but if his partner, even with foreplay, requires 35 minutes of stimulation before reaching climax, he may still consider his ejaculation and subsequent loss of erection premature because his partner will not have been satisfied (at least, not through intercourse).[71]

Because many females are unable to reach climax at all with vaginal intercourse, no matter how prolonged, the second situation described may actually represent delayed orgasm in the female partner rather than premature ejaculation in the male; the problem can be either or both, depending on the point of view. Such differences in perspective highlight the importance of obtaining a thorough sexual history from the patient (and preferably from the couple).

Premature ejaculation may be lifelong or acquired. Lifelong premature ejaculation applies to individuals who have had the condition since they became capable of functioning sexually (ie, post puberty).

Acquired premature ejaculation means that the condition began in an individual who previously experienced an acceptable level of ejaculatory control and, for unknown reasons, began experiencing premature ejaculation later in life. Acquired premature ejaculation is not related to a general medical disorder and usually is not related to substance inducement, though in rare cases, hyperexcitability might be associated with a psychotropic drug and resolve when the drug is withdrawn.

Diagnostic criteria

In 2014, the International Society for Sexual Medicine published an evidence-based unified definition of premature ejaculation that comprised the following criteria:

1. Ejaculation that always or nearly always occurs before, or within about 1 minute of, vaginal penetration from the first sexual experience (lifelong premature ejaculation) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired premature ejaculation);
2. Inability to delay ejaculation on all or nearly all vaginal penetrations;
3. Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

DSM-5 criteria

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), classifies premature (early) ejaculation as belonging to a group of sexual dysfunction disorders that are typically characterized by a clinically significant inability to respond sexually or to experience sexual pleasure.

Sexual functioning involves a complex interaction among biologic, sociocultural, and psychological factors, and the complexity of this interaction makes it difficult to ascertain the clinical etiology of sexual dysfunction. Before any diagnosis of sexual dysfunction is made, problems that are explained by a nonsexual mental disorder or other stressors must first be addressed. Thus, in addition to the criteria for premature (early) ejaculation, the following must be considered:

1. Partner factors (eg, partner sexual problems or health issues);
2. Relationship factors (eg, communication problems and differing levels of desire for sexual activity);
3. Individual vulnerability factors (eg, history of sexual or emotional abuse, existing psychiatric conditions such as depression, or stressors such as job loss);
4. Cultural or religious factors (eg, inhibitions or conflicted attitudes regarding sexuality);
5. Medical factors (eg, an existing medical condition or the effects of drugs or medications).

The specific DSM-5 criteria for premature (early) ejaculation are as follows:

1. In almost all or all (75-100%) sexual activity, the experience of a pattern of ejaculation occurring during partnered sexual activity within 1 minute after vaginal penetration and before the individual wishes it;
2. The symptoms above have persisted for at least 6 months;
3. The symptoms above cause significant distress to the individual;
4. The dysfunction cannot be better explained by nonsexual mental disorder, a medical

condition, the effects of a drug or medication, or severe relationship distress or other significant stressors.

The severity of premature (early) ejaculation is specified as follows:

1. Mild (occurring within approximately 30 seconds to 1 minute of vaginal penetration);
2. Moderate (occurring within approximately 15-30 seconds of vaginal penetration);
3. Severe (occurring before sexual activity, at the start of sexual activity, or within approximately 15 seconds of vaginal penetration).

The duration of the dysfunction is specified as follows:

1. Lifelong (present since first sexual experience);
2. Acquired (developing after a period of relative normal sexual functioning).

In addition, the context in which the dysfunction occurs is specified as follows:

1. Generalized (not limited to certain types of stimulation, situations, or partners);
2. Situational (limited to specific types of stimulation, situations, or partners).

Pathophysiology

Premature ejaculation is believed to be a psychological problem and does not represent any known organic disease involving the male reproductive tract or any known lesions in the brain or nervous system. The organ systems directly affected by premature ejaculation include the following:

1. Male reproductive tract (ie, penis, prostate, seminal vesicles, testicles, and their appendages);
2. Portions of the central and peripheral nervous system controlling the male reproductive tract;
3. Reproductive organ systems of the sexual partner (if female) that may not be stimulated sufficiently to achieve orgasm.

Perhaps the most pronounced effect of premature ejaculation, however, is psychological:

1. Both partners are likely to be dissatisfied emotionally and physically by this problem;
2. Attempted pregnancy is a particular concern;
3. If the premature ejaculation is so severe that it happens before commencement of sexual intercourse, conception will not be possible unless artificial insemination is used.

Some have questioned whether premature ejaculation is purely psychological. A number of investigators have found differences in nerve conduction/latency times and hormonal differences in men who experience premature ejaculation compared with individuals who do not. The theory is that some men have

hyperexcitability or oversensitivity of their genitalia, which prevents downregulation of their sympathetic pathways and delay of orgasm.

A group of nerves in the lumbar spinal cord has been identified as the possible generator of ejaculation. This nerve site is thought to be linked to excitatory and inhibitory dopamine pathways in the brain, which play significant roles in sexual behavior. While research continues, this knowledge is providing the foundation for possible development of medications specifically targeting delay of ejaculation. [70, 71]

Other questions have been raised regarding possible biochemical components of premature ejaculation. Testosterone is thought to play a role in the ejaculatory reflex. Higher free and total testosterone levels have been demonstrated in men with premature ejaculation than in men without premature ejaculation.

Research published in a Chinese andrology journal showed that semen from men with premature ejaculation contained significantly less acid phosphatase and alpha-glucosidase than did the semen of control subjects. The researchers concluded that these biochemical parameters may reflect dysfunction of the prostate and epididymis, possibly contributing to premature ejaculation; however, their conclusions have yet to be supported by subsequent studies.

A study by Corona et al found that many men with premature ejaculation have low serum prolactin levels. However, this same study found that men in the lowest quartile of serum prolactin levels who had premature ejaculation also demonstrated associated metabolic syndrome, erectile dysfunction, and anxiety. Thus, whereas biochemical markers (eg, prolactin) may contribute to premature ejaculation, organic and psychological associations (eg, anxiety) suggest that biochemical parameters play only a partial role. Further research is needed.

Psychological factors have been found to contribute greatly to premature ejaculation, beyond merely reducing the time to ejaculation. Whereas patients with premature ejaculation show significantly lower intravaginal ejaculatory latency time (IELT) overall, IELT in those who fit DSM-5 criteria for premature ejaculation overlaps with IELT in patients who do not fit the criteria.

However, whereas a shorter IELT has been the measure of premature ejaculation in many studies, the perception of ejaculation control has been shown to mediate patient or partner satisfaction with sexual intercourse and ejaculation-related distress. Although premature ejaculation probably is not a purely psychological disorder, such associations demonstrate that psychological factors play a significant role in its pathogenesis.

Aetiology

As noted, the cause of premature ejaculation is considered psychological, although this has not been definitively confirmed.

One psychological explanation for premature ejaculation is that males are conditioned by societal pressures to reach climax quickly because of fear of discovery when masturbating as teenagers or during early sexual experiences with others. This pattern of rapid attainment of sexual release is difficult to change in marital or long-term relationships. The increasing acknowledgment that female arousal and orgasm require more time than male arousal may lead to increased recognition and definition of premature ejaculation as a problem.

It has been theorized that evolutionary factors are involved. From an evolutionary perspective, it seems logical that males who can ejaculate rapidly might be more likely to fertilize a female than those who require prolonged stimulation to reach climax. The genes of a male who ejaculates rapidly (but not before intromission) would be more likely to be passed on. In some settings, a male who could not complete the fertilization process quickly might be pushed away or killed by a competing male because of his obvious vulnerability during intercourse.

Lifelong premature ejaculation

In patients with lifelong premature ejaculation, in which the male has never experienced sexual relations without also experiencing premature ejaculation, a deep-seated emotional disturbance may be present, and the causes may be multiple.

Sometimes, the behavior is a conditioned response resulting from teen masturbation practices, but it can also result from deep anxiety about sex that relates to traumatic experiences encountered by the patient during development (eg, incest, sexual assault, conflict with one or both parents, or other serious disturbances). In most cases of lifelong premature ejaculation, a primary care physician or a urologist should consult with a psychiatrist, psychologist, or other professional.

Acquired premature ejaculation

With regard to acquired premature ejaculation, some type of performance anxiety is often a major factor.

Performance pressure (ie, fear of failure to satisfy the partner) can arise from various precipitating events. Erectile dysfunction is one of the more common events of this type. Fear that an erection will not last may precipitate premature ejaculation. In such cases, the patient may say that the early climax was the result of being extremely excited by his partner, in an effort to avoid admitting that he was unable to maintain his erection throughout intercourse. [70]

Often, however, the situation is more complex. Erectile dysfunction may not be involved, and the key factor may be, for instance, a belittling attitude on the part of the partner. In addition, a female partner actually may have difficulty achieving climax through intercourse and may require direct clitoral stimulation to experience an orgasm. If she does not communicate this to the male partner

(and she may conceal it because of feelings about her own inadequacy), coital satisfaction is unlikely.

Because most physicians are not trained sex therapists, it is important to sort out conflicts in the relationship and then refer couples for counseling to professionals with experience and training in that area. Physicians who have some training or experience in treating premature ejaculation and are comfortable managing the problem may choose to begin treatment. If the patient does not respond favorably or if the physician is uncomfortable with treating the condition, the next step is referral to a sex therapist, psychologist, or psychiatrist.

Epidemiology

An estimated 30%-70% of American males experience premature ejaculation. The National Health and Social Life Survey (NHSLS) indicates a prevalence of 30%, which is fairly steady through all adult age categories. (In contrast, erectile dysfunction rises in prevalence with increasing age).

However, various surveys have shown that many men do not report premature ejaculation to their physician, possibly because of embarrassment or a feeling that no treatment is available for the problem. Some men might not even perceive premature ejaculation as a medical problem. Such survey data suggest that the percentage of men who experience premature ejaculation at some point in their lives is almost certainly more than the 30% reported in the NHSLS.

Estimates of premature ejaculation in European countries and India mirror the prevalence in the United States. The prevalence in other parts of Asia, Africa, Australia, and elsewhere is unknown.

According to the DSM-5, the estimated prevalence of premature (early) ejaculation is highly variable and depends on the definition being employed. Although more than 20-30% of men aged 8-70 years report being concerned about the rapidity of their ejaculation, only 1-3% would be classified as having premature (early) ejaculation according to the current DSM-5 criteria (ie, ejaculation occurring within 1 minute after intromission and before the individual wishes).

In a Korean study, the definition of premature ejaculation used yielded marked differences in outcome. The prevalence of premature ejaculation was 19.5% by self-reporting, 11.3% based on a premature ejaculation diagnostic tool (PEDT) score of 11 or higher, and 3% based on stopwatch-recorded intravaginal ejaculation latency time.

Premature ejaculation can occur at virtually any age in an adult man's life. As a reported condition, it is most common in men aged 18-30 years but may also occur in conjunction with secondary impotence in men aged 45-65 years. [71]

At present, there are no reproducible data indicating major differences between racial groups with respect to the incidence or prevalence

of premature ejaculation. However, a few surveys suggest that some degree of racial variation may exist.

A telephone survey of 1320 men without erectile dysfunction by Carson et al found that premature ejaculation was reported by 21% of non-Hispanic African Americans, 29% of Hispanics, and 16% of non-Hispanic whites. An analysis of the NHSLS by Laumann et al found that premature ejaculation was more prevalent among African American men (34%) and white men (29%) than among Hispanic men (27%).

In a small study of a sexual health clinic in Australia, 59% of premature ejaculation diagnoses were in men of Asian or Middle Eastern descent, whereas 41% were in men of Western or European birth. However, in view of the small number of such studies and the lack of suitable control subjects, it is difficult to draw firm conclusions from these data.

Prognosis

Masters and Johnson maintain that the great majority (>85%) of men with premature ejaculation can be treated successfully with the squeeze-pause technique alone, typically within 3 months of the start of therapy. However, clinical experience varies widely, and some authors have reported much poorer success rates.

With a combination of methods, including selective serotonin reuptake inhibitor (SSRI) therapy, improvement or cure should be possible in most cases, provided that the couple (not just the man) is committed to working on the problem together. Numerous published reports also indicate that counseling and medical therapy can help achieve success rates as high as 85%, matching the high rates originally reported by Masters and Johnson.

The problem with all treatments for premature ejaculation is that the relapse rate ranges from 20% to 50%, depending on the study cited; thus, the durability of the response can be questionable. Some males may need to make a long-term commitment to periodically repeating the behavioral techniques; long-standing habits can be difficult to modify.

Some men who achieve success with medical therapy (ie, SSRIs) might need to use the medication for the rest of their lives, just as some people with depression need lifelong antidepressant therapy to prevent repeated bouts of the disorder and many people with hypertension need lifelong antihypertensive therapy to control their blood pressure. Precise long-term failure rates are not well established and depend on the duration of follow-up for a particular cohort of patients.

No known direct morbidity or mortality results from premature ejaculation. Indirectly, premature ejaculation may alter self-esteem, may cause marital dysfunction, and may be a factor in depression, with its obvious consequences. Severe premature ejaculation can cause stress within a marriage or other relationship, which might contribute to conflicts and separation or divorce in some cases. Conception is also difficult in cases of

premature ejaculation before vaginal intromission.

Patient Education

Patients with premature ejaculation may be referred to a licensed sex therapist, psychologist, psychiatrist, or marital counselor for additional help. Numerous books and articles in the lay press are available at any public library. Many can also find information on the Internet regarding this subject.

Future research might indicate whether better sex education during adolescence can decrease the incidence of premature ejaculation in young men. Early successful treatment of erectile dysfunction may help prevent acquired premature ejaculation in older men.

History

A guideline from the International Society of Sexual Medicine recommends asking patients the following questions to establish the diagnosis of premature ejaculation:

1. What is the time between penetration and ejaculation (cumming)?
2. Can you delay ejaculation?
3. Do you feel bothered, annoyed, and/or frustrated by your premature ejaculation?

Optional questions cover assessment of erectile function, impact of the problem on the patient's relationship with his partner, any previous treatment, and effect on quality of life.

The history of the patient's premature (early) ejaculation is helpful because it ultimately guides the treatment that is best suited to the patient (and his partner). One should determine whether premature ejaculation is lifelong (ie, primary) or acquired (ie, secondary) and assess the severity of the problem.

If the patient has always experienced premature ejaculation from the time he began coitus, then he has lifelong premature ejaculation. If he had successful coital relationships in the past, yet began experiencing premature ejaculation with the current relationship, then he has acquired premature ejaculation. In most cases, acquired premature ejaculation is easier to treat and has a better prognosis.

For completeness, a general medical history should be taken to screen for other medical conditions that might be relevant. For example, if the patient has anginawith subsequent fear of myocardial infarction during sexual activity, he may present with premature ejaculation, but the actual underlying problem is the cardiac disease and the attendant mental insecurity. Resolution of the cardiac problem usually suffices, with no specific therapy required for the premature ejaculation.

For the purposes of this discussion, it is assumed that the patient is healthy and that sexual dysfunction is the only significant problem.

Lifelong premature ejaculation

In addition to the general medical history, it is important to inquire about any previous

psychological difficulties. Psychiatric conditions are more common in males with lifelong premature ejaculation than in the general population.

The history should include questions about the following:

1. Early sexual experiences – Did the patient experience a traumatic sexual episode as a child or teenager (eg, discovery by a parent during masturbation, with subsequent feelings of guilt and perhaps threatened or actual punishment)?
2. Family relationships during childhood and adolescence – How did the patient relate to his mother, father, brother(s), sister(s)? Does the family have a history of incest or sexual assault? Males can be sexually assaulted by other males and, in rare instances, by females, including siblings;
3. Peer relationships – Did the patient have other male friends or any female friends? How does he regard himself in comparison with peers (eg, inferior, superior, more athletic, frailer, more intelligent, or less intelligent)?
4. Work or school – Does the patient have any difficulties with work (or school, if still a student)?
5. General attitude toward sex – Does the patient regard sex as dirty? What is his sexual preference, fantasy, and arousal pattern? Did the patient have a strict religious upbringing? If so, what was he taught about sex?
6. Marital versus nonmarital context – If the premature ejaculation began with an initial nonmarital relationship, does he feel guilt about this? If the first coital experience was within a marital relationship that involved premature ejaculation from the start, was there premarital noncoital sexual play between the partners?
7. Sexual attitude and response of the female partner – If the female partner is having a problem (eg, dyspareunia), it could relate to the male's problem or may have preceded it;
8. Nonsexual aspects of the current relationship – Does the couple fight, or are they going through a power struggle?
9. Involvement of the sexual partner – If the patient's sexual partner is not present for this interview, why not? Is the partner failing to support the man or blaming him?

Clues from these and similar questions usually point toward causative factors that may be specifically addressed with therapy.

Acquired premature ejaculation

In addition to a general medical history, the history should include details about the following:

1. Previous relationships – Were there earlier relationships in which premature ejaculation was not a problem? Were there earlier relationships in which transient episodes of premature ejaculation occurred?
2. Current relationship – Was premature ejaculation always a problem, or did it start after an initial time frame when coitus was satisfactory to both partners?
3. Nonsexual aspects of the current relationship – Do the partners get along on most issues, or is conflict present? Who is dominant in the relationship, or is the relationship generally equal?
4. Involvement of the sexual partner – If the patient's female sexual partner did not accompany him to the clinic, why not? If she regards the problem as his alone, rather than theirs, this may be an important clue
5. Impotence problems – If the patient has erectile dysfunction, did it begin after the premature ejaculation or before? If the patient does not have erectile dysfunction, what is the general timing for the male (ie, the typical time from commencement of intromission to climax)?
6. Capacity for coitus – Can actual coitus be achieved, or does the premature ejaculation prevent it entirely?
7. Sexual context – Is the patient experiencing premature ejaculation with self-stimulation (ie, masturbation), with nonintercourse stimulation by the partner, or just with coitus?
8. Sexual response of partner – What is the time required for the female partner to reach climax? Can she reach climax with intercourse, or does she require direct clitoral stimulation (oral or manual)?

If the patient has erectile dysfunction that began after premature ejaculation, treatment of both conditions may be required; in some cases, the erectile difficulty resolves once the patient gains confidence in his ability to control ejaculation. If erectile dysfunction developed first, premature ejaculation may be a secondary sexual dysfunction; it may resolve when the patient is confident of being able to maintain his erection.

Physical Examination

Physical examination findings are normal in males whose only presenting condition is premature ejaculation. If other relevant medical conditions are present, signs of these conditions will be noted.

Diagnostic Considerations

Several other conditions must be considered in making a diagnosis of premature (early) ejaculation.

One such condition is severely delayed orgasm in the female partner. The term "delayed" is relative in this context; the average time to climax in females varies but averages 12-25 minutes, according to many studies, and 3 hours, for example, would be well outside the norm. In extreme cases of delayed or difficult orgasm in the female partner, almost any male would be considered to have premature ejaculation. The partner's sexual response must always be taken into account.

Another such condition is an adverse effect from a psychotropic drug. If the premature ejaculation started in association with the commencement of psychotropic pharmacotherapy but ceased when the drug was withdrawn, one should strongly consider a relationship between the two events.

In addition, preejaculate may be mistaken for premature ejaculation. Preejaculate is the lubricating fluid produced by Cowper glands and other glands during the excitement phase of sexual stimulation. A detailed sexual history should clarify this matter and enable the clinician to reassure the male as to what is actually happening.

Erectile dysfunction may be associated with premature ejaculation, and it may be difficult or impossible to establish which condition developed first. For lifelong premature ejaculation, associations with certain anxiety disorders have been noted. For acquired premature ejaculation, associations with drug withdrawal, thyroid disease, and prostatitis have been found. [70, 71]

A study of men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) found that the odds ratio (OR) for premature ejaculation significantly increased with the severity of pelvic pain, from 1.269 in men with mild prostatitis-like symptoms to 2.134 in men with moderate to severe symptoms. These authors suggested routine screening for CP/CPPS in men with premature ejaculation and for premature ejaculation in men with CP/CPPS.

Treatment

Medical treatment for premature (early) ejaculation includes several options. Any serious primary medical condition (eg, angina) should be treated; for the purposes of the following discussion, the patient is assumed to be healthy, and premature ejaculation is assumed to be his only problem.

In addition, any accompanying erection problem (eg, erectile dysfunction) should be treated; various methods are available, and excellent success can be expected. Accordingly, treatment of concomitant erectile dysfunction (ED) is mentioned only in passing.

To achieve the best outcome, the female partner should be included as fully as possible in the treatment and counseling sessions.

Pharmacologic therapy may include selective serotonin reuptake inhibitors (SSRIs) or desensitizing creams.

Outpatient care can be scheduled as appropriate for the clinical circumstances.

Surgical Intervention

No recommended surgical treatment exists for premature ejaculation.

Before the availability of nonsurgical methods for treating erectile dysfunction, a patient with premature ejaculation who was mistakenly diagnosed with erectile dysfunction might have undergone a penile prosthesis implantation, which would have yielded unsatisfactory results because of the incorrect initial diagnosis. In this scenario, the patient would be able to engage in sexual intercourse, because the penile implant would provide an adequate erection, but he would still climax prematurely.

Currently, penile implants are placed much more rarely, and with the use of nonsurgical treatments for erectile dysfunction, any permanent harm resulting from diagnosing erectile dysfunction rather than premature ejaculation is unlikely.

Consultations

Consultation with a sex therapist, psychologist, or psychiatrist may prove helpful if the primary care physician or urologist cannot provide successful treatment or does not have the time to explore psychological issues and implement behavioral techniques (eg, squeeze-pause). If the primary care physician or urologist is inexperienced or uncomfortable with treating premature ejaculation, early referral to a sex therapist, psychologist, or psychiatrist is indicated.

Some physicians are comfortable implementing pharmacologic therapy but not behavioral therapy. As with any medical condition, the patient should be offered all available treatment options, and the physician should proceed with referral for any option considered to require more specialized help than the physician can provide.

For men who may have a severe emotional disturbance underlying the premature ejaculation, referral to a mental health professional is most appropriate. Diagnosis and treatment of the various psychological factors that manifest partly as premature ejaculation are beyond the scope of this discussion.

Counseling and Sex Therapy

The first step is to attempt to relieve any underlying performance pressure on the male. If premature ejaculation occurs when intercourse is attempted, the couple should be instructed not to attempt intercourse until the ejaculatory problem is treated. In the meantime, the male may use manual stimulation, oral sex, or other means to satisfy the female partner.

If the male always experiences ejaculation with initial sexual excitement or early foreplay, this is a serious problem and probably indicates lifelong premature ejaculation (the

history should reveal this). Such cases will most likely call for treatment in conjunction with a mental health care professional. These more difficult cases should be screened out.

Next, the couple should be instructed in sex therapy techniques, such as the stop-start or squeeze-pause technique popularized by Masters and Johnson.

In this technique, the female partner slowly begins stimulation of the male but stops as soon as he senses a feeling of excessive excitement that may lead to ejaculatory inevitability. She then administers firm compression to the penis just behind the glans, pressing mainly on the underside. This compression should be uncomfortable but not painful. Once the male has the feeling that ejaculation is no longer imminent, the female resumes stimulation.

The process should be repeated and practiced at least 10 or more times. Over time, most males find that this technique helps decrease the impending inevitable need to ejaculate.

After practicing this technique for a while, the couple can move to another phase of the process. In this phase, the partners sit facing each other, with the woman's legs crossing on top of the male's legs. She stimulates him by manipulating his penis first close to and then with friction against her vulval area. Each time he senses excessive excitement, she applies the squeeze and stops all stimulation until he calms down enough for the process to be repeated.

Finally, coitus may be attempted, with the female partner in the superior position so that she may withdraw immediately and again apply a squeeze to remove the male partner's urge to climax.

Most couples find this technique to be highly successful. It can also help the female partner to be more aroused and can shorten her time to climax because it constitutes a form of extended foreplay in many cases.

Other nonpharmacologic approaches may be helpful. If the male is relatively young and can achieve another erection within a few minutes after a premature ejaculation, he may find that he is much less likely to experience a premature ejaculation the second time. The interval for achieving a second climax often includes a much longer period of latency, and the male can usually exert better control in this setting.

Accordingly, some therapists advise young men to masturbate (or have their partner stimulate them rapidly to climax) 1-2 hours before sexual relations are planned. In an older man, such a strategy may be less effective, because the older man may have difficulty achieving a second erection after his first rapid sexual release. If this occurs, it can damage his confidence and may result in secondary impotence.

Pharmacologic Therapy

To date, no drug has been specifically approved by the US Food and Drug Administration (FDA) for the treatment of premature ejaculation.

However, numerous studies have shown that SSRIs and drugs with SSRI-like side effects are safe and effective to treat this condition, and many physicians use these agents for this purpose. Desensitizing creams containing local anesthetic agents can also be useful in some men with premature ejaculation.

Premature ejaculation that relates to erectile dysfunction may resolve if the erectile dysfunction is treated successfully. If a patient has depression-related erectile dysfunction but not premature ejaculation, a drug with minimal adverse sexual effects might be considered so as to avoid causing delayed ejaculation or even anorgasmia. However, if the patient has premature ejaculation, erectile dysfunction, and depression, an antidepressant with SSRI side effects has the added benefit of possibly alleviating the premature ejaculation.

Desensitizing cream. In Korea and other areas of the Far East, SS (Super Secret) cream (a combination of 9 ingredients, mainly herbal) has been shown to desensitize the penis, decrease the vibratory threshold, and help men with premature ejaculation to delay their ejaculatory response significantly.

This preparation is not yet approved by the US Food and Drug Administration (FDA), but simple combinations of lidocaine cream or related topical anesthetic agents can be used with similar effects. These combinations are safe as long as the patient has no history of allergy to the substance.

Selective serotonin reuptake inhibitors and similar agents. The most effective pharmacologic therapy for premature ejaculation is to administer a drug from the SSRI class. Normally, these drugs are used as antidepressants in the clinical setting. Many of these agents were found to have the side effect of significantly delaying the achievement of orgasm in both male and female patients, and it was for this reason that such agents were applied to the treatment of premature ejaculation.

Some tricyclic antidepressants (TCAs) with SSRI-like activity have the same effect in orgasm that SSRIs do. The TCA that has been most frequently studied for treatment of premature ejaculation is clomipramine. Many investigators find that clomipramine is more effective for premature ejaculation than many SSRIs are.

In most cases, females require considerably more time to reach climax than males do; thus, the delayed climax caused by SSRIs and SSRI-like agents becomes an adverse effect in women. In many females, such an inability to reach orgasm can induce a pattern of sexual avoidance, along with a corresponding decrease in libido or sexual excitement (lubrication). In males, too-rapid orgasm can cause some of the same patterns of sexual avoidance and decreased libido. Thus, it is essential to determine the primary problem when instituting therapy.

SSRIs useful for treating premature ejaculation include the following:

1. Sertraline;
2. Paroxetine;
3. Fluoxetine;
4. Citalopram;
5. Dapoxetine.

Dapoxetine was developed specifically to treat this condition. It may be effective at the first dose (ie, on demand) when given 1-3 hours before sexual intercourse, and its adverse-effect profile is comparable to those of other SSRIs. Dapoxetine has been approved in a number of countries but not yet in the United States. In a study of men with both premature ejaculation and erectile dysfunction who were on phosphodiesterase type 5 (PDE5) therapy, dapoxetine provided treatment benefit and was generally well tolerated.

The optimal medical treatment regimen for premature ejaculation has not been established. The author's experience has been that in some males, single dosing before sexual relations can work well, whereas in others, it may be necessary to achieve and maintain a target blood level through daily use of the medication, as in the treatment of clinical depression.

Obviously, if single dosing is successful, therapy is simpler and has fewer adverse effects. Accordingly, this may be the preferred initial approach. If necessary, the dose may be increased in a stepwise fashion until a therapeutic effect is achieved or the maximum daily recommended dose is reached. No exact schedule for increasing the dose has been established; the experience of the physician, the response of the patient, the adverse effects experienced by the patient, and other general medical considerations should be the guiding factors.

If the initial SSRI fails to help the patient, it is certainly reasonable to try a second agent. However, if the second choice fails, it is not likely that a third choice will offer any benefit. As with treatment for depression, if a patient has been taking the maximal dose of the medication for 6 weeks without showing any improvement, the likelihood that a more prolonged course of therapy with a particular drug would be successful is remote.

There is no reason why pharmacotherapy cannot be combined with behavioral modification therapy, desensitizing creams, or both; the use of several simultaneous treatments can result in additive effects or even synergy. If all treatment fails, then the patient's only options are as follows:

1. To see a different health care professional, if he wishes;
2. To accept his condition as being untreatable with currently available therapeutic options.

Adverse effects of long-term SSRI use are a significant concern and should be considered by both the physician and the patient. Such adverse effects may include the following:

1. Psychiatric and neurologic sequelae;
2. Dermatologic reactions;
3. Anticholinergic effects;
4. Fluctuation in body weight;
5. Cognitive impairment;
6. Drug interactions;

7. Sexual side effects other than delayed ejaculation (eg, erectile dysfunction or loss of libido).

In addition, caution should be exercised in changing SSRIs; a washout period is necessary to avoid overdose. SSRI discontinuance syndrome (especially with paroxetine) has been associated with dose reduction or discontinuance and may cause dizziness, nausea and vomiting, headache, gait instability, lethargy, agitation, anxiety, and insomnia.

Phosphodiesterase type 5 inhibitors. Some studies have demonstrated that combining phosphodiesterase type 5 (PDE5) inhibitors with SSRIs provides better results in the treatment of premature ejaculation than using SSRIs alone. The reason for this is unknown, but part of the explanation may be that the improved (firmer, longer-lasting, or both) erection resulting from the PDE5 inhibitor provides inhibition of ejaculation via downregulation of receptors involved in somatosensory latency times. In addition, a reduction in performance anxiety may exist on a subconscious level.

Regardless of the mechanism, PDE5 inhibitors have been found to be safe and effective as a therapeutic adjunct for premature ejaculation in men for whom such therapy is not otherwise contraindicated. The only PDE5 inhibitors studied to any significant degree in the setting of premature ejaculation are sildenafil and tadalafil; vardenafil may also work, but the available data are insufficient to support its use.

To date, no studies have demonstrated the superiority of PDE5 inhibitors over placebo in the treatment of premature ejaculation. However, a recent meta analysis of 15 randomized clinical trials suggests that PDE5-Is are significantly more effective than placebo (231 participants, $p < 0.00001$), that there is no difference between PDE5-Is and selective serotonin reuptake inhibitors (SSRIs; 405 participants, $p=0.50$), and that PDE5-Is combined with an SSRI are significantly more effective than SSRIs alone (521 participants, $p = 0.001$).The use of PDE5 inhibitors for the treatment of premature ejaculation is not approved by the FDA and is considered an off-label use.

Other agents

A study by Safarinejad demonstrated that a single daily high dose of pindolol (a nonselective beta-adrenergic antagonist with 5-HT1A autoreceptor antagonist properties) in combination with paroxetine (or possibly another SSRI) delayed ejaculation in patients in whom paroxetine therapy alone failed to provide benefit. However, more studies must be performed before pindolol can be considered an ideal option for first- or second-line treatment of premature ejaculation.

In studies by Safarinejad and Hosseini and Salem et al, the opioid analgesic tramadol was found to be significantly more effective than placebo in terms of increased time to

ejaculation, increased sexual intercourse satisfaction, and tolerability. A systematic review and meta-analysis found that tramadol may be effective in treatment of premature ejaculation, especially when other therapies have failed, but that it remains necessary to consider, the possibility of drug addiction and side effects before initial use or after long-term use.

13.3 Delayed ejaculation.

Male orgasm is defined as a subjective, perceptual-cognitive event of peak sexual pleasure that in normal conditions coincides with the moment of ejaculation. Delayed ejaculation is typically a self-reported diagnosis; there is no firm consensus on what constitutes a reasonable time frame for reaching orgasm. [70]

The presence of a normal sexual excitement phase is a prerequisite for male orgasmic disorder (MOD). In other words, if the absence of orgasm follows a decreased desire for sexual activity, an aversion to genital sexual contact, or a decreased lubrication-swelling response, diagnoses such as hypoactive sexual desire disorder, sexual aversion disorder, or male erectile disorder might be more appropriate, even if they all have a final common outcome (ie, anorgasmia, defined as failure to experience an orgasm).

Patients with MOD can achieve firm erections and have normal sexual intercourse with penetration. Some patients reporting MOD with intercourse can achieve orgasm through manual or oral stimulation or at least report orgasm through nocturnal emissions ("wet dreams"). A report of generalized, lifelong MOD with no orgasm at all (across an array of stimulative techniques) suggests an organic etiology.

Urologic classifications are usually explicit in differentiating between failure to ejaculate and absence of orgasm.

Diagnostic criteria (DSM-5)

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies delayed ejaculation as belonging to a group of sexual dysfunction disorders typically characterized by a clinically significant inability to respond sexually or to experience sexual pleasure.

Sexual functioning involves a complex interaction among biologic, sociocultural, and psychological factors, and the complexity of this interaction makes it difficult to ascertain the clinical etiology of sexual dysfunction. Before any diagnosis of sexual dysfunction is made, problems that are explained by a nonsexual mental disorder or other stressors must first be addressed. Thus, in addition to the criteria for delayed ejaculation, the following must be considered:

1. Partner factors (eg, partner sexual problems or health issues)

2. Relationship factors (eg, communication problems, differing levels of desire for sexual activity, or partner violence)
3. Individual vulnerability factors (eg, history of sexual or emotional abuse, existing psychiatric conditions such as depression, or stressors such as job loss)
4. Cultural or religious factors (eg, inhibitions or conflicted attitudes regarding sexuality)
5. Medical factors (eg, an existing medical condition or the effects of drugs or medications)

The specific *DSM-5* criteria for delayed ejaculation are as follows:

1. In almost all or all (75-100%) sexual activity, the experience of either marked delay in ejaculation or marked infrequency or absence of ejaculation
2. The symptoms above have persisted for approximately 6 months
3. The symptoms above cause significant distress to the individual
4. The dysfunction cannot be better explained by nonsexual mental disorder, a medical condition, the effects of a drug or medication, or severe relationship distress or other significant stressors

The severity of delayed ejaculation is classified as mild, moderate or severe on the basis of the level of distress the patient exhibits over the symptoms. The duration of the dysfunction is specified as follows:

1. Lifelong (present since first sexual experience)
2. Acquired (developing after a period of relative normal sexual functioning)

In addition, the context in which the dysfunction occurs is specified as follows:

1. Generalized (not limited to certain types of stimulation, situations, or partners)
2. Situational (limited to specific types of stimulation, situations, or partners)

Pathophysiology

The succession of erection, emission, ejaculation, and orgasm creates the impression that these events might have a common physiologic substrate. In reality, they are separate events. This separateness is clearly illustrated by the typical patient with MOD, who complains of sustaining hard erections without being able to ejaculate, or by the typical patient with erectile dysfunction, who complains of ejaculating through a flaccid penis.

Emission and ejaculation usually require external genital stimulation (nocturnal emission being the notable exception). Efferent impulses travel from the pudendal nerves and reach the

upper lumbar spinal sympathetic nuclei. Via the hypogastric nerve, the impulses activate secretions and transport sperm from the distal epididymis, vasa deferentia, seminal vesicles, and prostate to the prostatic urethra. Closure of the internal urethral sphincter and concomitant relaxation of the external sphincter direct semen into the bulbous urethra, resulting in emission.

The somatomotor efferent of the pudendal nerve then produces subsequent rhythmic contractions of the bulbocavernous muscle, forcing the semen through a pressurized passage (the narrowed urethral lumen compressed by the engorged corpora cavernosa) and yielding 2-5 mL of ejaculate. Because this action is involuntary, integrated autonomic and somatic actions are required for completion.

The cerebral network modulating and controlling the final common output from all ejaculatory stimuli includes the posteromedial bed nucleus of the stria terminalis, the posterodorsal medial amygdaloid nucleus, the posterodorsal preoptic nucleus, and the parvicellular part of the subparafascicular thalamus.

It has been suggested that the ejaculatory reflex is primarily regulated by the central serotonergic and dopaminergic systems, with other neurotransmitters (eg, acetylcholine, adrenaline, neuropeptides, oxytocin, gamma-aminobutyric acid [GABA], and nitric oxide) playing secondary roles.

Experimental evidence indicates that serotonin (5-HT), throughout brain descending pathways, exerts an inhibitory role on ejaculation. To date, 3 serotonin receptor subtypes (5-HT1A, 5-HT1B, and 5-HT2C) have been postulated to mediate the modulating activity of serotonin on ejaculation. Pharmacologic manipulation of the serotonergic system has been performed in rats, with the selective serotonin reuptake inhibitors (SSRIs) exhibiting the greatest efficacy in delaying ejaculation.

It has been suggested that the presynaptic 5-HT1A somatodendritic autoreceptors, located in the mesencephalic and medullary raphe nuclei and responsible for decreasing 5-HT release into the synapse, decrease ejaculatory latency. In contrast, the postsynaptic 5-HT1B and 5-HT2C receptors have been shown to prolong ejaculatory latency. [71]

In animal models, dopamine levels in the medial preoptic area of the hypothalamus were shown to increase progressively during excitation and intercourse, GABA-receptor antagonists were found to inhibit sexual behavior, and muscular contractions during ejaculation appeared to be mediated by oxytocin.

In view of the relation between the serotonergic receptors and their inhibitory and excitatory effects, it is likely that altered levels of 5-HT or altered 5-HT receptor sensitivity in the ejaculatory modulating centers of the central nervous system (CNS) contribute to the pathophysiologic

mechanism behind ejaculatory disorders. Thus, 5-HT might suppress ejaculation by interrupting the action of oxytocin, which normally accompanies sexual behavior.

Despite significant advances, the specific role and importance of each individual neurotransmitter in the multifactorial and complex ejaculatory reflex remain to be clarified. Research into these subjects is ongoing.

The mechanism of orgasm is still the least well understood part of the sexual process. It probably involves central (cerebral) integration and response to sexual stimulation. Emission, ejaculation, and orgasm are typically associated with several other concomitant nongenital responses, which may include involuntary rhythmic contractions of the anal sphincter, hyperventilation, tachycardia, and elevation of blood pressure.

Transient sympathoadrenal activation during sexual activity, reflected by increases in epinephrine and norepinephrine plasma levels, together with increased cardiovascular activity, has been reported to be associated with orgasm in males.

The association of vasopressin, cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), beta-endorphin, and testosterone with male orgasm remains unclear. Whereas both oxytocin and prolactin levels have been reported to peak immediately after orgasm, plasma prolactin levels seem to represent a more sustained and reliable endocrine marker of orgasm in males.

Aetiology

Hyperprolactinemia has been associated with both decreased sexual desire and a decreased ability to reach orgasm in males.

Reportedly, the intensity of orgasm correlates with the ejaculatory volume; thus, declines in ejaculatory volume can result in reduced sexual pleasure. Because ejaculate volume is androgen-dependent, it tends to decrease with age, and this decrease may result in a blunted orgasm experience in the elderly.

In rare subjects, orgasm may alter central neurotransmission, provoking a postejaculatory pain syndrome or the postorgasmic illness syndrome (POIS) characterized by severe fatigue, intense warmth, and a flulike state with generalized myalgia.

The increased frequency of delayed ejaculation in men older than 50 years may be associated with age-related loss of fast-conducting peripheral sensory nerves, as well as with age-related reduction in the secretion of sex steroids.

Epidemiology

Epidemiologic research into orgasmic disorders must contend with the challenge of poor collateral confirmatory evidence based on subjective patient reports, the value of which is further limited by the fact that such disorders are highly sensitive topics in most cultures. Accordingly, it

is not surprising that despite their apparent prevalence, sexual disorders in general and orgasmic disorders in particular typically have not been included in large-scale epidemiologic studies such as the Epidemiologic Catchment Area (ECA) study.

Because of the lack of a precise definition of the condition, the true prevalence of delayed ejaculation is not well defined. This syndrome is considered to be the least common male sexual complaint. Only 75% of men report always ejaculating during sexual activity, and less than 1% complain of difficulties in reaching ejaculation that last longer than 6 months.

A review of 52 studies published over a 10-year span found MOD to have a prevalence of 0-8% in community samples, 0-36% (median, 9%) in primary care samples, and 0-38% in sexuality clinic samples. One of the authors had previously published a comprehensive review study that reported a community prevalence of 4-10% for MOD. Whether the apparent decrease in community prevalence in the latter study reflected a real decrease or merely a difference in research methodology is not clear.

Epidemiologic research in this field continues to be hindered by issues such as the following:

1. Lack of well-controlled studies
2. Wide variability of diagnostic criteria and definitions
3. Lack of objective markers for the diagnostic criteria used for MOD
4. Lack of incidence data

Consequently, the available epidemiologic evidence is, at best, informative. Further epidemiologic research is needed to derive an accurate estimate of the incidence of orgasmic disorder in men across age periods, races, cultures, relationship status, and countries.

The Global Study of Sexual Attitudes and Behaviors (GSSAB), which investigated attitudes, behaviors, beliefs, and satisfaction among 27,500 men and women aged 40-80 years, reported 13.2% of men as "not reaching orgasm." It should be noted that this definition includes MOD as well as delayed ejaculation and anejaculation.

The incidence of delayed ejaculation begins to increase after the age of 50 years. Compared with men younger than 59 years, men in their 80s report twice as much difficulty in ejaculating.

In a review of 52 studies, the estimated rate of MOD among gay men was 38% (notably higher than from other samples), leading the authors to speculate that this difference might reflect a greater recognition of the threat of infection with HIV.

Reports of delayed ejaculation vary across countries and cultures. In general, this complaint is more commonly reported by men in Asian populations than by men living in the United States, Australia, or Europe.

Such variation may be due to cultural or genetic differences.

History

A sexual history should be elicited. In many cases, there is a pattern of long-continued thrusting in an effort to achieve orgasm, which is maintained until the man becomes exhausted or experiences genital discomfort, eventually discontinuing his efforts. A repetitive pattern of difficulty in ejaculating may lead a man to avoid sexual activity altogether. In addition, this ejaculatory difficulty may lead some sexual partners to report feeling less sexually attractive.

Psychological factors (eg, a history of trauma, severe guilt, a fear of impregnation, or hostility toward a woman) have all been associated with primary inhibited male orgasm. Severe forms of major depressive disorder may also be linked with an increased frequency of delayed ejaculation.

A history of injury or surgery may be highly relevant. Ejaculatory dysfunction has been reported in about 40% of patients with bilateral sympathectomy at the L2 level. High bilateral retroperitoneal lymphadenectomy can cause an even higher percentage of emission failures. Dysfunction of the internal sphincter or the bladder neck (eg, post prostatectomy) following alpha-blocker therapy or autonomic neuropathy due to diabetes can result in retrograde ejaculation.

It should be noted that successful emission and ejaculation without orgasm occur in some patients with spinal cord injury. Phantom orgasm in a paraplegic man has also been described. A history of disease or surgery helps differentiate emission failure from retrograde ejaculation.

A good history of alcohol and illicit drug use is mandatory. In contrast with anecdotal reports of increased duration and intensity of the orgasmic experience associated with marijuana use, a large epidemiologic study of sexual disorders associated with drug use reported that in a sample of 3004 adult men and women, marijuana and alcohol use were clearly associated with anorgasmia.

Chronic use of cocaine, opioids, and amphetamines has also been reported to induce sexual disorders and anorgasmia in a high proportion of users. 3,4-Methylenedioxy-N-methylmphetamine (MDMA), most commonly known under the street name of ecstasy, has been associated with both delayed orgasm and anorgasmia.

Diagnostic Considerations

Debilitating medical conditions that have the potential to decrease sexual desire and performance can result in secondary inhibited male orgasm. The most common medical conditions associated with sexual difficulties are diabetes mellitus and hypertension, possibly because of the microvascular and neurovascular changes that are inherent in these conditions.

Pain syndromes, shortness of breath, angina pectoris, and muscle weakness should be included in the

differential diagnosis. Cigarette smoking can cause vascular insufficiency, as well as a decrease in intrapenile nitrous oxide (NO) levels. Excessive consumption of alcohol or the use of other recreational drugs can have a direct inhibitory effect on the genital neurovascular system, an indirect effect via increased prolactin or decreased testosterone production, or both.

The following classes of prescribed medications should be considered in the differential diagnosis:

1. Alpha-adrenergic blockers – Prazosin and terazosin (retrograde ejaculation)
2. Combined alpha- and beta-adrenergic blockers - Labetalol (inhibited ejaculation)
3. Sympathetic nerve blockers - Guanethidine (erectile dysfunction and retrograde ejaculation)
4. Antiulcer medications - Cimetidine (decreased libido)
5. Tricyclic antidepressants (via increased serotonin) - Amitriptyline, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline (inhibited ejaculation); clomipramine was reported to induce anorgasmia within days of starting treatment, which persisted with minimal tolerance over 5 months of clomipramine therapy)
6. Monoamine oxidase inhibitors (via increased serotonin) - Isocarboxazid, phenelzine, and tranylcypromine (inhibited ejaculation and decreased libido)
7. Selective serotonin reuptake inhibitors (via increased serotonin) - Fluoxetine (anorgasmia in 8-30%) and paroxetine (anorgasmia)
8. Other antidepressants - Venlafaxine (anorgasmia)
9. Neuroleptics (mainly via increased prolactin) – First-generation or typical (haloperidol, thiothixene, perphenazine, and trifluoperazine) and second-generation (risperidone) (inhibited ejaculation, decreased libido)
10. Mood stabilizers - Topiramate (anorgasmia)

Approach Considerations

Microscopic examination of the bladder urine after a dry ejaculation is informative in differentiating between retrograde ejaculation (sperm in bladder urine after a dry ejaculation) and emission failure (no sperm found in bladder urine). Additionally, in retrograde ejaculation, although no ejaculate is seen, orgasm and detumescence do occur.

Pharmacotherapy

When pharmacotherapy for delayed ejaculation is under

consideration, it is important to eliminate iatrogenic causes, including medications (eg, alpha-adrenergic blockers, other antihypertensives, antidepressants, and antipsychotics). In the case of antidepressant-induced inhibited male orgasm, consideration may be given to switching to bupropion (also used as adjunctive therapy), mirtazapine, or nefazodone (withdrawn from the US market), which have fewer sexual side effects than selective serotonin reuptake inhibitors (SSRIs) do.

Adjunctive therapies should be considered. Alpha sympathomimetics (eg, ephedrine or a combination of chlorpheniramine maleate and phenylpropanolamine hydrochloride) have been used successfully in patients with retrograde ejaculation.

Sildenafil and imipramine appear to be effective in psychotropic-induced male orgasmic disorder (MOD).

Psychological Interventions

Any psychological intervention must address both historical factors and current factors that might contribute to the present dysfunction.

Historical factors that can contribute to anorgasmia include the following:

1. Traumatic or unpleasant past sexual experiences
2. Negative cognitions about sex (eg, sex seen as a sin or genitals seen as dirty) based on a strict or rigid religious or moral background

A psychodynamic-oriented treatment aims to explore and understand such factors, decrease secondary feelings such as anxiety and guilt, and correct negative cognitions that can result in psychological inhibition and orgasmic dysfunction. A psychodynamic approach is recommended for persistent, treatment-resistant anorgasmia. Psychodynamic treatment can also be classified as a short-term approach, as opposed to an open-ended one.

Current factors that can contribute to anorgasmia include the following:

1. Performance anxiety – Cognitive-behavioral interventions to decrease anxiety include sexual education (to dispel misconceptions about sexuality or relieve feelings of inadequacy or inappropriate guilt), guided imagery, and sensate focus
2. Relationship problems – If anorgasmia appears to be secondary to relationship problems, couples or marital therapy might be indicated
3. Stress (due to causes other than relationship difficulties or sexual problems)
4. Environmental factors (eg, lack of privacy or

uncomfortable room temperature)

Counseling should be provided for patients who have normal wet dreams but cannot achieve orgasm and ejaculation during sexual activity.

In addition to psychotherapy, anecdotal reports suggest that an electrovibrator applied at the lower surface of the glans penis can be an effective intervention in cases of primary male anorgasmia.

Antidepressants, Other

The mixed serotonergic and noradrenergic drugs have effects on serotonin, norepinephrine, and, in some cases, dopamine, as well as nicotinic acetylcholine systems. Because of the empirical nature of psychopharmacology, they may be used as first-line drugs or as alternative agents when other antidepressants cause undesired side effects.

Phosphodiesterase (type 5) Enzyme Inhibitors

These agents increase the vasodilatory effects of nitric oxide by inhibiting the enzyme phosphodiesterase type 5, which, in turn, increases sensitivity for erections.

Sildenafil is a phosphodiesterase type 5 (PDE5) selective inhibitor. It appears to be effective in psychotropic-induced male orgasmic disorder (MOD). Inhibition of PDE5 increases the activity of cyclic guanosine monophosphate (cGMP), which increases the vasodilatory effects of nitric oxide. This agent is effective in men with mild-to-moderate ED.

Take on an empty stomach about 1 hour before sexual activity. Sexual stimulation is necessary to activate response. The increased sensitivity for erections may last 24 hours. Sildenafil is available as 25-, 50-, and 100-mg tabs.

Erectile dysfunction

The National Institutes of Health (NIH) Consensus Development Conference on Impotence (December 7-9, 1992) defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."

The first step in the management of ED is a thorough history that includes the following:

1. Sexual history;

2. Medical history;

3. Psychosocial history.

A physical examination is necessary for every patient, emphasizing the genitourinary, vascular, and neurologic systems. A focused examination entails evaluation of the following:

1. Blood pressure;

2. Peripheral pulses;

3. Sensation;

4. Status of the genitalia and prostate;

5. Size and texture of the testes;

6. Presence of the epididymis and vas deferens;

7. Abnormalities of the penis (eg, hypospadias, Peyronie plaques).

There is a strong correlation between hypertension and ED. There is also a correlation between benign prostatic hyperplasia and ED, though the causality is unclear.

Diagnostics

Laboratory testing for ED depends on information gathered during the interview; it is necessary for most patients, although not for all. Such testing may include the following:

1. Evaluation of hormonal status (testosterone, serum hormone–binding globulin, luteinizing hormone [LH], prolactin, thyroid-stimulating hormone [TSH]) – Note that the American College of Physicians (ACP) does not recommend for or against routine use of hormonal blood tests or hormonal treatment in ED patients;

2. Screening blood studies (hemoglobin A 1c, serum chemistry panel, lipid profile);

3. Prostate-specific antigen levels, if the patient is a candidate for prostate cancer screening (controversial);

4. Urinalysis.

Functional tests that may be helpful include the following:

1. Direct injection of prostaglandin E1 (PGE1; alprostadil) into the corpora cavernosa;

2. Biothesiometry – Infrequently indicated;

3. Nocturnal penile tumescence testing – Once frequently performed, this is rarely used in current practice, though it can be helpful when the diagnosis is in doubt;

4. Formal neurologic testing – Not needed in the vast majority of ED patients, though it may offer some benefit to patients with a history of central nervous system problems, peripheral neuropathy, diabetes, or penile sensory deficit.

Imaging studies are not commonly warranted, except in situations where pelvic trauma has been sustained or surgery performed. Modalities that may be considered include the following:

1. Ultrasonography of the penis (to assess vascular function within the penis);

2. Ultrasonography of the testes (to help disclose abnormalities in the testes and epididymides; rarely indicated);

3. Transrectal ultrasonography (to disclose abnormalities in the prostate and pelvis that may interfere with erectile function);

4. Angiography (in patients who are potential candidates for vascular surgery).

Treatment

Treatment options for ED include the following:

1. Sexual counseling, if no organic causes can be found for the dysfunction;

2. Oral medications;

3. Injected, implanted, or topically applied medications;

4. External vacuum and constriction devices;

5. Surgery.

Many patients with ED also have cardiovascular disease; thus, treatment of ED in these patients must take cardiovascular risks into account.

According to American Urological Association (AUA) guidelines, oral phosphodiesterase type 5 (PDE5) inhibitors are first-line therapy unless contraindicated. Agents include the following:

1. Sildenafil;

2. Vardenafil;

3. Tadalafil;

4. Avanafil.

In patients with ED refractory to oral PDE5 inhibitors, one of these agents can be combined with an injection of PGE1.

In a prospective, multicenter, single-armed study of ED patients who exhibited a suboptimal response to PDE5 inhibitors, the investigators found that percutaneous implantation of zotarolimus-eluting stents in focal atherosclerotic lesions was both safe and feasible and was associated with clinically meaningful improvement on subjective and objective measures of erectile function.

Hormone replacement may benefit men with severe hypogonadism and may possibly be useful as adjunctive therapy when other treatments are unsuccessful. Replacement androgens are available in oral (rarely used), injectable, gel, and transdermal preparations.

Intracavernosal injection therapy may be considered and is almost always effective if the vasculature within the corpora cavernosa is healthy. Agents used include the following:

1. Alprostadil (most common);

2. Phentolamine;

3. Papaverine.

The Medicated Urethral System for Erections (MUSE) involves the formulation of alprostadil (PGE1) into a small intraurethral suppository that can be inserted into the urethra. This may be useful for men who do not want to use self-injections or those in whom oral medications have failed.

External devices that may be used include the following:

1. Vacuum devices to draw blood into the penis;

2. Constriction devices placed at the base of the penis to maintain erection.

Selected patients with ED are candidates for surgical treatment. Procedures to be considered include the following:

1. Revascularization (rarely indicated);

2. Surgical elimination of venous outflow (rarely indicated).

Placement of penile implant (semirigid or malleable rod implant, fully inflatable implant, or self-contained inflatable unitary implant) – Once the only effective therapy for men with organic ED, this is the last option considered in current practice

Suggested measures for preventing ED include the following:

1. Optimal management of diabetes, heart disease, and hypertension;

2. Lifestyle modifications to improve vascular function (eg, not smoking, maintaining ideal body weight, and engaging in regular exercise).

Premature ejaculation

Premature (early) ejaculation is the most common sexual disorder in men younger than 40 years, with 30-70% of males in the United States affected to some degree at one time or another. It has historically been considered a psychological disease with no identified organic cause.

Premature ejaculation can be lifelong or acquired. With lifelong premature ejaculation, the patient has experienced premature ejaculation since first beginning coitus. With acquired premature ejaculation, the patient previously had successful coital relationships and only now has developed premature ejaculation.

Patient characteristics in lifelong premature ejaculation can include the following:

1. Psychological difficulties;

2. Deep anxiety about sex that relates to 1 or more traumatic experiences encountered during development.

In patients with lifelong premature ejaculation, inquire about the following:

1. Previous psychological difficulties;

2. Early sexual experiences;

3. Family relationships during childhood and adolescence;

4. Peer relationships;

5. Work or school;

6. General attitude toward sex;

7. Context of the event (eg, marital versus nonmarital);

8. Sexual attitude and response of the female partner;

9. Nonsexual aspects of the current relationship;

10. Level of involvement of the sexual partner in treatment.

Clues from these and similar questions usually point toward causative factors that may be addressed specifically with therapy.

Patient characteristics in cases of acquired premature ejaculation can include the following:

1. Erectile dysfunction;

2. Performance anxiety;

3. Psychotropic drug use.

In patients with acquired premature ejaculation, inquire about the following:

1. Previous relationships;

2. Current relationship;

3. Nonsexual aspects of the current relationship;

4. Level of involvement of the sexual partner in treatment;

5. Impotence problems;

6. Capacity for coitus;

7. Sexual context;

8. Sexual response of partner.

Diagnostics

In males with premature (early) ejaculation and no other medical problems, no specific conventional laboratory tests aid or affect treatment. Checking the patient's levels of serum testosterone (free and total) and prolactin may be appropriate if premature ejaculation is observed in conjunction with an impotence problem. If depression or other conditions coexist, laboratory studies specific to depression or to another medical or psychological problem are appropriate.

Other conditions that should be considered in making the diagnosis of premature ejaculation include the following:

1. Severely delayed orgasm in the female partner;

2. Adverse effect from a psychotropic drug;

3. Presence of preejaculate;

4. Erectile dysfunction.

Treatment

Medical treatment for premature (early) ejaculation includes several options. Any serious primary medical condition (eg, angina) should be treated, as should any accompanying erection problem (eg, erectile dysfunction). To achieve the best outcome, the female partner should be included as fully as possible in the treatment and counseling sessions. Outpatient care can be scheduled as appropriate for the clinical circumstances.

Nonpharmacologic therapy may include the following:

1. Efforts to relief of underlying performance pressure on the male;

2. Sex therapy (eg, instruction in the stop-start or squeeze-pause technique popularized by Masters and Johnson);

3. Second attempt at coitus – If another erection can achieve be achieved shortly after an episode of premature ejaculation, ejaculatory control may be much better the second time.

Pharmacologic therapy may include the following:

1. Topical desensitizing agents (eg, lidocaine and prilocaine) for the male;

2. Selective serotonin reuptake inhibitor (SSRI) therapy (eg, sertraline, paroxetine, fluoxetine, citalopram, or dapoxetine); alternatively, use of an agent with SSRI-like effect;

3. Phosphodiesterase type 5 (PDE5) inhibitor therapy (eg, sildenafil, tadalafil, or possibly vardenafil);

4. Other agents (eg, pindolol or tramadol);

5. No recommended surgical therapy exists.

Delayed ejaculation

Delayed ejaculation is typically a self-reported diagnosis; there is no firm consensus on what constitutes a reasonable time frame for reaching orgasm.

The history should address the following:

1. Sexual history (eg, repetitive pattern of difficulty in ejaculating);

2. Psychological factors (eg, a history of trauma, severe guilt, a fear of impregnation, hostility toward a woman, severe depression);

3. History of injury or surgery (eg, bilateral sympathectomy at L2, high bilateral retroperitoneal lymphadenectomy);

4. History of alcohol and illicit drug use (including marijuana, cocaine, opioids, amphetamines, and 3,4-methylenedioxy-N-methylmphetamine (ecstasy).

Diagnostics

Conditions that should be included in the differential diagnosis include the following:

1. Diabetes mellitus;

2. Hypertension;

3. Pain syndromes;

4. Shortness of breath;

5. Angina pectoris;

6. Muscle weakness;

7. Cigarette smoking;

8. Excessive consumption of alcohol or the use of other recreational drugs.

The following classes of prescribed medications should be considered in the differential diagnosis:

1. Alpha-adrenergic blockers;

2. Combined alpha- and beta-adrenergic blockers;

3. Sympathetic nerve blockers;

4. Antiulcer medications;

5. Tricyclic antidepressants;

6. Monoamine oxidase inhibitors;

7. Selective serotonin reuptake inhibitors;

8. Other antidepressants;

9. Neuroleptics;

10. Mood stabilizers.

Microscopic examination of the bladder urine after a dry ejaculation is informative in differentiating between retrograde ejaculation and emission failure.

Treatment

When pharmacotherapy for delayed ejaculation is under consideration, it is important to eliminate iatrogenic causes, including medications. Adjunctive therapies should be considered. Agents that have been used include the following:

1. Alpha sympathomimetics (eg, ephedrine or a combination of chlorpheniramine maleate and phenylpropanolamine hydrochloride);

2. Sildenafil;

3. Imipramine.

Any psychological intervention must address both historical factors and current factors that might contribute to the present dysfunction. Historical factors that can contribute to anorgasmia include the following:

1. Traumatic or unpleasant past sexual experiences;

2. Negative cognitions about sex.

Current factors that can contribute to anorgasmia include the following:

1. Performance anxiety;

2. Relationship problems;

3. Stress (due to causes other than relationship difficulties or sexual problems);

4. Environmental factors (eg, lack of privacy or uncomfortable room temperature).

Anecdotal reports suggest that an electrovibrator applied at the lower surface of the glans penis can be an effective intervention in cases of primary male anorgasmia.

Theme # 14: Male infertility. Male hypogonadism.

14.1 Male infertility

Gonadal and sexual functions are mediated by the hypothalamic-pituitary-gonadal axis, a closed-loop system with feedback control from the testicles. The hypothalamus, the primary integration center, responds to various signals from the central nervous system (CNS), pituitary gland, and testicles to secrete gonadotropin-releasing hormone (GnRH) in a pulsatile pattern approximately every 70-90 minutes. The half-life of GnRH is 2-5 minutes.

Release of GnRH is stimulated by melatonin from the pineal gland and inhibited by testosterone, inhibin, corticotropin-releasing hormone, opiates, illness, and stress. GnRH travels down the portal system to the anterior pituitary, located on a stalk in the sella turcica, to stimulate the release of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

FSH and LH, glycopeptides with a molecular weight of 10,000 Daltons, are each composed of an alpha chain that is identical to that of human chorionic gonadotropin (HCG) and thyroid-stimulating hormone (TSH), but with a beta chain that is unique for each. FSH has a lower plasma concentration and longer half-life than LH, and it has less obvious pulsatile changes. The pulsatile nature of GnRH is essential to normal gonadotropin release; a continuous stimulation inhibits their secretion. [72]

The hypothalamus also produces thyrotropin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP), both of which stimulate prolactin release from the anterior pituitary, and dopamine, which inhibits prolactin release. Men with elevated prolactin levels present with gynecomastia, diminished libido, erectile dysfunction, and occasionally galactorrhea. Prolactin inhibits the production of GnRH from the hypothalamus and LH and FSH from the pituitary. Gonadotropin release is modulated by various other signals, such as estradiol (a potent inhibitor of both LH and FSH release), and inhibin from the Sertoli cell, which causes a selective decrease in FSH release.

FSH and LH are released into the systemic circulation and exert their effect by binding to plasma membrane receptors of the target cells. LH mainly functions to stimulate testosterone secretion from the Leydig cells of the testicle, while FSH stimulates Sertoli cells to facilitate germ cell differentiation.

Testosterone is secreted in a diurnal pattern, peaking a few hours after the man awakens from sleep. In the body, testosterone circulates 2% in the free form, 44% bound to sex hormone-binding globulin (SHBG), and 54% bound to albumin. Testosterone is converted to dihydrotestosterone (DHT) by the action of 5-alpha reductase, both

locally and in the periphery, and to estrogen in the periphery. Testosterone and estradiol function as feedback inhibitors of gonadotropin release. [72]

The testicle contains the Leydig cells and the Sertoli cells and is covered by the tunica albuginea, which also provides septae that divide it into approximately 200-350 pyramids. These pyramids are filled with the seminiferous tubules. A normal testicle contains 600-1200 seminiferous tubules with a total length of approximately 250 meters. The interstitium between the seminiferous tubules contains the Leydig cells, fibroblasts, lymphatics, blood vessels, and macrophages. Histologically, Leydig cells are polygonal with eosinophilic cytoplasm. Occasionally, the cytoplasm contains crystalloids of Reinke after puberty.

Seminiferous tubules are made up of Sertoli cells and germ cells and are surrounded by peritubular and myoid cells.

Sertoli cells are columnar, with irregular basal nuclei that have prominent nucleoli and fine chromatin. They rest on the basement membrane and serve mainly to support, nourish, and protect the developing germ cells and to provide a blood-testis barrier to provide a microenvironment that facilitates spermatogenesis and maintains the germ cells in an immunologically privileged location. Sertoli cells also secrete inhibin, which provides negative feedback on the hypothalamus, and androgen-binding protein, which helps modulate androgen activity in the seminiferous tubules. In addition to FSH, Sertoli cell function is modulated by intratesticular testosterone and signals from peritubular myoid cells.

Germ cells (precursors to spermatozoa) are derived from the gonadal ridge and migrate to the testicle before testicular descent. In response to FSH stimulation at puberty, germ cells become spermatogonia and undergo an ordered maturation to become spermatozoa. The entire process of development from spermatogonium to spermatid takes 74 days and is described in 14 steps; as they mature, the developing spermatids progress closer to the lumen of the seminiferous tubule.

Spermatogonia rest on the basement membrane and contain dense nuclei and prominent nucleoli. Three types are described: A dark (Ad), A pale (Ap), and B cells. Ad cells (stem cells) divide to create more Ad cells (stem cell renewal) or differentiate into daughter Ap cells every 16 days. Ap cells mature into B spermatogonia, which then undergo mitotic division to become primary spermatocytes, which are recognized by their large centrally located nuclei and beaded chromatin. The mitotic division does not result in complete separation; rather, daughter cells maintain intracellular bridges, which have functional significance in cell signaling and maturation.

Primary spermatocytes undergo meiosis as the cells successively pass through the preleptotene, leptotene, zygotene, and pachytene stages to become secondary spermatocytes. During this time, the cells cross from

the basal to the adluminal compartments. Secondary spermatocytes contain smaller nuclei with fine chromatin. The secondary spermatocytes undergo a second meiosis and become spermatids. This reduction division (ie, meiosis) results in a haploid chromosome number. Therefore, a total of 4 spermatids are made from each spermatocyte.

Next, the spermatids undergo the process of spermiogenesis (through stages named Sb1, Sb2, Sc, Sd1, and Sd2), which involves the casting of excess cytoplasm away as a residual body, the formation of the acrosome and flagella, and the migration of cytoplasmic organelles to their final cellular location. The acrosome, a derivative of the Golgi process, surrounds the nucleus anteriorly and contains enzymes necessary to penetrate the ovum. The mature spermatid is then located adjacent to the tubule lumen and contains dark chromatin with an oval-shaped nucleus.

After their release from the Sertoli cells into the lumen of the seminiferous tubules, the spermatids successively pass through the tubuli recti, rete testis, ductuli efferentes, and, finally, the epididymis. The epididymis is a 3- to 4-cm long structure with a tubular length of 4-5 m. As sperm move from the head to the tail, they mature and acquire fertilization capacity. Sperm from the head move with immature wide arcs and are generally unable to penetrate the egg, while those from the tail propel forward and have better penetration capacity. The transit time varies with age and sexual activity but is usually from 1-12 days. The epididymis additionally secretes substances for sperm nutrition and protection such as glycerophosphorylcholine, carnitine, and sialic acid.

Sperm next enter the vas deferens, a 30- to 35-cm muscular conduit of Wolffian duct origin. The vas is divided into the convoluted, scrotal, inguinal, retroperitoneal, and ampullary regions and receives its blood supply from the inferior vesical artery. In addition to functioning as a conduit, the vas also has absorptive and secretory properties.

During emission, sperm are propelled forward by peristalsis. After reaching its ampullary portion behind the bladder, the vas joins with the seminal vesicles, at the ejaculatory duct, which empties next to the verumontanum of the prostate.

During ejaculation, the ejaculate is propelled forward by the rhythmic contractions of the smooth muscle that surrounds the ducts and by the bulbourethral muscles and other pelvic muscles. Bladder neck closure during ejaculation is vital to ensure antegrade ejaculation.

Normal ejaculate volume ranges from 1.5 to 5 mL and has a pH level of 7.05-7.8. The seminal vesicles provide 40-80% of the semen volume, which includes fructose for sperm nutrition, prostaglandins and other coagulating substances, and bicarbonate to buffer the acidic vaginal vault. Normal seminal fructose concentration is 120-450 mg/dL, with lower levels

suggesting ejaculatory duct obstruction or absence of the seminal vesicles.

The prostate gland contributes approximately 10-30% (0.5 mL) of the ejaculate. Products include enzymes and proteases to liquefy the seminal coagulum. This usually occurs within 20-25 minutes. The prostate also secretes zinc, phospholipids, phosphatase, and spermine. The testicular-epididymal component includes sperm and comprises about 5% of the ejaculate volume.

In addition to the components already listed, semen is also composed of secretions from the bulbourethral (Cowper) glands and the (periurethral) glands of Litre, each producing 2-5% of the ejaculate volume, serving mainly to lubricate the urethra and to buffer the acidity of the residual urine. The ordered sequence of release is important for appropriate functioning.

For conception, sperm must reach the cervix, penetrate the cervical mucus, migrate up the uterus to the fallopian tube, undergo capacitation and the acrosome reaction to digest the zona pellucida of the oocyte, attach to the inner membrane, and release its genetic contents within the egg. The cervical mucus changes consistency during the ovulatory cycle, being most hospitable and easily penetrated at mid cycle. After fertilization, implantation may then take place in the uterus. Problems with any of these steps may lead to infertility.

Epidemiology

An estimated 10-15% of couples are considered infertile, defined by the World Health Organization (WHO) as the absence of conception after at least 12 months of unprotected intercourse. In American men, the risk correlates to approximately 1 in 25. Low sperm counts, poor semen quality, or both account for 90% of cases; however, studies of infertile couples without treatment reveal that 23% of these couples conceive within 2 years, and 10% more conceive within 4 years. Even patients with severe oligospermia (<2 million sperm/mL) have a 7.6% chance of conception within 2 years.

Patterns of male infertility vary greatly among regions and even within regions. The highest reported fertility rates are in Finland, while Great Britain has a low fertility rate. A combination of social habits, environmental conditions, and genetics is suspected to contribute to this variation.

Recent debate has occurred in the literature regarding a poorer semen quality, decreased sperm counts (113 million/mL in 1940 compared with 66 million/mL in the 1990s), and decreased fertility in men today compared with fertility 50 years ago. Investigators hypothesize that environmental conditions and toxins have led to this decline; however, others argue that this is solely because of differences in counting methods, laboratory techniques, and geographic variation.

Mortality/Morbidity

Many patients who present with infertility as their primary symptom have a serious underlying medical disease, such as pituitary adenomas,

hormonally active tumors, testicular cancer, liver and renal failure, and cystic fibrosis (CF). Evaluating patients for life-threatening or life-altering conditions during the workup is important.

In addition, the risk of cancer appears to be increased in infertile men. In a study of 2238 infertile men, 451 with azoospermia and 1787 without, male infertility was associated with an increased risk of developing cancer in comparison with the general population. Median age at initial evaluation was 35.7 years, and median follow-up was 6.7 years.

Overall, 29 men developed some type of cancer, including 10 (2.2%) with azoospermia and 19 (1.1%) without azoospermia. Compared with the general population of Texas, infertile men had a higher risk of overall cancer (standardized incidence ratio [SIR], 1.7; 95% confidence interval [CI], 1.2-2.5).

The risk was significantly higher in azoospermic men than in nonazoospermic men (SIR, 2.9; 95% CI, 1.4-5.4). The risk of cancer in nonazoospermic infertile men was similar to that in the general population (SIR, 1.4; 95% CI, 0.9-2.2), although there was a trend toward an elevated risk.

The men who developed cancer in the study developed a variety of malignancies, including prostate cancer, testicular cancer, CNS cancer, melanoma, and stomach cancer.

Isolated conditions of the female are responsible for infertility in 35% of cases, isolated conditions of the male in 30%, conditions of both the male and female in 20%, and unexplained causes in 15%. Even if one partner has an obvious cause for the infertility, a thorough evaluation of both partners for completeness is prudent. In addition, both partners may be aided by evaluation of their sexual practices.

The effect of aging on fertility is unclear. As men age, their testosterone levels decrease, while estradiol and estrone levels increase. Studies have shown that, as men age, their sperm density decreases. Young men have spermatids present in 90% of seminiferous tubules, which decreases to 50% by age 50-70 years and to 10% by age 80 years. Additionally, 50% of Sertoli cells are lost by age 50 years, 50% of Leydig cells are lost by age 60 years. Despite this, aging men may achieve fertility rates similar to those in younger men, although conception often takes longer.

History

The initial step in the evaluation of an infertile male is to obtain a thorough medical and urologic history. Important considerations include the duration of infertility, previous fertility in the patient and the partner, and prior evaluations. The couple should be asked specifically about their sexual habits, including their level of knowledge of the optimal timing of intercourse and the use of potentially spermatotoxic drugs and lubricants.

Patients should be asked about a history of childhood illnesses such as testicular torsion, postpubertal

mumps, developmental delay, and precocious puberty, as well as urinary tract infections, sexually transmitted diseases, and bladder neck surgery. A history of neurological diseases, diabetes, and pulmonary infections should be elicited. Anosmia (lack of smell), galactorrhea, visual-field defects, and sudden loss of libido could be signs of a pituitary tumor. The status of the partner's workup should also be known.

Precocious puberty, defined as the onset of puberty before age 9 years in males, may be the sign of a serious underlying endocrinologic disorder. Hormonally active tumors from the testicle, adrenal gland, or pituitary, along with adrenal hyperplasia, may result in early puberty. [72]

In contrast, a delay in puberty may be caused by problems with testosterone secretion due to hypothalamic, pituitary, or testicular insufficiency or to end-organ androgen insensitivity.

Both unilateral and bilateral cryptorchidism are associated with a decrease in sperm production and semen quality, regardless of the timing of orchidopexy.

Patients with hypospadias may not place the semen at the cervical os.

Prenatal exposure to diethylstilbestrol (DES) may cause epididymal cysts and cryptorchidism.

Prior bladder neck procedure, such as a V-Y plasty performed at the time of ureteral reimplantation, may lead to retrograde ejaculation.

The vas deferens or the testicular blood supply may be injured or ligated at the time of inguinal surgery, hernia repair, hydrocelectomy, or varicocelectomy.

Testicular torsion and trauma may result in testicular atrophy and the production of antisperm antibodies.

Medical history

In males, decreased general health status appears to be associated with impaired male reproductive health. Effects of specific disorders on fertility include the following:

1. Diabetes may cause autonomic neuropathy, neurogenic impotence, and retrograde ejaculation;
2. Obesity alters hormonal metabolism, leading to increased peripheral conversion of testosterone to estrogen and decreased luteinizing hormone (LH) pulse amplitude, and has been linked with reduced sperm concentration;
3. Sickle cell disease may lead to direct testicular ischemia and damage;
4. Patients with sickle cell disease or thalassemia may have infertility due tohemosiderosis from multiple blood transfusions;
5. Chronic kidney disease leads to hypogonadism and feminization;
6. Liver disease may result in decreased male secondary sexual characteristics.

testicular atrophy, and gynecomastia due to increased estrogen levels;
7. Hemochromatosis leads to hypogonadism and signs of androgen deficiency without gynecomastia and is associated with decreased estradiol levels;
8. Postpubertal mumps may lead to testicular atrophy;
9. Sexually transmitted diseases and tuberculosis can cause obstruction of the vas deferens or epididymis;
10. Mycoplasma fastens itself to sperm, decreasing sperm motility;
11. Smallpox, prostatitis, orchitis, seminal vesiculitis, and urethritis may lead to obstructive azoospermia;
12. Acute and chronic medical illnesses.

Patients should be asked about recent acute febrile illnesses, which may temporarily suppress gonadotropin release. The decrease in sperm production may not be realized until 1-3 months later.

Anesthesia, surgery, starvation, myocardial infarction, hepatic coma, head injury, stroke, respiratory failure, congestive heart failure, sepsis, and burns are associated with a suppression of gonadotropin release, possibly through an increase in dopamine and opiate levels.

Chronic medical illnesses may directly suppress sex hormone production and sperm production, leading to end-organ failure.

Sexual history

The frequency, timing, and methods of coitus and knowledge of the ovulatory cycle should be elicited. Studies show that the optimal timing for intercourse is every 48 hours at mid cycle.

Lubricants such as Surgilube, Keri lotion, KY Jelly, and saliva are spermatotoxic, whereas egg whites, peanut oil, vegetable oil, and petroleum jelly are not known to be spermatotoxic but still should be used in only the smallest amounts possible if needed for lubrication during intercourse.

Testicular cancer. Testicular cancer is associated with impaired spermatogenic function, even before orchiectomy, with a degree of dysfunction higher than that explained by local tumor effect.

Oligospermia is observed in more than 60% of patients at the time of diagnosis of testicular cancer.

Germ cell tumors may share common etiological factors with testicular dysfunction, such as testicular dysgenesis, androgen insensitivity, and cryptorchidism. Contralateral abnormalities of spermatogenesis are more common in patients with testicular cancer. Sperm function often remains impaired, even after orchiectomy.

Treatment for testicular cancer. Chemotherapy has a dose-dependent effect on germ cells. Alkylating agents, such as cyclophosphamide, mustine, and chlorambucil, severely alter the

seminiferous tubules and destroy spermatogonia. (Note that chemotherapy is also mutagenic, so sperm should be donated before treatment, or attempts at conception should be postponed until >1 year after treatment.)

Retroperitoneal lymph node dissection (RPLND) may impair emission (of semen into the urethra) and/or cause retrograde ejaculation.

Radiation therapy affects mainly type B spermatogonia and, possibly, spermatocytes. A dose of as little as 0.15 Gy may cause irreversible damage, although complete recovery may be possible if stem cell numbers are not depleted. After exposure of less than 1 Gy, sperm production may return in 9-18 months, while 4-6 years may be necessary to recover sperm production after a dose of up to 5 Gy. Despite radiation therapy and chemotherapy, nearly two thirds of patients retain the ability to father a child if the ejaculatory function is retained.

To potentially decrease the morbidity of adjunct therapy, select patients with grade I germ cell tumors are now undergoing unilateral orchiectomy with surveillance. However, RPLND performed for salvage therapy is associated with a higher risk of retrograde ejaculation than that performed initially.

Patients with reference range FSH levels at baseline usually observe an improvement in semen parameters and sperm density after orchiectomy. This is thought to be unrelated to the orchiectomy, stress factors, and release of substances by the tumor because decreased sperm counts are observed even before surgery and they do not return to baseline after surgery. Therefore, the disturbance that leads to testicular cancer is thought to be inherent and present in the primordial cell.

Patients with a testicular tumor in a solitary testicle may be offered a partial orchiectomy in an attempt to retain fertility. Additionally, healthy testicular tissue away from the tumor can be dissected free and cryopreserved at the time of orchiectomy for future use in in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI).

Social history

Cigarette and marijuana smoking lead to a decrease in sperm density, motility, and morphology. Abuse of anabolic steroids has been associated with hypogonadism as well as structural and genetic sperm damage.

Alcohol produces both an acute and a chronic decrease in testosterone secretion.

Emotional stress blunts GnRH release, leading to hypogonadism.

Excessive heat exposure from saunas, hot tubs, or the work environment may cause a temporary decrease in sperm production.

Contrary to widely held beliefs, no evidence supports that wearing constrictive underwear, or "briefs," decreases fertility. Even with an

elevation in temperature of 0.8-1° caused by wearing constrictive underwear, no changes in sperm parameters, no decrease in spermatogenesis, and no changes in sperm function are observed.

Medicines. Drugs that may impair male fertility include the following:

1. Spironolactone, cyproterone, ketoconazole, and cimetidine have antiandrogenic properties;
2. Tetracycline lowers testosterone levels 20%;
3. Nitrofurantoin suppresses spermatogenesis;
4. Sulfasalazine leads to a reversible decrease in sperm motility and density;
5. Colchicine, methadone, methotrexate, phenytoin, thioridazine, and calcium channel blockers have all been associated with infertility.

Family history. Congenital midline defects, cryptorchidism, hypogonadotropism, and testicular atrophy in family members may be a sign of a congenital disease. A history of cystic fibrosis (CF) or hypogonadism should be elicited.

Respiratory disease. Infertility and recurrent respiratory infections may be due to immotile cilia syndrome, which may be isolated or part of Kartagener syndrome (with situs inversus).

CF is associated with congenital bilateral absence of the vas deferens (CBAVD), leading to obstructive azoospermia. While both copies of this recessive gene are necessary for clinical disease, the presence of only one copy may lead to CBAVD.

Young syndrome results in recurrent pulmonary infections and azoospermia due to inspissated material in the epididymis causing obstruction.

Environmental and/or occupational exposure. Many pesticides have estrogen-like effects.

Dibromochloropropane (DBCP) is a nematocide widely used in agriculture that causes azoospermia without recovery by an unknown mechanism.

Lead exposure depresses the hypothalamic-pituitary axis.

Carbon disulfide exposure from the rayon industry leads to semen, pituitary, and hypothalamic changes.

Heat exposure, as seen in workers in the steel and ceramic fields, decreases spermatocyte maturation.

Spinal cord injury. Severe spinal cord injury (SCI) may lead to anejaculation. These men may be treated with electroejaculation or sperm retrieval techniques.

In addition, the semen quality in patients with SCI may gradually decline. Within a year after injury, many of these patients have semen with dead sperm, with signs of neutrophil infiltration on semen analysis.

In patients with SCI, sperm aspirated from the vas deferens show

54% motility and 74% viability, while only 14% motility and 26% viability is observed in ejaculated sperm, which suggests an abnormality of seminal plasma. Studies of seminal plasma point to functional failure of the prostate gland, likely from lack of neurogenic stimulation, along with hyperactivation of the immune system, which is probably not triggered by microbial infection, as causal elements for infertility related to SCI.

Additionally, infertile men with SCI has been shown to have disruptions in nuclear maturity and DNA integrety of spermatozoa and as a consequence may have higher rates of apoptosis, which possibly contributes to infertility.

Physical examination

The physical examination should include a thorough inspection of the testicles, penis, secondary sexual characteristics, and body habitus. It should include a detailed examination of other body functions based on the history.

Testicles

The testicular examination should occur in a warm room with the patient relaxed. The testicles should be palpated individually between the thumb and first 2 fingers. The examiner should note the presence, size, and consistency of the testicles, and the testicles should be compared with each other.

A Prader orchidometer or ultrasonography may be used to estimate the testicular volume, with normal considered to be greater than 20 mL.

Calipers may be used to measure testicular length, which is usually greater than 4 cm, although the lower limits of normal length (mean minus 2 standard deviations) is 31 mm in white men and 34 mm in black men. The testes of Japanese men are typically smaller than the testes of white men.

Testicular atrophy may be observed in primary testicular failure, Klinefelter syndrome, endocrinopathies, postpubertal mumps, liver disease, and myotonic dystrophy.

Swelling with pain indicates orchitis, whereas nontender enlargement may be observed in testicular neoplasms, tuberculosis, and tertiary syphilis.

Epididymis

The head, body, and tail of the epididymis should be palpated and assessed for their presence bilaterally.

Note induration and cystic changes. An enlarged indurated epididymis with a cystic component should alert the examiner to the possibility of ductal obstruction.

Tenderness may be due to epididymitis.

Vas deferens

Evaluate the vas for its presence bilaterally and palpate along its entire length to check for defects, segmental dysplasia, induration, nodularity, or swelling.

The complete absence bilaterally is observed almost exclusively in patients with either one or two copies of the gene for CF, although even a small defect or gap indicates the possibility of a CF gene mutation.

A thickened nodular vas deferens may be observed in patients with a history of tuberculosis.

If a prior vasectomy has been performed, the presence of a nodular sperm granuloma at the proximal vasal end should be assessed.

Spermatic cord

Check patients for the presence of a varicocele, which is the most common surgically correctable cause of infertility.

To elicit this, the patient should perform a Valsalva maneuver in the sitting and standing positions in a warm room.

Grade 1 varicocele is defined as palpable only with Valsalva, while grade 2 is palpable at standing, and grade 3 is visible at rest. The presence of asymmetry or an impulse with Valsalva may best help the examiner find a varicocele.

The sudden onset of a varicocele, a solitary right-sided varicocele, or a varicocele that does not change with Valsalva indicates the possibility of a retroperitoneal neoplastic process or vein thrombosis.

Penis

The examination should focus on the location and patency of the urethral meatus and the presence of meatal strictures.

Patients with hypospadias or epispadias may not deposit semen appropriately at the cervix.

Penile curvature and the presence of penile plaques should be noted.

Rectal examination

The prostate should be of normal size and without cysts, induration, or masses.

The seminal vesicles are usually not palpable.

A midline prostatic cyst or palpable seminal vesicles may be due to obstruction of the ejaculatory ducts.

Body habitus

A eunuchoid body habitus, consisting of infantile hair distribution, poor muscle development, and a long lower body due to a delayed closure of the epiphyseal plates, may be observed in patients with endocrinological disorders.

Truncal obesity, striae, and moon facies may be due to Cushing syndrome.

Gynecomastia, galactorrhea, headaches, and a loss of visual fields may be observed in patients with pituitary adenomas.

Focus the neck examination on thyromegaly and bruits.

Palpate the liver for hepatomegaly and examine the lymph nodes to rule out lymphoma.

Causes

Causes generally can be divided into pretesticular, testicular, and post-testicular.

Pretesticular causes of infertility. Pretesticular causes of infertility include congenital or acquired diseases of the hypothalamus, pituitary, or peripheral organs that alter the hypothalamic-pituitary axis.

Disorders of the hypothalamus lead to hypogonadotropic hypogonadism. If GnRH is not secreted, the pituitary does not release LH and FSH. Ideally, patients respond to replacement with exogenous GnRH or HCG, an LH analogue, although this does not always occur.

Idiopathic hypogonadotropic hypogonadism. A failure of GnRH secretion without any discernible underlying cause may be observed alone (isolated) or as part of Kallmann syndrome, which is associated with midline defects such as anosmia, cleft lip and cleft palate, deafness, cryptorchidism, and color blindness. Kallmann syndrome has been described in both familial (X-linked and autosomal) and sporadic forms, and its incidence is estimated as 1 case per 10,000-60,000 births.

A failure of GnRH neurons to migrate to the proper location in the hypothalamus has been implicated. Patients generally have long arms and legs due to a delayed closure of the epiphyseal plates, delayed puberty, and atrophic testis. Testosterone therapy may allow patients to achieve normal height but does not improve spermatogenesis. Exogenous testosterone should never be administered in an attempt to boost sperm production because it actually decreases intratesticular testosterone levels owing to feedback inhibition of GnRH release.

Pulsatile GnRH and HCG have been used but result in only 20% achieving complete spermatogenesis.

Adding recombinant human FSH to HCG has been shown to be effective in achieving spermatogenesis in most patients.

Select patients with adult-onset idiopathic hypogonadotropic hypogonadism may respond to clomiphene citrate therapy.

Prader-Willi syndrome. Patients have characteristic obesity, mental retardation, small hands and feet, and hypogonadotropic hypogonadism due to a GnRH deficiency. Prader-Willi syndrome is caused by a disorder of genomic imprinting with deletions of paternally derived chromosome arm 15q11-13.

Laurence-Moon-Biedl syndrome. Patients with this syndrome have retinitis pigmentosa and polydactyly. Infertility is due to hypogonadotropic hypogonadism.

Other conditions. Various other lesions and diseases, such as CNS tumors, temporal lobe seizures, and many drugs (eg, dopamine antagonists)

may interrupt the hypothalamic-pituitary axis at the hypothalamus.

Both pituitary insufficiency and pituitary excess cause infertility. Pituitary failure may be congenital or acquired. Acquired causes include tumor, infarction, radiation, infection, or granulomatous disease. Nonfunctional pituitary tumors may compress the pituitary stalk or the gonadotropic cells, interrupting the proper chain of signals leading to pituitary failure. In contrast, functional pituitary tumors may lead to unregulated gonadotropin release or prolactin excess, interrupting the proper signaling.

Prolactinoma. A prolactin-secreting adenoma is the most common functional pituitary tumor. Prolactin stimulates breast development and lactation; therefore, patients with infertility due to a prolactinoma may have gynecomastia and galactorrhea. In addition, loss of peripheral visual fields bilaterally may be due to compression of the optic chiasm by the growing pituitary tumor.

A prolactin level of more than 150 mcg/L suggests a pituitary adenoma, while levels greater than 300 mcg/L are nearly diagnostic. Patients should undergo an MRI or CT scan of the sella turcica for diagnostic purposes to determine whether a microprolactinoma or a macroprolactinoma is present.

Bromocriptine and cabergoline are dopamine agonists used to suppress prolactin levels. These are both treatment options for microprolactinoma. Some men respond with an increase in testosterone levels; many also recover normal sperm counts. Transsphenoidal resection of a microprolactinoma is 80-90% successful, but as many as 17% recur. Surgical therapy of a macroprolactinoma is rarely curative, although this should be considered in patients with visual-field defects or those who do not tolerate bromocriptine.

Isolated LH deficiency (fertile eunuch). In these patients, LH levels are decreased while FSH levels are within the reference range. Patients have eunuchoidal body habitus, large testis, and a low ejaculatory volume. The treatment of choice is exogenous HCG.

Isolated FSH deficiency. This is a very rare cause of infertility. Patients present with oligospermia but have LH levels within the reference range. Treatment is with human menopausal gonadotropin (HMG) or exogenous FSH.

Thalassemia. Patients with thalassemia have ineffective erythropoiesis and undergo multiple blood transfusions. Excess iron from multiple transfusions may get deposited in the pituitary gland and the testis, causing parenchymal damage and both pituitary and testicular insufficiency. Treatment is with exogenous gonadotropins and iron-chelating therapy. [72]

Cushing disease. Increased cortisol levels cause a negative

feedback on the hypothalamus, decreasing GnRH release.

Peripheral organ. The hypothalamus-pituitary axis may be interrupted by hormonally active peripheral tumors or other exogenous factors, due to cortical excess, cortical deficiency, or estrogen excess.

Excess cortisol may be produced by adrenal hyperplasia, adenomas, carcinoma, or lung tumors. High cortisol levels may also be seen with exogenous steroid use, such as that administered to patients with ulcerative colitis, asthma, arthritis, or organ transplant. For example, high cortisol levels are seen in patients with Cushing syndrome, which causes negative feedback on the pituitary to decrease LH release.

Cortical deficiency may be seen in patients with adrenal failure due to infection, infarction, or congenital adrenal hyperplasia (CAH). CAH may be due to the congenital deficiency of one of several adrenal enzymes, the most common of which is 21-hydroxylase deficiency. Because cortisol is not secreted, a lack of feedback inhibition on the pituitary gland occurs, leading to adrenocorticotropic hormone (ACTH) hypersecretion. This leads to increased androgen secretion from the adrenal gland, causing feedback inhibition of GnRH release from the hypothalamus. Patients present with short stature, precocious puberty, small testis, and occasional bilateral testicular rests. Screening tests include increased plasma 17-hydroxylase and urine 17-ketosteroids.

Estrogen excess may be seen in patients with Sertoli cell tumors, Leydig tumors, liver failure, or severe obesity. Estrogen causes negative feedback on the pituitary gland, inhibiting LH and FSH release.

Primary testicular causes of infertility

Primary testicular problems may be chromosomal or nonchromosomal in nature. While chromosomal failure is usually caused by abnormalities of the sex chromosomes, autosomal disorders are also observed.

Chromosomal abnormalities. An estimated 6-13% of infertile men have chromosomal abnormalities (compared with 0.6% of the general population). Patients with azoospermia or severe oligospermia are more likely to have a chromosomal abnormality (10-15%) than infertile men with sperm density within the reference range (1%). A karyotype test and a Y chromosome test for microdeletions are indicated in patients with nonobstructive azoospermia or severe oligospermia (< 5 million sperm/mL), although indications are expanding.

Klinefelter syndrome. Klinefelter syndrome is the most common chromosomal cause of male infertility, estimated to be present in 1 per 500-1000 male births. Classic Klinefelter syndrome has a 47, XXY karyotype and is caused by a nondisjunction during the first meiotic division, more commonly of maternal origin; mosaic forms are due to nondisjunction following fertilization. The only known risk factor for

Klinefelter syndrome is advanced maternal age.

Infertility is caused by primary testicular failure, and most patients are azoospermic. Hormonal analysis reveals increased gonadotropin levels, while 60% have decreased testosterone levels. Surprisingly, most patients have normal libido, erections, and orgasms, so testosterone therapy has only a limited role; exogenous testosterone may also suppress any underlying sperm production.[65]

Physical examination reveals gynecomastia, small testis, and eunuchoid body habitus due to delayed puberty. In some patients, secondary sex characteristics develop normally, but they are usually completed late. These men are at a higher risk for breast cancer, leukemia, diabetes, empty sella syndrome, and pituitary tumors. Testicular histology reveals hyalinization of seminiferous tubules.

Some men with Klinefelter syndrome may be able to conceive with the help of assisted reproductive techniques. Of azoospermic patients with Klinefelter syndrome, 20% show the presence of residual foci of spermatogenesis. Although the XXY pattern is observed in the spermatogonia and primary spermatocytes, many of the secondary spermatocytes and spermatids have normal patterns. The chromosomal pattern of the resultant embryos can be assessed with preimplantation genetic diagnosis.

XX male (sex reversal syndrome). An XX karyotype is due to a crossover of the sex-determining region (SRY) of the Y chromosome (with the testis determining factor) to either the X chromosome or an autosome. Patients are often short, with small firm testis and gynecomastia, but they have a normal-sized penis. Seminiferous tubules show sclerosis.

XYY male. An XYY karyotype is observed in 0.1-0.4% of newborn males. These patients are often tall and severely oligospermic or azoospermic. This pattern has been linked with aggressive behavior. Biopsy reveals maturation arrest or germ cell aplasia. Functional sperm that are present may have a normal karyotype.

Noonan syndrome (46, XY). Patients with Noonan syndrome, also known as male Turner syndrome, have physical characteristics similar to that of women with Turner syndrome (45, X). Features include a webbed neck, short stature, low-set ears, ptosis, shield-like chest, lymphedema of hands and feet, cardiovascular abnormalities, and cubitus valgus. Leydig cell function is impaired, and most patients are infertile due to primary testicular failure.

Mixed gonadal dysgenesis (45, X/46, XY). Patients usually have ambiguous genitalia, a testis on one side, and a streaked gonad on the other.

Androgen receptor dysfunction. Because the androgen receptor is essential for the process of spermatogenesis, dysfunctions in this receptor can cause infertility. Reifenstein syndrome in males involves partial androgen insensitivity

in males and presents as a spectrum of abnormal external genitalia and infertility. Because cells inadequately respond to androgen stimulation, spermatogenesis is impaired. This results in negative feedback stimulation of the hypothalamic-pituitary axis, causing an increase release of gonadotropins and testosterone.

These receptor dysfunctions may be explained by defects in specific chromosomal areas. A specific portion of the androgen receptor gene, exon 1, has been studied in infertile males and a meta-analysis that involved males with idiopathic infertility and fertile controls found that infertility was directly correlated with the length of CAG repeats in this exon.

Y chromosome microdeletion syndrome. The long arm of the Y chromosome (Yq) is considered critical for fertility, especially Yq11.23 (interval 6). Macroscopic deletions of Yq11 are often observed in patients with azoospermia, although many new microdeletions have been implicated as a significant cause of infertility. These microdeletions are not observed on regular karyotype testing; rather, their identification requires polymerase chain reaction (PCR)–based sequence-tagged site mapping or Southern blot analysis. Three regions have been described, called azoospermic factors a, b, and c (AZFa, AZFb, AZFc).

These deletions are observed in 3-19% of patients with idiopathic infertility and 6-14% of patients with oligospermia, although up to 7% of patients with other known causes of infertility may also be found to have a deletion. Patients with azoospermia or severe oligospermia seeking assisted reproductive techniques should be screened.

Bilateral anorchia (vanishing testes syndrome). Patients have a normal male karyotype (46, XY) but are born without testis bilaterally. The male phenotype proves that androgen was present in utero. Potential causes are unknown, but it may be related to infection, vascular disease, or bilateral testicular torsion. Karyotype shows a normal SRY gene. Patients may achieve normal virilization and adult phenotype by the administration of exogenous testosterone, but they are infertile.

Down syndrome. These patients have mild testicular dysfunction with varying degrees of reduction in germ cell number. LH and FSH levels are usually elevated.

Myotonic dystrophy. This is an autosomal dominant defect in the dystrophin gene that causes a delay in muscle relaxation after contraction. Seventy-five percent of patients have testicular atrophy and primary testicular failure due to degeneration of the seminiferous tubules. Leydig cells are normal. Histology reveals severe tubular sclerosis. No effective therapy exists.

Nonchromosomal testicular failure. Testicular failure that is nonchromosomal in origin may be idiopathic or acquired by gonadotoxic drugs, radiation, orchitis, trauma, or torsion.

Varicocele. A varicocele is a dilation of the veins of the pampiniform plexus of the scrotum. Although varicoceles are present in 15% of the male population, a varicocele is considered the most common correctable cause of infertility (30-35%) and the most common cause of secondary (acquired) infertility (75-85%). Varicoceles are observed more commonly on the left side than the right. Those with isolated right-sided varicoceles should be evaluated for retroperitoneal pathology.

Varicoceles are generally asymptomatic, and most men with varicoceles do not have infertility or testicular atrophy. However, varicoceles may lead to impaired testicular spermatogenesis and steroidogenesis, potentially due to an increased intratesticular temperature, reflux of toxic metabolites, and/or germ cell hypoxia as potential causes of these changes, and this appears to be progressive over time.

Additionally, because insulin-like growth factor (IGF) has been shown to have an effect on semen quality, its role in varicocele pathology has been studied. One study showed that IGF levels significantly increased after a varicocelectomy to levels that were no different than fertile controls, suggesting that varicocele-related infertility may involve IGF.

Varicoceles lead to an increased incidence of sperm immaturity, apoptosis, and necrosis with severe disturbances in meiotic segregation compared to fertile men without varicoceles, and these parameters generally improve after repair.

Patients with a grade 1-3 varicocele (visible or palpable) associated with infertility should consider having the varicocele repaired. After repair, 40-70% of patients have improved semen parameters, while 40% are able to impregnate their partner without other interventions. Those with a varicocele diagnosable only on scrotal ultrasonography have subclinical varicoceles and will likely not benefit from repair. Adolescents with a varicocele and testicular atrophy or lack of growth should similarly consider repair. Controversy exists regarding whether to routinely repair an adolescent varicocele not associated with testicular atrophy.

In those with azoospermia and a varicocele, sperm may appear after repair in up to one third, but most of these men return to an azoospermic state within a few months. If sperm appears, these men should be offered cryopreservation.

Cryptorchidism. An estimated 3% of full-term males are born with an undescended testicle, but fewer than 1% remain undescended by age 1 year. Undescended testicle may be isolated or may be observed as part of a syndrome such as prune belly syndrome. Patients are at increased risk of infertility, even if the testicle is brought down into the scrotum, as the testicle itself may be inherently abnormal. The farther from the scrotum, and the longer duration that the testicle resides outside the scrotum,

the greater the likelihood of infertility. Testicular histology typically reveals a decreased number of Leydig cells and decreased spermatogenesis. Cryptorchidism may be due to inherent defects in both testes because even men with unilateral cryptorchidism have lower than expected sperm counts.

Trauma. Testicular trauma is the second most common acquired cause of infertility. The testes are at risk for both thermal and physical trauma because of their exposed position.

Sertoli-cell-only (germinal cell aplasia). Patients with germinal cell aplasia have LH and testosterone levels within the reference range but have an increased FSH level. The etiology is unknown but is probably multifactorial. Patients have with small- to normal-sized testes and azoospermia, but normal secondary sex characteristics. Histology reveals seminiferous tubules lined by Sertoli cells and a normal interstitium, although no germ cells are present.

Chemotherapy. Chemotherapy is toxic to actively dividing cells. In the testicle, germ cells (especially up to the preleptotene stage) are especially at risk. The agents most often associated with infertility are the alkylating agents such as cyclophosphamide. For example, treatment for Hodgkin disease has been estimated to lead to infertility in as many as 80-100% of patients.

Radiation therapy. While Leydig cells are relatively radioresistant because of their low rate of cell division, the Sertoli and germ cells are extremely radiosensitive. If stem cells remain viable after radiation therapy, patients may regain fertility within several years. However, some have suggested that patients should avoid conception for 6 months to 2 years after completion of radiation therapy because of the possibility of chromosomal aberrations in their sperm caused by the mutagenic properties of radiation therapy. Even with the testis shielded, radiation therapy below the diaphragm may lead to infertility due to the release of reactive oxygen free radicals.

Orchitis. The most common cause of acquired testicular failure in adults is viral orchitis, such as that caused by the mumps virus, echovirus, or group B arbovirus. Of adults with who are infected with mumps, 25% develop orchitis; two thirds of cases are unilateral, and one third are bilateral. While orchitis develops a few days after the onset of parotid gland inflammation, it may also precede it. The virus may either directly damage the seminiferous tubules or indirectly cause ischemic damage as the intense swelling leads to compression against the tough tunica albuginea. After recovery, the testicle may return to normal or may atrophy. Atrophy is observed within 1-6 months, and the degree of atrophy does not correlate with the severity of orchitis or infertility. Normal fertility is observed in three fourths of patients with unilateral mumps orchitis and in one third of patients in bilateral orchitis.

Human-beta defensin abnormalities. Epididymis human-beta defensin is a protein that has been

shown to have an important role in sperm maturation, and defects in it have been associated with decreased egg-penetrating ability. One specific subtype, human-beta defensin-1 (HBD1), which has a wide distribution in various epithelia throughout the body and plays a role in antimicrobial activities against viruses, bacteria, and fungi, has also been investigated.

HBD1 is expressed in the seminal plasma and ejaculated sperm, more specifically in the lower head and midpiece of the sperm from fertile individuals. Expression of HBD1 is reduced in individuals with asthenozoospermia and leukocytospermia. In one study, treatment with recombinant HBD1 in asthenozoospermic and leukocytospermic patients who were deficient in HBD1 resulted in improved bactericidal activity and sperm quality, which supports this protein's role in fertility and its potential role in managing infertility.

Other causes. Causes of testicular failure also include the following:

1. Granulomatous disease – Leprosy and sarcoidosis may infiltrate the testicle;
2. Sickle cell disease – Sickling of cells within the testis leads to microinfarcts;
3. Excessive use of alcohol, cigarettes, caffeine, or marijuana;

Despite a thorough workup, nearly 25% of men have no discernible cause for their infertility.

Post-testicular causes of infertility

Post-testicular causes of infertility include problems with sperm transportation through the ductal system, either congenital or acquired. Genital duct obstruction is a potentially curable cause of infertility and is observed in 7% of infertile patients. Additionally, the sperm may be unable to cross the cervical mucus or may have ultrastructural abnormalities.

Congenital blockage of the ductal system. An increased rate of duct obstruction is observed in children of mothers who were exposed to DES during pregnancy. Segmental dysplasia is defined as a vas deferens with at least 2 distinct sites of vasal obstruction.

Cystic fibrosis. CF is the most common genetic disorder in whites. Patients with CF nearly uniformly have CBAVD. The cystic fibrosis transmembrane regulator (CFTR) protein plays a role in mesonephric duct development during early fetal life, so these patients may also have urinary tract abnormalities. Patients may be candidates for assisted reproduction techniques after appropriate genetic screening in the partner.

Acquired blockage of the ductal system. Genital ducts may become obstructed secondary to infections, such as chlamydia, gonorrhea, tuberculosis, and smallpox. Young syndrome is a condition that leads to inspissation of material and subsequent blockage of the epididymis.

Trauma, previous attempts at sperm aspiration, and inguinal surgery may also result in ductal blockage. Small calculi may block the ejaculatory ducts, or prostatic cysts may extrinsically block the ducts. Scrotal surgery, including vasectomy, hydrocelectomy (5-6%), and spermatocelectomy (up to 17%), may lead to epididymal injury and subsequent obstruction.

Antisperm antibodies. Antisperm antibodies bind to sperm, impair motility, and lead to clumping, impairing movement through the female reproductive tract and interaction with the oocyte.

Defects in cilia. Immotile cilia syndrome may occur as an isolated disorder or as part of Kartagener syndrome with situs inversus. Because of a defect in the dynein arms, spokes, or microtubule doublet, cilia in the respiratory tract and in sperm do not function properly. In addition to sperm immobility, patients experience sinusitis, bronchiectasis, and respiratory infections.

Ejaculatory duct obstruction. Complete and partial ejaculatory duct obstruction has been implicated as a cause of 1-5% of patients with male infertility. Patients may have a normal palpable vas deferens bilaterally but show decreased ejaculate volume and hemospermia and may experience pain upon ejaculation. Etiologies include cysts (midline and eccentric), ductal calcification and stones, postinfectious, and postoperative. Transrectal ultrasonography (TRUS) may reveal enlarged seminal vesicles, but this is not universal. Seminal vesicle aspiration revealing numerous sperm or a dynamic test such as injection of indigo carmine into the seminal vesicle or ejaculatory duct may be necessary for diagnosis.

Ejaculation issues. Anejaculation/retrograde ejaculation may be due to an open bladder neck or a lack of rhythmic contractions during ejaculation. Etiologies include the following:

1. Diabetic neuropathy;
2. Bladder neck surgery;
3. Retroperitoneal lymph node dissection;
4. Transurethral prostatectomy;
5. Colon or rectal surgery;
6. Multiple sclerosis;
7. Spinal cord injury;
8. Use of medicines such as alpha-antagonists.

The diagnosis of anejaculation or retrograde ejaculation is suggested by the following:

1. Compatible medical or surgical history;
2. Low ejaculate volume;
3. Presence of 10-15 sperm per high-power field (HPF) in the postejaculatory urine.

Laboratory Studies

Semen analysis. The semen analysis is the cornerstone of the male infertility workup. A specimen is collected by masturbation into a clean, dry, sterile container or during coitus using special condoms (containing no spermicidal lubricants). The patient should be abstinent for 2-3 days prior to maximize sperm number and quality.

Each day of abstinence is typically associated with an increase in semen volume of 0.4 mL and an increase in sperm density by 10-15 million sperm/mL, for up to 7 days.

The sample should be processed within 1 hour, and 2-3 samples (at a minimum of 2-3 days apart) should be evaluated because of daily variations in sperm number and quality. Various parameters are measured, such as ejaculate volume and sperm density, quality, motility, and morphology. Individual tests evaluate only one aspect of a quality necessary for fertility and do not imply the ability or inability to achieve conception.

The World Health Organization (WHO) published reference ranges for semen testing in 2010.These include "lower reference limits" representing the 5th centiles for semen characteristics. Note that the numbers represent the 5th centile values and do not serve as a cut-point between "fertile" and "infertile."

Volume. Normal ejaculate volume is 1.5-5 mL, and the WHO 2010 lower reference limit (5th centile) is 1.5 mL. A small ejaculate volume may be observed in patients with retrograde ejaculation, absence of the vas deferens or seminal vesicles, ductal obstruction, hypogonadotropism, or poor sympathetic response. An increased volume is rarely observed and is often caused by a contaminant, such as urine.

Semen quality. Semen is initially a coagulum that liquefies in 5-25 minutes due to prostatic enzymes. At this point, pouring the semen drop by drop should be possible. Semen that is not initially a coagulum is often caused by an ejaculatory duct obstruction or the absence of seminal vesicles. Nonliquefication of the semen can be differentiated from benign hyperviscosity by a normal postcoital test finding. No excessive sperm agglutination should exist.

Sperm density. Normal sperm density is greater than 20 million sperm/mL and the WHO 2010 lower reference limit (5th centile) is 15 million sperm per mL, or greater than 50-60 million total sperm. Oligospermia is defined as fewer than 20 million sperm/mL, severe oligospermia is less than 5 million/mL, and azoospermia is defined as no sperm present. To verify azoospermia, the semen should be centrifuged and evaluated under a light microscope for the presence of sperm. Patients with azoospermia should have a postejaculatory urine sample analyzed for sperm, should be evaluated for ejaculatory duct obstruction, and should undergo a hormonal evaluation.

Sperm motility. Motility is described as the percent of sperm present with flagellar motion viewed on a bright-field or phase-contrast microscope. Normal motility is defined as more than 60% of sperm having normal movement, and the WHO 2010 lower reference limit (5th centile) is 40%. Grading is as follows: Grade 0 is no movement, grade 1 is sluggish movement, grade 2 is slow movement but not straight, grade 3 is movement in a straight line, and grade 4 is terrific speed. Patients with abnormal motility

should be evaluated for pyospermia, antisperm antibodies, varicocele, sperm ultrastructural abnormalities, or partial ductal obstruction.

Sperm morphology. The head, acrosome, mid piece, and tail of individual spermatozoa are analyzed with phase-contrast microscopy after fixation with Papanicolaou stain. At least 200 sperm are analyzed. Normal sperm have a smooth oval head approximately 3-5 µm long and 2-3 µm wide. More than 60% of sperm should be normal, and less than 2-3% should be immature. These sperm show a high level of retained cytoplasmic droplets around the mid piece.

Teratospermia is defined as less than 30% normal morphology, and the WHO 2010 lower reference limit (5th centile) is 4%. Abnormal head shapes are described as tapered, duplicated, small, large, amorphous, and pyriform. The acrosome should be 40-70% of the size of the head, and no mid piece or tail abnormalities should be present.

Patients with a high number of immature sperm should be evaluated for excessive exposure to heat or radiation or for infectious processes.

To help objectify sperm morphology and therefore enhance the consistency and reproducibility among laboratories, Kruger introduced a definition of "strict criteria" in 1986. Using these criteria, he reported a clinically significant threshold of 14% normal forms as an excellent predictor of IVF success. Patients with less than of 14% normal forms had a substantially reduced success rate.

Computer-aided semen analysis (CASA). Introduced in the late 1980s, CASA uses a video camera and computer to visualize and analyze sperm concentration and movement. This semiautomated technique is thought to potentially standardize the evaluation of semen. Parameters measured include the curvilinear velocity, defined as the average distance per unit time between successive sperm positions; the straight-line velocity, which is the speed of forward direction; and linearity, which is the straight-line velocity divided by the curvilinear velocity.

In addition, the program measures the average path velocity, the amplitude of lateral head displacement, and the flagellar beat frequency, and it is used to evaluate for evidence of hyperactivation. Although CASA produces good qualitative data, it is a labor-intensive procedure that includes a high initial cost and is plagued with inaccuracies when sperm concentrations are very high or very low. It has not been shown to improve patient outcomes but, rather, is helpful for research purposes.

Infection. An increased number of white blood cells in the semen may be observed in patients with infectious or inflammatory processes. While germ cells and white blood cells both appear as round cells on microscopic examination, immunohistochemical stains are used to differentiate between the 2 cell types. Immunohistochemical stains are performed if more than 5-10 round cells/HPF are present. An increased number of white blood cells

may signify infection or inflammation of the genital tract.

Other tests. Semen may be analyzed for levels of zinc, citric acid, acid phosphatase, and alpha-glucosidase. These tests are used to determine gland failure or obstruction.

Antisperm antibody test. Sperm contain unique antigens that are not recognized as self by the body's immune system because of the blood-testis barrier.

Antisperm antibodies may form when the blood-testis barrier is breached because of infection, vasectomy, testicular torsion, cryptorchidism, or testicular trauma. Antibodies that are bound to sperm decrease the sperm's ability to penetrate the cervical mucus and bind to the zona pellucida.

Although 60% of patients have evidence of antisperm antibodies after vasectomy, the clinical significance has not been completely elucidated. In addition, antibodies are present in 35% of patients with CBAVD. Evidence of antibodies found in serum or seminal plasma is less prognostic than antibodies bound to sperm.

Suspect antisperm antibodies when semen analysis reveals abnormal clumping, agglutination, unexplained decreased motility, or an abnormal postcoital test result.

Several methods are available to detect antisperm antibodies, such as radioimmunoassay and enzyme-linked immunosorbent assay, but the most specific test is the immunobead test. More than 15-20% bound is considered a positive test result.

Hormonal analysis. Fewer than 3% of cases of male infertility are estimated to be due primarily to a hormonal cause.

A routine part of the initial evaluation is testing of specific serum hormone levels, which usually includes FSH, LH, testosterone, and prolactin.

Abnormalities may be a sign of a primary hypothalamic, pituitary, or testicular problem.

Imaging Studies

Transrectal ultrasonography. TRUS is indicated in patients with azoospermia or severe oligospermia to evaluate for complete or partial ejaculatory duct obstruction. TRUS is also useful to evaluate for the presence or absence of the seminal vesicles.

A 6.5- to 7.5-MHz probe is used with the bladder partially filled.

Obstruction is suggested by enlarged seminal vesicles (>1.5 cm width).

Scrotal ultrasonography. Scrotal ultrasonography is used to evaluate the anatomy of the testis, epididymis, and spermatic cord. It is a useful adjunct for evaluating testicular volume, testicular and paratesticular masses, and the presence or absence of varicoceles.

A large review reported a 38% rate of abnormalities on testicular ultrasonography in infertile men,

including 30% with varicocele and 0.5% with testicular cancer.

Routine testicular ultrasonography in infertile men is controversial, but some suggest it because of the increased risk of testicular cancer in infertile men (1 of 200 versus 1 of 20,000 in the general population).

Color-flow ultrasonography is used to evaluate for varicocele using a 7- to 10-MHz probe.

A varicocele is diagnosed on a sonogram if a spermatic vein is greater than 3 mm or vein size increases with Valsalva. Repair of subclinical varicoceles (those diagnosed only with ultrasonography) has not been proven to improve fertility.

Vasography. Vasography is used to evaluate patency of the ductal system.

Indications for vasography include azoospermia with sufficient mature spermatids present on testicular biopsy and at least one palpable vas.

Relative indications include severe oligospermia with a normal finding on testis biopsy, antisperm antibodies, and decreased semen viscosity.

This test may be performed either as an open procedure at the same time as testicular biopsy or by a percutaneous puncture.

The patient may be placed in a 10-15° Trendelenburg position to bring the symphysis pubis out of the radiation field.

Unilateral patency rules out vasal or ejaculatory duct obstruction as the cause of azoospermia.

Other Tests

Postcoital test. An abnormal postcoital test result is observed in 10% of infertile couples. Indications for performing a postcoital test include semen hyperviscosity, increased or decreased semen volume with good sperm density, or unexplained infertility.

After coitus at mid cycle, the female's cervical mucus is examined for the presence or absence of sperm. Usually, 10-20 sperm/HPF are observed. Abnormal results may be due to antisperm antibodies, sperm ultrastructural abnormalities, an abnormal hormonal milieu, male or female genital tract infection, poor semen quality, inhospitable cervical mucus, or male sexual dysfunction. If no sperm are observed, the couple's coital technique should be analyzed.

If the test result is normal, consider a test of sperm function and ability to penetrate the egg.

Sperm function tests. When a primary sperm defect is suspected or when other tests do not reveal the cause of infertility, sperm function tests may determine if a significant sperm abnormality exists. These tests analyze specific sperm functions, such as the ability to undergo capacitation and the acrosome reaction and the ability to bind to and to penetrate the egg (Tab. 19).

The capacitation assay is used to evaluate the ability of sperm to undergo capacitation. After capacitation, sperm have hyperactivated motility, which can be recognized under microscopy. Sperm that do not undergo capacitation portend a poor response to IVF, and ICSI should be considered.

The acrosome reaction assay tests the ability of the sperm to undergo the acrosome reaction when exposed to inducing substances. The acrosome process, which covers the anterior two thirds of the sperm head, contains hyaluronidase and other enzymes used to digest the zona pellucida of the egg. After sperm binding and capacitation, the plasma membrane of the egg induces the acrosome to release its contents. This reaction occasionally occurs spontaneously (< 10% of the time), although a spontaneous reaction is more common in infertile men. Under the microscope, acrosome-inducing substances are added to the sample after the sperm have undergone capacitation, which usually takes approximately 3 hours. Usually, 15-40% of the sperm undergo the acrosome reaction when stimulated, and fewer undergo the reaction in infertile men. The results of the test correlate with IVF success; patients with an abnormal test result may need to undergo ICSI.

Sperm penetration assay (SPA). First described in 1976 by Yanagimachi et al, the SPA is used to check the ability of sperm to function in vitro by evaluating capacitation, the acrosome reaction, and the ability of the sperm to fuse with the oolemma. Cross-specie fertilization is usually prevented by the zona pellucida. Hamster ova, with the zona pellucida removed, are incubated with the donor's sperm and the number of sperm penetrated per ovum is measured. A normal result is more than 5 sperm penetrations per ovum. Fewer penetrations probably indicate a problem. Patients with a poor SPA should proceed directly to ICSI.

Hypoosmotic swelling (HOS). The HOS test is used to provide functional information to differentiate between viable but immotile sperm and dead sperm. Normal sperm are able to maintain an osmotic gradient when exposed to hypoosmotic conditions, whereas dead sperm cannot. After exposure to a dilute solution (150 mmol/L), sperm are observed under the microscope. Normal sperm swell, with bulging of the plasma membrane and curling of the tail. This test is commonly used clinically to select viable (but nonmotile) sperm for ICSI.

Inhibin B. Inhibin B is usually produced by sperm for the acrosome reaction. An increased level or an inability to clear acrosomal enzymes may lead to self-destruction and lipid peroxidation of the sperm membrane. Increased inhibin B levels may be caused by ductal obstruction or abnormalities within the seminiferous tubules.

Vitality stains. Vitality stains using substances such as eosin Y and trypan blue help determine whether a sperm is alive and the membrane is intact or if the sperm is dead. Live sperm can exclude dye, while dead sperm cannot. These tests are of little use unless very low numbers of sperm exist or motility is absent and

necrospermia must be ruled out. The subsequent process of slide fixation kills all of the sperm, thus preventing their clinical use.

Procedures

Testicular biopsy. Testicular biopsy is indicated in azoospermic men with a normal-sized testis and normal findings on hormonal studies to evaluate for ductal obstruction, to further evaluate idiopathic infertility, and to retrieve sperm.

Relative indications for testicular biopsy include ruling out partial obstruction in patients with severe oligospermia, evaluating patients with hypogonadotropism to select those likely to respond to gonadotropin replacement, and retrieving spermatozoa in azoospermic patients undergoing IVF or ICSI.

The procedure may be performed under spinal, general, or even local anesthesia, and it may be performed as an open procedure or percutaneously. Open surgery allows better testicular control and generally results in a better test, allowing multiple areas to be sampled for the presence or absence of sperm. A touch preparation of the testicular tissue, obtained from either an open or needle-core biopsy, may aid in a prompt evaluation during the procedure and, if used on a sterile slide, may even be cryopreserved for later use.

An operating microscope is often helpful to assist in identification of healthy-appearing tubules, especially in patients with Sertoli-cell-only syndrome.

In addition, vasography may be performed at the same time to evaluate for obstruction.

Potential complications include pain, bleeding, and inadvertent epididymal biopsy that may give false results and can lead to secondary obstruction.

A small window should be used if a later reconstruction is anticipated to decrease the risk of adhesions within the tunica vaginalis. Hemostasis must be pristine to decrease the risk of a hematocele.

When performing diagnostic biopsies, consider obtaining biopsies from both testicles due to a reported 40% discordance in pathology between the 2 sides.

Usually, the authors cryopreserve testicular tissue at the time of biopsy for potential future use in IVF.

Tab. 19 - Parameters of ejaculate

Analysis	Finding	Conclusion
Ejaculate volume	Low (< 1.5 mL)	Postejaculation urine (retrograde ejaculation) TRUS (absence of vas deferens)

		Hormonal evaluation (hypogonadism)
High (>5 mL)	Likely contaminant	
Semen quality	Does not coagulate	TRUS (ejaculatory duct obstruction)
Does not liquefy	Hormonal analysis	
Sperm density	Oligospermia (< 20 million per mL) Severe oligospermia (< 5 million per mL)	TRUS (partial ejaculatory duct obstruction) Antisperm antibody evaluation Hormonal analysis Physical examination for varicocele
Azoospermia	Sperm centrifuged to verify azoospermia Postejaculation urine (retrograde ejaculation) Hormonal evaluation Testicular biopsy (testicular failure) TRUS (ejaculatory duct obstruction)	
Motility	Decreased	Antisperm antibodies Physical examination for varicocele

Histologic findings. Biopsy samples in patients with infertility due to pretesticular causes have atrophic cells due to a lack of gonadotropin stimuli. Prepubertal hypogonadotropism leads to small immature seminiferous tubules with delicate tunica propria and a lack of elastic fibers. In contrast, patients with postpubertal hypogonadism show few or no germ cells, shrunken tubules, and a thickened hyalinized tunica propria.

Primary testicular failure causes various defects. Normal-sized seminiferous tubules, normal Leydig cells and Sertoli cells, and a normal tunica propria characterize maturation arrest, but germ cells are arrested at any premature stage. Patients with hypospermatogenesis have a thin germinal epithelium and a decreased number of germinal elements. Germ cell aplasia (Sertoli-cell-only syndrome) is associated with vacuolated Sertoli cells and no

germinal epithelium but otherwise normal seminiferous tubules. Klinefelter syndrome is characterized by a decreased number of spermatogonia, germ cell hypoplasia, Sertoli cell atrophy, tubular hyalinization, prominent Leydig cells (hyperplasia), and deformed tubules. Cryptorchid testes have small immature tubules, spermatogonia of variable size, and a hyalinized tunica propria.

Acute mumps orchitis is associated with interstitial edema, mononuclear infiltrate, and a degeneration of germinal epithelium, while recovery is characterized by a patchy loss of germ cells with tubular hyalinization and sclerosis.

Posttesticular obstruction leads to increased tubule diameter, increased thickness of the tunica propria, and a decreased number of Sertoli cells and spermatids. These patients sometimes demonstrate sloughing of the germinal epithelium.

Medical Care

Limited numbers of medical treatments are aimed at improving chances of conception for patients with known causes of infertility.

Endocrinopathies. A number of patients with hypogonadotropic hypogonadism respond to gonadotropin-releasing hormone (GnRH) therapy or gonadotropin replacement. Pulsatile GnRH therapy can be used in those with intact pituitary function. Gonadotropin replacement can be effective in hypothalamic and pituitary dysfunction.

Human chorionic gonadotropin (hCG) is a luteinizing hormone (LH) analogue that may be used alone or in combination with human menopausal gonadotropin (hMG) for Leydig cell stimulation. hCG is biologically similar to LH, but has a longer half life and is less costly than LH. hMG is a purified combination of follicle-stimulating hormone (FSH) and LH. When using hCG in combination with hMG or FSH, one should use hCG first, as it increases testosterone levels, which is essential for spermatogenesis and thus may better augment the overall effect of the therapy. FSH alone is not effective in inducing spermatogenesis, although recent studies suggest otherwise.

Estrogen modulators can also be of use. Aromatase inhibitors (eg, anastrozole) block the conversion of testosterone to estrogen, thus increasing the serum testosterone concentration. They are especially useful in improving semen parameters in patients with decreased testosterone: estradiol ratios.

Clomiphene citrate is a weak estrogen-receptor antagonist that works by blocking the negative feedback inhibition of estrogen on the anterior pituitary, thus increasing the release of FSH and LH. This will then result in increased testosterone production, ultimately augmenting spermatogenesis. Clomiphene citrate is effective in improving the semen parameters in patients with hypogonadotropic hypogonadism. Tamoxifen is another estrogen-receptor antagonist that, in combination with clomiphene, can

increase sperm concentration, sperm motility, and pregnancy rates in males with idiopathic infertility.

Patients with congenital adrenal hyperplasia (CAH) may respond to therapy with glucocorticoids, while those with isolated testosterone deficiency may respond to testosterone replacement.

Exogenous testosterone decreases intratesticular testosterone production, thus inhibiting Sertoli cell function and spermatogenesis.

Treat patients with hyperprolactinemia with dopamine antagonists, such as bromocriptine or cabergoline. [66, 67]

Antisperm antibodies. Patients with antisperm antibody levels greater than 1:32 may respond to immunosuppression using cyclic steroids for 3-6 months. However, patients need to be aware of the potential side effects of steroids, including avascular necrosis of the hip, weight gain, and iatrogenic Cushing syndrome.

Retrograde ejaculation. Imipramine or alpha-sympathomimetics, such as pseudoephedrine, may help close the bladder neck to assist in antegrade ejaculation. However, these medicines are of limited efficacy, especially in patients with a fixed abnormality such as a bladder neck abnormality occurring after a surgical procedure.

Alternatively, sperm may be recovered from voided or catheterized postejaculatory urine to be used in assisted reproductive techniques. The urine should be alkalinized with a solution of sodium bicarbonate for optimal recovery.

More recently, the injection of collagen to the bladder neck has allowed antegrade ejaculation in a patient who had previously undergone a V-Y plasty of the bladder neck and for whom pseudoephedrine and intrauterine insemination had failed.

Semen processing. Patients with poor semen quality or numbers may benefit from having their semen washed and concentrated in preparation for intrauterine insemination.

Couples with an abnormal postcoital test result due to semen hyperviscosity may benefit from a precoital saline douche or semen processing with chymotrypsin.

Lifestyle. Patients should be encouraged to stop smoking cigarettes and marijuana and to limit environmental exposures to harmful substances and/or conditions.

Stress-relief therapy and consultation of other appropriate psychological and social professionals may be advised.

Infections should be treated with appropriate antimicrobial therapy.

Dietary supplements and vitamins. Safarinejad et al published a prospective, double-blind, randomized controlled trial assessing the effects of coenzyme Q 10 (ubiquinol) 200 mg po daily (n = 114 men) compared with placebo (n = 114 men) over 26 weeks.

The authors found a statistically significant increase in sperm concentration, motility, and strict morphology in subjects who received ubiquinol compared to those who received placebo, and these effects gradually returned to baseline levels during the off-drug time period. While pregnancy rates were not tracked or reported, the study does appear to support the use of ubiquinol in men trying to achieve a pregnancy based on improvement in semen parameters.

Surgical Care

Varicocelectomy. Various techniques for varicocelectomy have been proposed and used, each with advantages and disadvantages.

The retroperitoneal approach may be performed as an open procedure or laparoscopically.

The inguinal approach (see image below) allows for ligation of individual veins with decreased risk of inadvertent arterial damage. A 3-5 cm incision is made over the inguinal canal and the spermatic cord is identified and elevated. The external veins parallel to the cord are ligated, followed by microscopic ligation of the spermatic veins Collateral vessels entering the cord distally may also be directly addressed with this technique. This is in contrast to the subinguinal approach, in which a greater number of arteries and veins are exposed and the dissection may be more difficult.

Successful varicocelectomy results in improvement in semen parameters in 60-70% of patients. The repair also typically halts further testicular damage and improves Leydig cell function.. Success with these repairs can be predicted by certain preoperative factors, such as younger patient age, greater sperm density, larger varicoceles, and high preoperative testosterone and lower FSH levels. [67]

Persistent dilatation after repair is not unusual and does not necessarily represent surgical failure. Rather, the veins may remain clinically apparent owing to chronic stretching or thrombosis, even if venous reflux is no longer present. Semen analysis may show improvement as early as the 3-month follow-up visit.

Results from a prospective, randomized, controlled trial from Saudi Arabia provide an evidence-based endorsement of the superiority of subinguinal microsurgical varicocele repair over observation in infertile men with palpable varicoceles and impaired semen quality. Inclusion criteria included infertility lasting 1 year or longer, demonstration of a palpable varicocele, and presence of at least one impaired semen parameter (sperm concentration <20 million/mL, progressive motility <50%, or normal morphology <30%). A total of 145 participants had follow-up within 1 year; spontaneous pregnancy was achieved in 13.9% of controls compared with 32.9% of treated men (odds ratio, 3.04). In treated men, the mean of all semen parameters significantly improved on follow-up compared with baseline ($p < 0.0001$).

A meta-analysis that compared the various varicocelectomy

approaches found that pregnancy rates increased in inguinal, subinguinal, open inguinal, and laparoscopic approaches. However, the subinguinal and inguinal groups had the lowest recurrence rates, highest pregnancy rates, greatest increases in sperm parameters, and lowest rate of hydrocele formation.

Interest in the use of robotic surgery has been growing across various medical fields, including varicocelectomy. The potential advantages of robotic-assisted microsurgery include the following:

1. Elimination of tremor;
2. Improved stability;
3. Surgeon ergonomics;
4. Scalability of motion;
5. Multi-input visual interphases with multiple visual views;
6. Enhanced magnifications;
7. Ability to manipulate multiple instruments and cameras simultaneously.

Robot-assisted subinguinal varicocelectomy has been shown to be safe and efficacious, with one group reporting improved sperm parameters in 76% of patients. Operative times are similar to those with microscopic inguinal varicocelectomy, although the robotic technique does have a learning curve.

Vasovasostomy or vasoepididymostomy. These microsurgical techniques are performed in patients with known epididymal or vasal obstruction, both congenital and acquired (eg, due to surgery, trauma, infection). Improved surgical techniques and the use of the operating microscope have improved the outcomes in patients requiring vasectomy reversal or those with primary vas obstruction. In a study by Fenig et al, the timing of a reversal along with a sperm granuloma identified during the patient's physical examination have been identified as predictors of the need for epididymovasostomy.

In addition, men with increased follicle-stimulating hormone levels of >10 U/l may have an increased likelihood of needing assisted reproduction to achieve pregnancy after vasectomy reversal according to a study by the Goldstein group of Weill Cornell Medical College.

After scrotal exploration, the patency of the duct system proximal to the proposed site of anastomosis is confirmed by examination of expressed fluid for the presence of sperm. If no fluid is expressed, a 24-gauge angiocatheter with 0.1 mL of saline should be used to gently barbotage the proximal vas. If no sperm are observed, inspect the vasal fluid aspirated.

A thickened, white, toothpaste-like fluid usually contains no sperm or nonviable sperm fragments and is likely merely from the vasal epithelium, whereas a watery thin fluid often implies proximal patency. If viable sperm are observed, send an additional sample for cryopreservation prior to vasovasostomy. These sperm may be used for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) if the man remains azoospermic after the repair.

The patency of the distal duct system is confirmed by injecting 10 mL of sterile saline through the vas; if no resistance is encountered, the system is deemed patent. Alternatively, radiographic vasography or chromogenic vasography with methylene blue can be performed, with radiographic contrast visualized passing into the bladder or blue coloration of the urine proving patency, respectively. A 2-0 nylon suture can be passed into the vasal lumen to check the distance to obstruction if the above tests reveal distal blockage.

A vasovasostomy is generally performed in 2 layers, the inner lining with interrupted 10-0 nylon suture and the outer layer with interrupted 9-0 nylon suture. Optimally, a tension-free, mucosa-to-mucosa, watertight anastomosis is created.

A vasoepididymostomy is also closed in 2 layers. Factors that predict a more favorable outcome include a shorter time from the original injury/surgery, a vasovasostomy performed on one side rather than bilateral vasoepididymostomies, and reconstruction because of an infectious etiology rather than a surgical or idiopathic etiology.

When performing a vasoepididymostomy, an end-to-side technique is easier to perform and yields better outcomes than an end-to-end anastomosis. More recently, a triangular technique for vasoepididymostomy has been proposed. Although more motile sperm are present at the proximal epididymis in patients with ductal obstruction, the technique is easier and more successful if it is performed at the distal end.

A varicocelectomy and vasovasostomy should never be performed at the same time because of a risk of testicular atrophy.

Robotic vasovasostomy has been shown to yield similar patency rates as the microsurgical approach, but no difference in pregnancy rates (~60%). The mean operating times for robotic vasovasostomy and vasoepididymostomy have also been shown to be comparable to the microsurgical approaches.

Robotic assistance also permits microsurgical procedures to be used in areas that are normally difficult to access. For example, in patients who have a vasal obstruction as a result of a prior inguinal hernia repair, robotic-assisted intra-abdominal vasovasostomy has been effectively employed. It provides an advantage to these patients because it requires very small inguinal incisions to mobilize the external vas and it allows for tension-free anastomosis because the testicular vas is brought into the pelvis for the procedure.

Transurethral resection of the ejaculatory ducts

Patients with a known or suspected obstruction of the ejaculatory ducts may be eligible for transurethral resection of the ejaculatory ducts (TURED), which durably improves semen quality in patients with ejaculatory duct obstruction.

In the operating room, with patients under spinal or general anesthesia, the resectoscope with a 24F cutting loop is used to excise the verumontanum of the prostate. Using the O'Connor drape to enable placement of a finger in the rectum to elevate the prostate may be helpful.

Resection is performed with care to avoid injuring the bladder neck or external sphincter.

Risks with this procedure include watery (urine) ejaculate, chemical or bacterial epididymitis due to reflux, bleeding, and retrograde ejaculation.

Sperm retrieval techniques. Testicular sperm extraction (TESE) is performed at the time of testicular biopsy or as a separate procedure using the same technique. In a study spanning 15 years, TESE from men with azoospermia followed by cryopreservation was more effective at fertilization than fresh sperm from biopsies (62% vs 47% for all diagnoses).

Microscopic TESE (microTESE) has been shown to improve sperm retrieval rates with minimal tissue excision.During microdissection, the surgeon can identify sperm-producing areas in the testicles, as opposed to standard TESE, where this is not possible. Robotic-assisted TESE (ROTESE) has been employed in select studies and has been shown to be safe and feasible for sperm retrieval. An advantage of ROTESE over microTESE is that ROTESE can provide surgeons with multiple imaging modalities to use during the procedure, which may assist in identifying tubules that have sperm.

Testicular sperm aspiration (TESA) is less invasive than TESE but yields fewer sperm and is suboptimal in cases of nonobstructive azoospermia.

Microsurgical epididymal sperm aspiration (MESA) involves directly retrieving sperm from the epididymis. Sperm in the epididymis are more mature than that in the testis. Using a microscope, the epididymis is uncovered and incised to express sperm. Epididymal fluid is aspirated into a tuberculin syringe primed with human tubal fluid (HTF).

Percutaneous epididymal sperm aspiration (PESA) involves direct sperm aspiration from the epididymis. This procedure can be performed under local anesthesia in the office setting. While effective in sperm retrieval, this does not allow sampling from multiple sites and is associated with an increased risk of epididymal and testicular injury and secondary epididymal obstruction.

An autogenous spermatocele can be created in patients with an unreconstructable ductal system. A buttonhole is created within the viscera, and repeated percutaneous aspirations of sperm can be performed using ultrasonographic guidance. An intact tunica vaginalis with no adhesions is needed, so it is ideal for use in patients with normal spermatogenesis and a congenital absence of the vas. This procedure is rarely used.

An alloplastic spermatocele uses an artificial silicone sperm reservoir in

place of the tunica vaginalis for sperm storage and subsequent retrieval. This technique has been unsuccessful so far.

Electroejaculation. Under general anesthesia, an unlubricated Foley catheter is placed in the bladder and a buffer (ie, human tubal fluid [HTF] medium) is instilled through the catheter. A rectal probe is inserted with its electrodes positioned against the posterior seminal vesicles. Electrical stimulation is begun at 3-5 volts and increased as necessary. Electroejaculation achieves up to a 90% sperm retrieval rate.

The penile vibratory stimulator has been shown to be a useful alternative to electroejaculation in select patients. The US Food and Drug Administration (FDA)has approved this device for home use, using 2.2 mm at 100 Hz. This is associated with fewer adverse effects and lower cost than electroejaculation. In addition, collection may take place at home instead of in the operating room.

Artificial insemination. Artificial insemination (AI) involves the placement of sperm directly into the cervix (ie, intracervical insemination [ICI]) or the uterus (ie, intrauterine insemination [IUI]). AI is most useful for couples in whom the postcoital test indicated no sperm, those who have very low sperm density or motility, or those who have unexplained infertility.

IUI allows the sperm to be placed past the inhospitable cervical mucus and increases the chance of natural fertilization. This results in a 4% pregnancy rate if used alone and a pregnancy rate of 8-17% if combined with superovulation. Both processes require semen processing.

Older age in the male has been associated with lower pregnancy rates and higher rates of subsequent spontaneous abortions in patients undergoing IUI. Patients in whom IUI has failed 3-6 times should consider proceeding to IVF.

Assisted reproduction techniques. Patients with severe oligospermia, azoospermia, unexplained infertility, or known defects that preclude fertilization by other means are candidates for assisted reproduction techniques. Assisted reproduction techniques use donated or retrieved eggs that are fertilized by the male partner's sperm or donor sperm. The fertilized embryos are then replaced within the female reproductive tract. These techniques result in a 15-20% delivery rate per cycle and may eventually be successful in 50% of cases. However, the high cost and technical difficulty of the procedures generally preclude their routine use as first-line therapy.

In vitro fertilization. IVF involves fertilization of the egg outside the body and reimplantation of the fertilized embryo into the woman's uterus. Indications for IVF include previous failures with IUI and known conditions of the male or female precluding the use of less-demanding techniques.

IVF generally requires a minimum of 50,000-500,000 motile sperm. Harvesting eggs initially

involves down-regulating the woman's pituitary with a GnRH agonist and then performing controlled ovarian hyperstimulation.

Follicular development is monitored by ultrasonographic examination and by checking serum levels of estrogen and progesterone. When the follicles are appropriately enlarged, a transvaginal follicular aspiration is performed.

A mean of 12 eggs are typically retrieved per cycle, and they are immediately placed in an agar of fallopian-tube medium. After an incubation period of 3-6 hours, the sperm are added to the medium using approximately 100,000 sperm per oocyte. After 48 hours, the embryos have usually reached the 3- to 8-cell stage. Two to 4 embryos are usually implanted in the uterus, while the remaining embryos are frozen for future use. Pregnancy rates are 10-45%.

Overall, IVF is a safe and useful procedure. Risks include multiple pregnancies and hyperstimulation syndrome, as well as a slightly higher rate of major birth defects. Additionally, an increased risk of hypospadias occurs in boys (1.5% vs 0.3%), probably because of the increased maternal progesterone used for egg harvesting.

Finally, the use of this technology has led to many ethical issues, such as the fate of embryos after divorce.

Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT)

These procedures allow the placement of semen (GIFT) or a fertilized zygote (ZIFT) directly into the fallopian tube by laparoscopy or laparotomy. Success rates have been estimated to be 25-30% using these techniques. Unfortunately, these procedures require general anesthesia and have associated risks. Fertilization and implantation within the uterus are not guaranteed, and these procedures cannot be performed in patients with fallopian tube obstruction. GIFT and ZIFT are rarely used as a therapeutic option.

Intracytoplasmic sperm injection. ICSI involves the direct injection of a sperm into an egg under microscopy (see image below). It is indicated in patients who have failed more conservative therapies or those with severe abnormalities in which no other treatment would be effective, including patients with sperm extracted directly from the epididymis or testicle.

Sperm samples are collected either via masturbation or surgically. Surgical extraction may be more useful in cases of persistent necrozoospermia, due to the high DNA fragmentation rates in ejaculated sperm. Sperm can then be evaluated microscopically in terms of their motility, morphology, DNA quality, and/or the ability to bind a hyaluronic acid assay. The embryologist then chooses the most adequate sperm for the procedure.

Oocytes are processed with hyaluronidase to remove the cumulus mass and corona radiata. A micropipette is used to hold the egg while a second micropipette injects the sperm. The oocyte is positioned with the polar body at the 6-o'clock or 12-o'clock position, and the sperm is injected at the 3-o'clock position to minimize the risk of chromosomal damage in the egg. After incubation for 48 hours, the embryo is implanted in the woman.

Van Steirteghem et al reported a 59% fertilization rate and a 35% pregnancy rate with the use of ICSI in 1409 oocytes. Fresh sperm and cryopreserved sperm appear to have similar success rates. In female partners of men with infertility who are undergoing ICSI, diminished ovarian reserve may adversely affect the success of TESE (ie, reduce the clinical pregnancy rate). Some studies also suggest that a direct correlation exists between endometrial thickness and pregnancy rates after ICSI.

The potential complications, ethical issues, and high costs of ICSI must be considered and individualized.

Consultations

Geneticist. A genetics consultation may be indicated in patients with a known or suspected genetic cause of infertility and in patients with nonobstructive azoospermia or severe oligospermia (< 5 million sperm/mL). In addition, in the era of IVF and ICSI, determining the risks of passing on chromosomal abnormalities to a potential offspring is important.

Use a peripheral karyotype and a PCR-based evaluation of the Y chromosome to evaluate for microdeletions. Patients with nonobstructive azoospermia have a 13-17% chance of genetic abnormalities, 4-16% of which are due to Klinefelter syndrome and 9% are due to a partial Y deletion.

Patients with CBAVD nearly uniformly have a mutation in the CFTR gene. An estimated 50-82% of men with CBAVD have a genital-only form of CF, which may manifest in patients with only one copy of the abnormal CF gene. In contrast, patients with clinical CF usually have two copies of the abnormal gene.

As for men who do have the digestive and pulmonary complications of CF, technology is allowing them to live longer. These men are now candidates for assisted reproductive techniques. The female partner must be evaluated for a *CFTR*gene mutation before attempted fertilization to determine the risk of producing offspring with CF, which is an autosomal recessive trait.

Endocrinologist. Patients with severe oligospermia or azoospermia should be evaluated with a hormonal evaluation.

Patients with unexplained hypogonadism or hyperprolactinemia should undergo a CT scan or MRI of the sella turcica to evaluate for a pituitary tumor.

Abnormalities may indicate the need for a formal endocrinology consultation.

Diet. A diet high in antioxidants such as vitamin C and vitamin E has been proposed to improve the quality of sperm by decreasing the number of free radicals that may cause membrane damage.

Additionally, the use of zinc, fish oil, and selenium has been shown to be of benefit in some studies.

Activity. Patients should limit the use of potentially spermatotoxic substances such as cigarettes, marijuana, and anabolic steroids. Environmental exposures to harmful substances and/or conditions should be minimized.

The optimal timing to perform intercourse for conception is every 2 days at mid cycle.

The use of spermatotoxic lubricants should be avoided.

14.2 Male hypogonadism

Male hypogonadism is a clinical and biochemical syndrome associated with low testosterone levels, as well as the insensitivity of the receptor apparatus to androgens, which can have a negative effect on many organs and systems, worsening the quality of life and life expectancy. Androgens, the main one of which is testosterone, play a key role in the development and maintenance of the reproductive and sexual functions of the male reproductive system. Low testosterone levels can cause impaired sexual development of the male body, which leads to abnormalities of the male reproductive system. In later life, this can lead to a decrease in fertility, sexual dysfunction, a decrease in the intensity of the formation of muscle mass and bone mineralization, impaired fat metabolism and cognitive dysfunction. [66]

Testosterone levels also decrease with aging, and this decrease may be associated with certain chronic diseases. In patients with a clinical picture and laboratory-confirmed hypogonadism, therapy with testosterone drugs may be effective.

With age, men have a decrease in testosterone levels (an annual decrease in circulating testosterone levels of 0.4-2.0% has been recorded since the age of 30). In middle-aged men without comorbidity, the prevalence of hypogonadism is 6%. The prevalence of hypogonadism in obesity and uncompensated diabetes mellitus may exceed 50%. [67]

Hypogonadism may occur if the hypothalamic-pituitary-gonadal axis is interrupted at any level. Hypergonadotropic hypogonadism (primary hypogonadism) results if the gonad does not produce the amount of

sex steroid sufficient to suppress secretion of LH and FSH at normal levels. Hypogonadotropic hypogonadism may result from failure of the hypothalamic LHRH pulse generator or from inability of the pituitary to respond with secretion of LH and FSH. Hypogonadotropic hypogonadism is most commonly observed as one aspect of multiple pituitary hormone deficiencies resulting from malformations (eg, septooptic dysplasia, other midline defects) or lesions of the pituitary that are acquired postnatally. In 1944, Kallmann and colleagues first described familial isolated gonadotropin deficiency. Recently, many other genetic causes for hypogonadotropic hypogonadism have been identified.

Prognosis

No increase in mortality is observed in patients with hypogonadism. Morbidity for men and women includes infertility and an increased risk of osteoporosis. In women, an increased risk of severe osteoporosis is noted. In men, hypogonadism causes decreased muscle strength and sexual dysfunction.

Men and women with hypogonadism can lead a normal life with hormone replacement.

Approximately 10-20% of females with Turner syndrome have some spontaneous puberty. Spontaneous estrogenization occurs more commonly in women with mosaic karyotypes and those karyotypes with an abnormal second X chromosome, such as 46,XXiq or 46,XXip. Reports exist of women with mosaic Turner syndrome becoming pregnant without in vitro fertilization.

History

For both males and females with hypogonadism, determining whether evidence of a genital abnormality is present at birth or determining the timing and extent of puberty is important. In addition, because Kallmann syndrome (hypogonadotropic hypogonadism and anosmia [ie, lack of a sense of smell]) is a common cause of hypogonadotropic hypogonadism, inquiring about the sense of smell is important

For prepubertal males or females with delayed puberty (ie, lack of sexual characteristics by age 13 years in females or ages 13-14 years in males; also, the presence of primary amenorrhea at age 16 years), inquire about a family history of constitutional delay of growth and development. Constitutional delay in pubertal development is the most frequent clinical scenario.

Inquire about chronic illness (including frequent headaches), intentional or unintentional weight loss, and strenuous exercise.

Specific issues include the presence of developmental anomalies associated with the genital system (eg, hypospadias, micropenis, cryptorchidism). Guidelines for micropenis have been established.

For postpubertal males, inquire about the rate of beard growth, libido and sexual function, muscle strength, and energy levels.

Investigate possible causes of acquired testicular failure (eg, mumps orchitis, trauma, radiation exposure of the head or testes, chemotherapy, frequent transfusions). Drugs that may interrupt testicular function include agents that interfere with testosterone synthesis, such as spironolactone and cyproterone. Agents such as cortisol, marijuana, heroin, and methadone may interfere with gonadotropin secretion.

Physical

The presence of congenital anomalies and dysmorphic features may suggest a specific syndrome. For example, the existence of dysmorphology associated with obesity and developmental delays may suggest syndromes such as Prader-Willi and Laurence-Moon. The presence of nystagmus in an individual with suspected panhypopituitarism raises the suspicion for septo-optic dysplasia.

Evaluation of the testes is the most important feature of the physical examination. Determine whether both testes are palpable, their position in the scrotum, and their consistency. Testes size can be quantitated by comparison with testicular models (orchidometer), or their length and width may be measured. Before puberty, testes usually are 1-3 cm3 in volume (approximately 2 cm in length). During puberty, testes grow up to 25 cm3 in size.

Examining the genitalia for hypospadias is the next important step. Check the scrotum to see if it is completely fused. (Hypospadias is usually not related to an endocrine abnormality, but it may be seen in disorders associated with a testosterone biosynthesis defect, partial androgen insensitivity syndrome, or a defect in testicular determination.) Finally, evaluate the extent of virilization.

The presence of microphallus suggests Kallmann syndrome or panhypopituitarism.

Puberty should be staged using the Tanner criteria for genitalia, pubic hair, and axillary hair.

Look for signs of Klinefelter syndrome, such as tall stature (especially if the legs are disproportionately long), gynecomastia, small or soft testes, and a eunuchoid body habitus.

Causes

Hypogonadism can occur in association with miscellaneous congenital disorders, including Prader-Willi syndrome, Laurence-Moon syndrome, Bardet-Biedl syndrome, and Gaucher disease. Leptin deficiency (also associated with morbid obesity) and iron overload from chronic transfusions or hemochromatosis are other sources of hypogonadism.

Causes of hypogonadotropic hypogonadism include the following:

1. Central nervous system (CNS) disorders:

2. Tumors;

3. Craniopharyngioma;

4. Germinoma;

5. Other germ cell tumors;

6. Hypothalamic and optic glioma;

7. Astrocytoma;

8. Pituitary tumor;

9. Miscellaneous causes involving the pituitary/hypothalamic area;

10. Langerhans histiocytosis;

11. Postinfectious lesions of the CNS;

12. Vascular abnormalities of the CNS;

13. Radiation therapy;

14. Congenital malformations (especially associated with craniofacial anomalies);

15. Head trauma;

16. CNS surgery;

17. Genetic causes;

18. Kallmann syndrome (mutation in the *KAL* [anosmin-1] gene, as well as *FGFR1*, *PROK2*, and *PROKR2*), with hyposmia or anosmia or without anosmia;

19. Mutations in *GNRH1*, *KISS1R*, *GNRHR*, *TAC3*, *TACR3*;

20. Congenital adrenal hypoplasia (mutation in the *DAX1* gene);

21. Mutations in the *PROP1* and *HESX1* genes;

22. Mutations in the gene coding for the gonadotropin-releasing hormone (GnRH) receptor;

23. Isolated luteinizing hormone (LH) deficiency;

24. Isolated follicle-stimulating hormone (FSH) deficiency;

25. Miscellaneous congenital disorders;

26. Congenital deficiencies of multiple pituitary hormones - septo-optic dysplasia;

27. Miscellaneous congenital disorders, including Prader-Willi syndrome, Laurence-Moon syndrome, Bardet-Biedl syndrome, and Gaucher disease; leptin deficiency (also associated with morbid obesity) and iron overload from chronic transfusions or hemochromatosis are also associated with hypogonadism;

28. Miscellaneous acquired disorders;

29. Chronic systemic disease and malnutrition;

30. Exercise-induced hypogonadism;

31. Psychogenic hypogonadism;

32. Hyperprolactinemia;

33. Cushing syndrome;

34. HIV infection/AIDS;

35. Morbid obesity;

36. Type II diabetes mellitus;

37. Medications - Chronic glucocorticoid therapy, chronic opioids, psychotropic medications resulting in hyperprolactinemia, anabolic steroids;

38. Older men with testosterone deficiency.

Hypergonadotropic hypogonadism in males

Causes include the following:

1. Klinefelter syndrome;

2. Inactivating mutations;

3. LH beta subunit;

4. FSH beta subunit;

5. LH receptor;

6. FSH receptor;

7. Other causes of primary testicular failure;

8. Chemotherapy;

9. Radiation therapy;

10. Gonadectomy;

11. Anorchism and cryptorchidism;

12. Testicular biosynthetic defects (17β-hydroxylase dehydrogenase deficiency, 5α-reductase deficiency, 17-hydroxylase deficiency);

13. Defects in testicular determination (gonadal dysgenesis);

14. Other rare disorders of sex development (DSDs) (ovotesticular DSD, XX males);

15. Sertoli-cell-only syndrome;

16. LH resistance.

Diagnostic Considerations

Hypogonadism is diagnosed in the presence of clinical symptoms associated with androgen deficiency and detection of a persistent decrease in testosterone levels (at least twice confirmation) by a reliable method (for example, by enhanced chemiluminescence).

Symptoms

The symptoms of testosterone deficiency are not specific and vary among individuals. However, it is worth noting that earlier symptoms may include decreased libido, changes in mood, fatigue and irritability, sleep disturbances, loss of vital energy.

Clinical symptoms detected in men with hypogonadism:

- Delayed puberty
- Small testicle size
- Male infertility
- Mild body hair
- Gynecomastia
- Decreased fat free component of body mass and muscle strength
- Visceral obesity
- Decreased bone mineral density (osteoporosis), fractures with minor trauma

- Decreased libido and sexual activity
- erectile disfunction
- Reducing the severity of night erections
- Tides
- Mood changes, fatigue and irritability
- Sleep disturbance
- Metabolic syndrome
- Decreased cognitive abilities

Most of these symptoms are non-specific, and in clinical diagnosis of hypogonadism should focus on three main features:

- decreased libido and sexual activity,
- reducing the number of morning erections,
- decrease in adequate erections.

Symptoms of sexual dysfunction, both with and without testosterone deficiency, may be associated with concomitant diseases or medications (for example, spironolactone, cyproterone, non-selective beta-blockers).

It should be noted that in the process of diagnostics, differential diagnostics, as well as assessing the safety of therapy for testosterone-deficient states, if necessary, such specialists as cardiologists, urologists, therapists, etc. should be included.

Anamnesis should be collected to identify the symptoms of hypogonadism mentioned above. The published questionnaires (AMS, ADAM) are unreliable and are characterized by low specificity, so they are not always effective in detecting the disease. However, these questionnaires may be useful for monitoring the clinical response to testosterone therapy.

In prepubertal hypogonadism (defined as hypogonadism in humans, which arose before puberty), there is a lack of minimal sexual development and secondary sexual characteristics, possibly an eunuchoid physique and high timbre of voice.

Post-pubertal hypogonadism is defined as a testosterone deficiency, usually accompanied by the corresponding symptoms, in a man who has undergone normal puberty, leading to the development of normal secondary sex characteristics of the male sex. Causes the loss of androgen-dependent functions of the body and the appearance of symptoms that may have a different etiology, in addition to reducing testosterone levels.

When examining a patient, it is important to identify and / or exclude systemic diseases, signs of malnutrition, as well as acute diseases that can cause loss of androgen-dependent body functions and the appearance of symptoms of hypogonadism. These diseases must be identified with appropriate treatment.

Thyroid dysfunction should be excluded in all patients with hypogonadism, since the symptoms of hypothyroidism may overlap with the symptoms of hypogonadism.

When collecting anamnesis, you should also ask questions regarding the pharmacological treatment of corticosteroids, dependence on narcotic substances, prior to the use of testosterone drugs, anabolic steroids.

Physical examination should include an assessment of body mass index, waist circumference, body hair growth, the presence of gynecomastia and testicle size (measurement using an orchidometer or ultrasound), as well as examination of the penis and prostate gland.

Laboratory Studies

The threshold value, allowing distinguishing between a normal state and a potential testosterone deficiency, should be considered 12.1 nmol/l for total serum testosterone.

When the level of total testosterone is from 8 to 12 nmol/l, it is advisable to determine the level of globulin that binds sex steroids, with further calculation of the level of free testosterone, the lower limit of which is 225-250 pmol / l according to various sources, but most researchers suggest a value of 243 pmol / l.

Blood sampling to determine the level of testosterone is shown to produce on an empty stomach, between 7 and 11 am.

To differentiate the primary and secondary forms of hypogonadism, as well as to identify subclinical hypogonadism, it is necessary to determine the serum level of PH. Analysis of serum levels of LH, like testosterone, should be performed twice.

The onset of hypogonadism may be hidden and not always characterized by a decrease in testosterone levels. In men with primary lesions of the testes, in some cases, there is a normal level of testosterone with a high level of PH - this can be considered as a subclinical or compensated form of hypogonadism. Symptoms of hypogonadism are potentially possible in these men in the future, therefore they require observation, and during the clinical manifestation of hypogonadism, patients are shown replacement testosterone therapy.

The definition of prolactin in serum is indicated for suspected secondary hypogonadism caused by a pituitary tumor (eg, prolactinoma).

Imaging Studies

Magnetic resonance imaging (MRI) of the brain should be considered in cases of anosmia and suspected hypogonadotropic hypogonadism. Absence of the olfactory bulbs is associated with Kallmann syndrome.

Moreover, brain MRI should be ordered in cases of hypogonadotropic hypogonadism that are either isolated or occurring in combination with pituitary defects.

MRI of the pelvis is usually performed in DSD cases, such as androgen insensitivity or ovotesticular DSD, to help delineate the anatomy of internal genitalia. Uterine aplasia in a pubertal girl with normal gonadal

function and amenorrhea can be seen in Mayer-Rokitansky-Küster-Hauser syndrome.

Pelvic ultrasonography may be helpful in females.

Bone age may be helpful in the evaluation of adolescents with delayed puberty and provides insight into their growth potential.

Other Tests

Adrenocorticotropic hormone (ACTH) stimulation testing: In patients in whom a form of congenital adrenal hyperplasia is suspected, adrenal steroid synthesis is best evaluated by performing a cosyntropin (ACTH 1-24) stimulation test. Baseline serum adrenocortical hormone levels are measured, then 0.25 mg of cosyntropin is intravenously injected, and serum hormone levels are remeasured after 60 minutes. Precursor product ratios are compared with those in age-matched control subjects to determine whether a steroidogenic defect is involved in sex hormone synthesis.

Luteinizing-hormone releasing hormone (LHRH) stimulation testing: To distinguish between true hypogonadotropic hypogonadism and constitutional delay in growth and maturation, performing a stimulation test with LHRH may be helpful.

LHRH is intravenously injected, and LH and FSH levels are determined at 15-minute intervals following LHRH administration.

A shortened version of the study has been used, in which LHRH is subcutaneously injected, and the specimen for LH and FSH levels is taken at 30-40 minutes.

Obtaining LHRH for testing over the past several years has been difficult. Some centers have substituted testing LH response to aqueous leuprolide.

Testicular tissue testing: If testes are not palpable and whether any testicular tissue is present is unclear, administering human chorionic gonadotropin (hCG) and measuring testosterone response may be helpful.

Procedures

In prepubertal males with delayed puberty, priming with testosterone (usually testosterone enanthate 50 mg IM monthly for a total of 3 months) may lead to puberty initiation and help in the differential diagnosis of hypogonadotropic hypogonadism.

In postpubertal females with amenorrhea, withdrawal bleeding after a 5-10 day course of progestin (such as medroxyprogesterone 10mg hs) indicates adequate estrogen secretion and implies intact gonadal function.

Occasionally, testicular biopsy findings are helpful, particularly if azoospermia or oligospermia is present.

Approach Considerations

Patients with hypogonadism are typically treated with sex steroid replacement. The goals of treatment are:

1. To promote the development of and maintain secondary sexual characteristics and normal sexual function;

2. To build and sustain normal bone and muscle mass;

3. To assist in the proper psychosocial adjustment of adolescents with hypogonadism.

Fertility options can be explored in consultation with a reproductive endocrinologist or urologist. Pulsatile LHRH or gonadotropin therapy can induce fertility in individuals with hypogonadotropic hypogonadism.

Medical Care

In prepubertal patients with hypogonadism, treatment is directed at initiating pubertal development at the appropriate age. Age of therapy initiation takes into account the patient's psychosocial needs, current growth, and growth potential. Treatment entails hormonal replacement therapy with sex steroids, ie, estrogen for females and testosterone for males.

Introduction of sex steroids in such cases starts with the use of small, escalating doses over a period of a couple of years. In females, introduction of puberty can begin with administration of small doses of estrogen given either orally or transdermally. One traditional regimen uses conjugated estrogen starting at doses as low as 0.15 mg daily and titrating upwards in 6-12 month intervals to typically 0.625 mg daily, at which point menses can be induced with the introduction of a progestin. Alternatively, transdermal 17β-estradiol (0.08 to 0.12 mcg estradiol/kg) can be used.

In boys, introduction of puberty is achieved with the use of testosterone, administered intramuscularly or transdermally (in the form of a patch or gel). A typical regimen involves testosterone enanthate injections 50 mg monthly, titrating up to 200-250 mg every 2 weeks, which is a typical adult replacement dose. Adult testosterone dose can be adjusted to maintain serum testosterone concentrations in the normal adult range.

Therapy with sex steroid replacement ensures development of secondary sexual characteristics and maintenance of normal sexual function. In patients with hypergonadotropic hypogonadism, fertility is not possible. However, patients with hypogonadotropic hypogonadism have fertility potential, although therapy with sex steroids does not confer fertility or stimulate testicular growth in men. An alternative for men with hypogonadotropic hypogonadism has been treatment with pulsatile LHRH or hCG, either of which can stimulate testicular growth and spermatogenesis.

Because such treatment is more complex than testosterone replacement, and because treatment with testosterone does not interfere with later therapy to induce fertility, most male patients with hypogonadotropic hypogonadism prefer to initiate and maintain virilization with testosterone. At a time when fertility is desired, it may be induced with either pulsatile LHRH or

(more commonly) with a schedule of injections of hCG and FSH. Similarly, fertility can be achieved in females with pulsatile LHRH or exogenous gonadotropin. Such therapy results in ovulation in 95% of women.

A phase III, multicenter, open-label, single-arm trial by Nieschlag et al indicated that corifollitropin-alfa therapy combined with hCG treatment can significantly increase testicular volume and induce spermatogenesis in adult males with hypogonadotropic hypogonadism whose azoospermia could not be cured by hCG treatment alone. Patients in the study who remained azoospermic, though with normalized testosterone levels, after 16 weeks of hCG treatment underwent 52 weeks of twice-weekly hCG therapy along with every-other-week corifollitropin-alfa treatment (150 µg). Mean testicular volume in these patients rose from 8.6 mL to 17.8 mL, while spermatogenesis was induced in more than 75% of subjects.

The use of oral testosterone preparations, such as 17α-alkylated androgens (eg, methyltestosterone), is discouraged because of liver toxicity. However, oral testosterone undecanoate is available in some countries and is now approved in the United States. Intramuscular testosterone is available as testosterone enanthate or cypionate. Transdermal testosterone can be administered either in the form of a patch or gel. A nasal testosterone replacement therapy has been approved by the US Food and Drug Administration (FDA) for adult males with conditions such as primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) resulting from a deficiency or absence of endogenous testosterone. The recommended dosage is 33 mg/day in three divided doses. The drug has not been approved for males younger than 18 years.

For older men with testosterone deficiency, a review by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) found that the evidence concerning the risk of serious cardiovascular side effects from the use of testosterone in men with hypogonadism was inconsistent. The PRAC determined that the benefits of testosterone outweigh its risks but stressed that testosterone-containing medicines should be used only when lack of testosterone has been confirmed by signs and symptoms, as well as by laboratory tests. However, a literature review by Albert and Morley indicated that testosterone supplementation in males aged 65 years or older may increase the risk of cardiovascular events, particularly during the first year of treatment, although intramuscular testosterone seemed to carry less risk than other forms.

On the other hand, a study by Traish et al suggested that long-term testosterone therapy in men with hypogonadism significantly reduces cardiovascular disease–related mortality. Patients in the study's testosterone-treated group (n=360) underwent therapy for up to 10 years, with median follow-up being 7 years. The investigators found no cardiovascular event–related deaths in the treated patients, compared with 19

such deaths in the group that received no testosterone therapy (n=296). According to the study, mortality in the testosterone-treated patients was reduced by an estimated 66-92%.

The latest Endocrine Society clinical practice guidelines suggest testosterone therapy for men receiving high doses of glucocorticoids who also have low testosterone levels, to promote bone health. The guidelines also suggest such therapy in human immunodeficiency virus (HIV)–infected men with low testosterone levels, to maintain lean bone mass and muscle strength.

Surgical Care

Because of the significant risk of gonadoblastoma and carcinoma, gonadal tissue should be removed in females with karyotypes containing a Y chromosome. This situation is observed in females with XY gonadal dysgenesis or in patients with Turner syndrome who have a karyotype that contains a Y chromosome (usually in 1 of 2 or more mosaic karyotypes). Males with nonfunctioning testicular tissue should undergo orchiectomy and replacement with prostheses.

Consultation with a reproductive endocrinologist or urologist is required for patients with hypogonadotropic hypogonadism who would like to become fertile. Administration of pulsatile LHRH or gonadotropins in females results in ovulation in 95% of the cases. In males, pulsatile LHRH therapy or hCG alone or in combination with gonadotropins can induce spermatogenesis and results in normal adult male testosterone levels.

Patients with hypergonadotropic hypogonadism are traditionally considered infertile. However, men with Klinefelter syndrome may benefit from a consultation with a reproductive urologist and testicular sperm extraction (TESE) followed by in vitro fertilization. This technique has allowed men with Klinefelter syndrome to father children. For boys with Klinefelter syndrome who have reached puberty, cryopreservation of semen samples containing very low numbers of spermatozoa is possible and should be offered before testosterone supplementation, since supplementation may suppress spermatogenesis.

In men, complications of untreated hypogonadism include loss of libido, failure to achieve physical strength, the social implications of failing to go through puberty with peers (if hypogonadism occurs before puberty), and osteoporosis.

In addition, if hypogonadism occurs before epiphyseal closure, the result is usually tall stature with a eunuchoid body habitus. Males with hypergonadotropic hypogonadism are typically infertile, although procedures such as TESE have resulted in fertility in Klinefelter syndrome.

Men who have hypogonadism due to hypothalamic or pituitary dysfunction can potentially become fertile with administration of gonadotropins.

A retrospective study by Baillargeon et al indicated that males with untreated hypogonadism are at increased risk for the development of any rheumatic autoimmune disease, as well as for rheumatoid arthritis and lupus.

Long-Term Monitoring

Patients with hypogonadism require lifelong treatment, with the exception of persons with congenital hypogonadotropic hypogonadism (spontaneous recovery having been described in 10-20% of these individuals). Patients with hypogonadism receiving hormone replacement therapy are typically evaluated every 6-12 months. Monitoring may include measurement of testosterone concentrations in males, evaluation of bone mass by dual radiographic absorptiometry, and assessment of cardiovascular risk factors.

Polycythemia can be a complication of testosterone replacement. For older adult men with testosterone deficiency, the Endocrine Society clinical guidelines recommend monitoring hematocrit values to avoid polycythemia. Also in these individuals, prostate examination and prostate-specific antigen (PSA) measurements should be performed before testosterone therapy and periodically after treatment is instituted. Referral to a urologist can be considered based on individual assessment for prostate cancer.

Medication Summary

Treatment of patients with hypergonadotropic hypogonadism involves replacement of sex steroids in both males and females.

For treatment of patients with hypogonadotropic hypogonadism, the usual approach is replacement of sex steroids that initiate development and maintain secondary sex characteristics.

Sex steroid replacement does not result in increased testicular size in males or fertility in either males or females. Gonadotropin or GnRH replacement is offered to the patient when fertility is desired.

Many oral contraceptives can provide estrogen and progesterone in a combination that meets the replacement needs of the patient. Selection of a specific oral contraceptive agent needs to be individualized. All of the contraindications, cautions, and drug interactions for estrogens and progesterones apply, as listed in the tables below.

Treating aging with testosterone

Although some off-label medication use is justified, the use of testosterone for nonspecific symptoms of aging is not. Using testosterone to treat older men with decreased energy, decreased strength, low libido, erectile dysfunction, mood disorders, sleep disorders, or poor memory is inappropriate because symptoms do not correlate with testosterone levels. testosterone supplementation is unimpressive in clinical trials, and

inappropriate testosterone therapy is not safe.

Many nonspecific symptoms treated with testosterone are due to normal aging or pathologies for which there are more effective, safer therapies. For example, depression should be treated with antidepressants, not testosterone, and erectile dysfunction is appropriately treated with phosphodiesterase inhibitors. A systematic review of 40 studies found only weak correlations between low testosterone and any symptoms. Symptoms associated with low testosterone are also associated with chronic disease, psychogenic factors, and substance use. Erectile dysfunction, for example, is associated with diabetes mellitus, vascular dysfunction, and neurologic impairment—all of which are common in older men.

Although there are more than 100 trials of testosterone therapy, there is little evidence that testosterone works for any symptoms. Evidence from randomized controlled trials and a systematic review conducted by our team found that testosterone does not benefit physical function, mood, cognition, or cardiovascular health. A recent set of testosterone studies that included men 65 years or older with a serum testosterone level less than 275 ng per mL (9.5 nmol per L) found that topical testosterone therapy over one year improved bone density and anemia but had no effect on age-associated memory impairment.

Evidence on sexual function is mixed. Out of 47 studies, 24 found no benefit of testosterone over placebo on any sexual function end point. Although 23 studies found a benefit on at least one end point, most end points were negative. About one-half (16 out of 31) of erectile dysfunction studies found a benefit.

Testosterone levels vary hourly, daily, weekly, and seasonally. There is no reliable evidence that raising testosterone levels prevents or treats any disease. Although many persons with chronic diseases have low testosterone levels, it is much more likely to be an effect rather than a cause of chronic disease. Our systematic review found no evidence of benefit for any clinical end points of cardiovascular disease. Although trials have occasionally found a benefit for a marker of cardiovascular disease, clinical end points are more important, and evidence must be considered as a whole.

Adverse effects of testosterone therapy are a concern. Testosterone may increase prostate cancer rates, and it is also linked to thromboembolic events, especially in those with thrombophilia-hypofibrinolysis. Testosterone probably increases cardiovascular risks, especially soon after treatment commences. It bears noting that long-term observational studies showing no increased cardiovascular risk censored short-term events. All prevalence studies will have this bias; it is vital to study new users prospectively, and in the case of testosterone therapy, long-term prospective trials would contribute to a more accurate

understanding of all-cause adverse effects.

Studies of testosterone and cardiovascular risk have received attention recently. One trial found that in a subset of 170 men (mean age of 71.2 years; one-half with severe atherosclerosis), testosterone treatment significantly increased noncalcified plaque volume over a year compared with placebo, as measured by coronary computed tomographic angiography. This is not a good sign, possibly indicating increased future cardiovascular risk.

On the other hand, a recent retrospective cohort study within an integrated health care delivery system found that men older than 40 years with androgen deficiency who were ever prescribed any form of testosterone had a reduced risk of cardiovascular events (a composite end point of acute myocardial infarction, coronary revascularization, unstable angina, stroke, transient ischemic attack, and sudden cardiac death) over a median follow-up of 3.4 years. However, this was not a randomized trial, and benefit cannot be proven in observational studies. It may be that physicians prescribed testosterone to healthier men, or avoided prescribing testosterone in men with comorbidities. There is precedent for this with menopausal hormone therapy—dozens of observational studies seemed to show that hormones decreased cardiovascular risk, but the Women's Health Initiative, a definitive, long-term, federally-funded, randomized controlled trial, showed that hormone therapy actually increased cardiovascular risk.

The labeling of normal older men as "hypogonadal" and in need of hormone treatment closely parallels the social construction of menopause as a disease in the latter part of the 20th century. Estrogen manufacturers paid physicians to convince their peers that all menopausal women were in a state of hormonal deficiency. The concept that all menopausal women should take estrogen lasted for decades and was harmful to many patients. Hormone prescriptions plummeted after the Women's Health Initiative found that risks outweighed benefits in 2002, and breast cancer rates subsequently dropped in every country with a breast cancer registry.

True testosterone deficiency should be treated with testosterone. Klinefelter syndrome, pituitary or hypothalamic disease, hyperprolactinemia, or radiation exposure can cause incomplete sexual development, low-trauma fractures, infertility, and hot flashes. However, most patients on testosterone are being treated for normal symptoms of aging. Given that the diagnostics are questionable and the benefits are unconvincing, the risks of testosterone, some of which may be life-threatening, are not worth taking.

Male infertility

Causes of **infertility in men** can be explained by deficiencies in sperm formation, concentration, or transportation. This general division allows an appropriate workup of potential underlying causes of infertility and helps define a course of action for treatment.

The initial step in the evaluation of an infertile male is to obtain a thorough medical and urologic history. Such a history should include consideration of the following:

1. Duration of infertility;

2. Previous fertility in the patient and the partner;

3. Timing of puberty (early, normal, or delayed);

4. Childhood urologic disorders or surgical procedures;

5. Current or recent acute or chronic medical illnesses;

6. Sexual history;

7. Testicular cancer and its treatment;

8. Social history (eg, smoking and alcohol use);

9. Medications;

10. Family history;

11. Respiratory disease;

12. Environmental or occupational exposure;

13. Spinal cord injury.

The physical examination should include a thorough inspection of the following:

1. Testicles (for bilateral presence, size, consistency, symmetry);

2. Epididymis (for presence bilaterally, as well as any induration, cystic changes, enlargement, tenderness);

3. Vas deferens (for presence bilaterally, defects, segmental dysplasia, induration, nodularity, swelling);

understanding of all-cause adverse effects.

Studies of testosterone and cardiovascular risk have received attention recently. One trial found that in a subset of 170 men (mean age of 71.2 years; one-half with severe atherosclerosis), testosterone treatment significantly increased noncalcified plaque volume over a year compared with placebo, as measured by coronary computed tomographic angiography. This is not a good sign, possibly indicating increased future cardiovascular risk.

On the other hand, a recent retrospective cohort study within an integrated health care delivery system found that men older than 40 years with androgen deficiency who were ever prescribed any form of testosterone had a reduced risk of cardiovascular events (a composite end point of acute myocardial infarction, coronary revascularization, unstable angina, stroke, transient ischemic attack, and sudden cardiac death) over a median follow-up of 3.4 years. However, this was not a randomized trial, and benefit cannot be proven in observational studies. It may be that physicians prescribed testosterone to healthier men, or avoided prescribing testosterone in men with comorbidities. There is precedent for this with menopausal hormone therapy—dozens of observational studies seemed to show that hormones decreased cardiovascular risk, but the Women's Health Initiative, a definitive, long-term, federally-funded, randomized controlled trial, showed that hormone therapy actually increased cardiovascular risk.

The labeling of normal older men as "hypogonadal" and in need of hormone treatment closely parallels the social construction of menopause as a disease in the latter part of the 20th century. Estrogen manufacturers paid physicians to convince their peers that all menopausal women were in a state of hormonal deficiency. The concept that all menopausal women should take estrogen lasted for decades and was harmful to many patients. Hormone prescriptions plummeted after the Women's Health Initiative found that risks outweighed benefits in 2002, and breast cancer rates subsequently dropped in every country with a breast cancer registry.

True testosterone deficiency should be treated with testosterone. Klinefelter syndrome, pituitary or hypothalamic disease, hyperprolactinemia, or radiation exposure can cause incomplete sexual development, low-trauma fractures, infertility, and hot flashes. However, most patients on testosterone are being treated for normal symptoms of aging. Given that the diagnostics are questionable and the benefits are unconvincing, the risks of testosterone, some of which may be life-threatening, are not worth taking.

Male infertility

Causes of **infertility in men** can be explained by deficiencies in sperm formation, concentration, or transportation. This general division allows an appropriate workup of potential underlying causes of infertility and helps define a course of action for treatment.

The initial step in the evaluation of an infertile male is to obtain a thorough medical and urologic history. Such a history should include consideration of the following:

1. Duration of infertility;
2. Previous fertility in the patient and the partner;
3. Timing of puberty (early, normal, or delayed);
4. Childhood urologic disorders or surgical procedures;
5. Current or recent acute or chronic medical illnesses;
6. Sexual history;
7. Testicular cancer and its treatment;
8. Social history (eg, smoking and alcohol use);
9. Medications;
10. Family history;
11. Respiratory disease;
12. Environmental or occupational exposure;
13. Spinal cord injury.

The physical examination should include a thorough inspection of the following:

1. Testicles (for bilateral presence, size, consistency, symmetry);
2. Epididymis (for presence bilaterally, as well as any induration, cystic changes, enlargement, tenderness);
3. Vas deferens (for presence bilaterally, defects, segmental dysplasia, induration, nodularity, swelling);

4. Spermatic cord (for varicocele);

5. Penis (for anatomic abnormalities, strictures, or plaques);

6. Rectum (for abnormalities of the prostate or seminal vesicles);

7. Body habitus.

Depending on the findings from the history, detailed examination of other body functions may also be warranted.

Diagnostics

The semen analysis is the cornerstone of the male infertility workup and includes assessment of the following:

1. Semen volume (normal, 1.5-5 mL);

2. Semen quality;

3. Sperm density (normal, >15 million sperm/mL);

4. Total sperm motility (normal, >40% of sperm having normal movement);

5. Sperm morphology (sample lower limit for percentage of normal sperm is 4%);

6. Signs of infection – An increased number of white blood cells (WBCs) in the semen may be observed in patients with infectious or inflammatory processes;

7. Other variables (eg, levels of zinc, citric acid, acid phosphatase, or alpha-glucosidase);

8. Other laboratory tests that may be helpful include the following:

9. Antisperm antibody test;

10. Hormonal analysis (FSH, LH, TSH, testosterone, prolactin);

11. Genetic testing (karyotype, CFTR, AZF deletions if severe oligospermia (<5 million sperm/mL).

Imaging studies employed in this setting may include the following:

1. Transrectal ultrasonography;

2. Scrotal ultrasonography;

3. Vasography.

An abnormal postcoital test result is observed in 10% of infertile couples. Indications for performing a postcoital test include semen hyperviscosity, increased or decreased semen volume with good sperm density, or unexplained infertility.

If the test result is normal, consider sperm function tests, such as the following:

1. Capacitation assay;
2. Acrosome reaction assay;
3. Sperm penetration assay;
4. Hypoosmotic swelling test;
5. Inhibin B level;
6. Vitality stains.

Testicular biopsy is indicated in azoospermic men with a normal-sized testis and normal findings on hormonal studies to evaluate for ductal obstruction, to further evaluate idiopathic infertility, and to retrieve sperm.

Treatment

The following causes of infertility, if identified, can often be treated by medical means:

1. Endocrinopathies;
2. Antisperm antibodies;
3. Retrograde ejaculation;
4. Poor semen quality or number;
5. Lifestyle issues;
6. Infections.

Surgical interventions to be considered include the following:

1. Varicocelectomy;
2. Vasovasostomy or vasoepididymostomy;
3. Transurethral resection of the ejaculatory ducts;
4. Sperm retrieval techniques;
5. Electrocjaculation;
6. Artificial insemination;

7. Assisted reproduction techniques;

8. In vitro fertilization;

9. Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT);

10. Intracytoplasmic sperm injection.

Infertility is defined as the inability to achieve pregnancy after one year of unprotected intercourse. An estimated 15% of couples meet this criterion and are considered infertile, with approximately 35% due to female factors alone, 30% due to male factors alone, 20% due to a combination of female and male factors, and 15% unexplained. Conditions of the male that affect fertility are still generally underdiagnosed and undertreated.

Causes of infertility in men can be categorized as obstructive or nonobstructive. Infertile men may have deficiencies in sperm formation, concentration (eg, oligospermia [too few sperm], azoospermia [no sperm in the ejaculate]), or transportation. This general division allows an appropriate workup of potential underlying causes of infertility and helps define a course of action for treatment.

The initial evaluation of the male patient should be rapid, noninvasive, and cost-effective, as nearly 70% of conditions that cause infertility in men can be diagnosed with history, physical examination, and hormonal and semen analysis alone. More detailed, expensive, and invasive studies can then be ordered if necessary.

Treatment options are based on the underlying etiology and range from optimizing semen production and transportation with medical therapy or surgical procedures to complex assisted reproduction techniques. Technological advancements have made conceiving a child possible with as little as one viable sperm and one egg. Although the workup was traditionally delayed until a couple was unable to conceive for 12 months, evaluation may be initiated at the first visit in slightly older couples.

Male hypogonadism

Morbidity for men and women with hypogonadism includes infertility and an increased risk of osteoporosis; there is no increase in mortality.

Hypogonadotropic hypogonadism (see the image below) is one of several types of hypogonadism.

Considerations in the evaluation of males with hypogonadism include the following:

1. Developmental anomalies associated with the genital system (eg, hypospadias, micropenis, and cryptorchidism);

2. For postpubertal males, the rate of beard growth, libido and sexual function, muscle strength, and energy levels;

3. Possible causes of acquired testicular failure (eg, mumps orchitis, trauma, radiation exposure of the head or testes, and chemotherapy).

Drugs that may interrupt testicular function - Including agents that interfere with testosterone synthesis, such as spironolactone and cyproterone. Agents such as cortisol, marijuana, heroin, and methadone may interfere with gonadotropin secretion.

Considerations in the evaluation of females with hypogonadism include the following:

1. Signs associated with Turner syndrome (eg, lymphedema, cardiac or renal congenital anomalies, and short growth pattern);

2. Age of menarche.

Physical examination

Considerations in the physical examination of males with hypogonadism include the following:

1. Evaluation of the testes: This is the most important feature of the physical examination; determine whether both testes are palpable, their position in the scrotum, and their consistency; testes size can be quantitated by comparison with testicular models (orchidometer), or their length and width may be measured;

2. Examination of the genitalia for hypospadias;

3. Examination of the scrotum to see if it is completely fused;

4. Evaluation of the extent of virilization;

5. Staging of puberty: Use the Tanner criteria for genitalia, pubic hair, and axillary hair;

6. Examination for signs of Klinefelter syndrome (eg, tall stature, especially if the legs are disproportionately long, gynecomastia, small or soft testes, and a eunuchoid body habitus).

Considerations in the physical examination of females with hypogonadism include the following:

1. Examination of the genitalia is important;

2. Determination of the extent of androgenization: May be adrenal or ovarian in origin and is demonstrated in pubic and axillary hair;

3. Determination of the extent of estrogenization: As evidenced by breast development and maturation of the vaginal mucosa;

4. Examination for signs of Turner syndrome (eg, short stature, webbing of the neck [such as pterygium colli], a highly arched palate, short fourth metacarpals, widely spaced nipples, or multiple pigmented nevi).

Diagnostics

The following studies may be indicated in males with hypogonadism:

1. Follicle-stimulating hormone (FSH) levels;

2. Luteinizing hormone (LH) levels;

3. Prolactin levels;

4. Testosterone levels;

5. Thyroid function;

6. Seminal fluid examination;

7. Karyotyping;

8. Testicular biopsy.

For males after puberty, the Guidelines of the Endocrine Society require that the diagnosis of hypogonadism be based on symptoms and signs of hypogonadism plus the presence of a low testosterone level measured on at least 2 occasions.

Additional tests in the evaluation of patients with hypogonadism include the following:

Adrenocorticotropic hormone (ACTH) stimulation testing: In patients in whom a form of congenital adrenal hyperplasia is suspected, adrenal steroid synthesis is best evaluated by performing a cosyntropin (ACTH 1-24) stimulation test

Luteinizing-hormone releasing hormone (LHRH) stimulation testing: To distinguish between true hypogonadotropic hypogonadism and constitutional delay in growth and maturation

Testicular tissue testing: If the testes are not palpable and if it is not certain whether any testicular tissue is present, administering human chorionic gonadotropin (hCG) and measuring testosterone response may be helpful

Treatment

Hormonal replacement. The simplest and most successful treatment for males and females with either hypergonadotropic or hypogonadotropic hypogonadism is replacement of sex steroids, but the therapy does not confer fertility or, in men, stimulate testicular growth.

When fertility is desired, an alternative therapy for men with hypogonadotropic hypogonadism is administration of pulsatile LHRH or injections of hCG and FSH. (In patients with hypergonadotropic hypogonadism, fertility is not possible.)

In a 6-year European study of men being treated for hypogonadism, long-term transdermal testosterone treatment did not increase prostate-specific antigen (PSA) levels or influence prostate cancer risk.

Investigators used data from a 5-year, open-label extension of a 1-year trial of a transdermal testosterone patch (Testopatch) in men with hypogonadism. Study subjects wore two 60 cm2 patches, each of which delivered 2.4 mg of testosterone per day. More than 90% of patients had PSA concentrations below 2 ng/mL during the 6-year study, and no prostate cancer was found in patients over the course of the trial.

Hypogonadism manifests differently in males and in females before and after the onset of puberty. If onset is in prepubertal males and testosterone replacement is not instituted, the individual has features of eunuchoidism, which include sparse body hair, poor development of skeletal muscles, and delay in epiphyseal closure, resulting in long arms and legs. When hypogonadism occurs in postpubertal males, lack of energy and decreased sexual function are the usual concerns. In females with hypogonadism before puberty, failure to progress through puberty or primary amenorrhea is the most common presenting feature. When hypogonadism occurs in postpubertal females, secondary amenorrhea is the usual concern.

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Conclusion

In conclusion, we would like to note that there is always something to work on: medical information is updated almost every day. Confirmation of this - daily published original articles, manuals, and recommendations.

These treatment regimens are taken from the guidelines and recommendations of the European Association of Urology, published in recent years, in connection with this, we present the data from the textbook as meeting the criteria of evidence-based medicine.

In this textbook, we tried to reflect the most important points in the diagnosis and treatment of diseases of the genitourinary system, which would be of interest to students and practitioners and young professionals.

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