**МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ**
**Харківський національний медичний університет**

# MODULE 1
# SUBSTANTIAL MODULE 6
# THEME 17
# URUNARY TRACT INFECTIONS IN CHILDREN

***Practical policies for students***

# МОДУЛЬ 1
# ЗМІСТОВИЙ МОДУЛЬ 6
# ТЕМА 17
# ІНФЕКЦІЇ СЕЧОВИХ ШЛЯХІВ У ДІТЕЙ

***Методичні вказівки для студентів***

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Urinary tract infection (UTI) is one of the most common pediatric infections and represents the most common bacterial infection in children under 2 years of age. Urinary tract infection (UTI) is defined as the presence of bacteria in urine along with symptoms of infection. UTIs occur in as many as 5 percent of girls and 1 to 2 percent of boys. The incidence of UTIs varies depending on age and sex. In the first 3 months of life, UTIs were present in 7.5% of girls, 2.4% of circumcised boys, and 20.1% of uncircumcised boys, who presented with fever (Shaikh N, Morone NE, Bost JE, Farrell MH, 2008)[1]. In the first year of life, UTIs are more common in boys (3.7%) than in girls (2%). Later, the incidence changes and ~3% of pre-pubertal girls and 1% of pre-pubertal boys are diagnosed with UTIs [2]. In studies by Hoberman et al (1993), the prevalence of febrile UTIs in white infants exceeded that in black infants [3]. These investigators found that among white female infants younger than 1 year who had a temperature of 39°C or more and were seen in an emergency department, 17% had UTI.

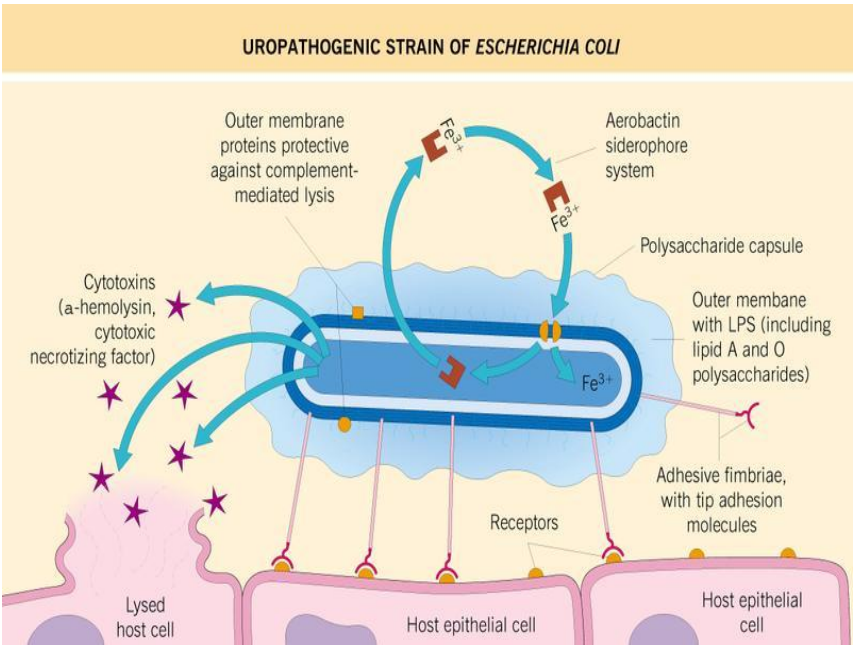
Pyelonephritis (upper UTI) and cystitis (lower UTI) are two broad clinical categories of UTI. Lower UTI (cystitis) is an inflammatory condition of the urinary bladder and characterized by voiding-related symptoms. Pyelonephritis is a bacterial inflammation of the renal pelvis and tubular-interstitial tissue of the kidney and characterized by symptoms of intoxication, pain with or without voiding-related symptoms. Pyelonephritis takes up a leading place in a structure of renal pathology, often has undulation course, connected with exacerbation of disease due to various provocative factors contributing to its gradual progress, followed by the future damage of vascular system of kidney with chronic ischemia which is the main cause of progressive kidney deficiency. Chronic or recurrent pyelonephritis results in renal damage, scarring, and chronic renal failure (end-stage renal disease). Early recognition and prompt treatment of UTIs is important to prevent late complications, such as renal scarring, hypertension, and renal failure.

## Etiology and Pathogenesis

Bacterial infections are the most common cause of UTI, with E. coli being the most frequent pathogen, causing 75–90% of UTIs. There are some features of E. coli virulence (*picture 1*).

Other bacterial sources of UTI include the following:

- Klebsiella species
- Proteus species
- Enterococcus species
- Staphylococcus saprophyticus, especially among female adolescents and sexually active females
- Streptococcus group B, especially among neonates
- Pseudomonas aeruginosa




**Picture 1**

Fungi (Candida species) may also cause UTIs, especially after instrumentation of the urinary tract. Adenovirus is a rare cause of UTI and may cause hemorrhagic cystitis.

E. coli is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial. In the latter, Klebsiella pneumoniae, Enterobacter spp., Enterococcus spp., Pseudomonas spp. and Candida spp. are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia in around 12% (8), however, it is less frequent in community-acquired than in nosocomial UTI.

## Pathophysiology

### Routes of contagion

### Ascending route (the most common)

Fecal flora ascends through the urethra to the urinary bladder and leads to cystitis. If pyelonephritis occurs, this means that organisms have ascended the ureters by vesicoureteric reflux (retrograde flow of urine from bladder up the ureters). The most common organisms are E.Coli, Klebsiella species, Proteus species, Enterococcus species, Staphylococcus faecalis, Pseudomonas aeruginosa.

### Hematogenous route (common in the neonatal period)

Organisms are blood borne to the kidney from GIT, respiratory tract, osteomyelitis or skin infection. In addition to Gram negative organisms, Gram positive as Staphylococcus aureus and Streptococcus viridans may cause the infection.

### Other routes (rare)

By lymphatics or direct spread from perinephric abscess.

Typically, UTIs develop when uropathogens that have colonized the periurethral area ascend to the bladder via the urethra. From the bladder, pathogens can spread up the urinary tract to the kidneys (pyelonephritis) and possibly to the bloodstream (bacteremia). Poor containment of infection, including bacteremia, is more often seen in infants younger than 2 months.

Urine in the proximal urethra and urinary bladder is normally sterile. Entry of bacteria into the urinary bladder can result from turbulent flow during normal voiding, voiding dysfunction, or catheterization. In addition, sexual intercourse or genital manipulation may foster the entry of bacteria into the urinary bladder. More rarely, the urinary tract may be colonized during systemic bacteremia (sepsis); this usually happens in infancy. Pathogens can also infect the urinary tract through direct spread via the fecal-perineal-urethral route.

### Genetic factors of UTIs

Deregulation of candidate genes may predispose patients to recurrent UTIs. The identification of a genetic component may allow the identification of at-risk individuals and, therefore, prediction of the risk of recurrent UTI in their offspring. Genes that are possibly responsible for susceptibility to recurrent UTIs include HSPA1B, CXCR1, CXCR2, TLR2, TLR4, and TGFβ1.

### Risk factors of UTIs

These include: Susceptibility to UTI may be increased by any of the following factors:

- Structural renal abnormalities
- Calculi and urinary tract catheterisation
- Stents or drainage procedures
- Pregnancy
- Diabetes
- Primary biliary cirrhosis
- Immunocompromised patients
- Alteration of the periurethral flora by antibiotic therapy
- Bowel (constipation) and bladder dysfunction (neuropathic bladder)

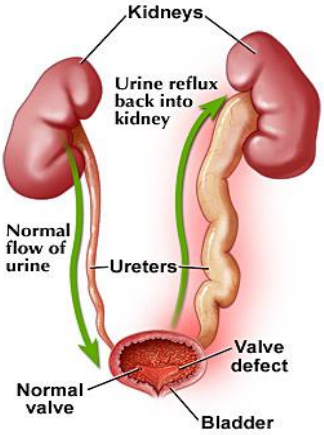
Children who receive antibiotics (eg, amoxicillin, cephalexin) for other infections are at increased risk for UTI. These agents may alter gastrointestinal

and periurethral flora, disturbing the urinary tract's natural defense against colonization by pathogenic bacteria.

Prolonged retention of urine may permit incubation of bacteria in the bladder. Voiding dysfunction is not usually encountered in a child without neurogenic or anatomic abnormality of the bladder until the child is in the process of achieving daytime urinary control.

A child with uninhibited detrusor contractions may attempt to prevent incontinence during a detrusor contraction by increasing outlet resistance. This may be achieved by using various posturing maneuvers, such as tightening of the pelvic-floor muscles, applying direct pressure to the urethra with the hands, or performing the Vincent curtsy, which consists squatting on the floor and pressing the heel of one foot against the urethra. As a result, bacteria-laden urine in the distal urethra may be milked back into the urinary bladder (urethrovesical reflux).

Constipation, with the rectum chronically dilated by feces, is an important cause of voiding dysfunction. Neurogenic or anatomic abnormalities of the urinary bladder may also cause voiding dysfunction.




**Picture 2**

Voiding dysfunction should be evaluated and managed appropriately. Surgical correction of underlying anatomic disorders may be indicated in select cases. Vesicoureteric reflux (VUR), or the retrograde flow of urine from the bladder into the ureter (*picture 2*), is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension, and renal failure. Fortunately, patients with VUR present within a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention. VUR is a very common urological anomaly in children, with an incidence of nearly 1%.

For male infants, neonatal circumcision substantially decreases the risk of UTI. Schoen et al found that during the first year of life, the rate of UTI was 2.15% in uncircumcised boys, versus 0.22% in circumcised boys. Risk is particularly high during the first 3 months of life; Schaikh et al reported that in febrile boys younger than 3 months, UTI was present in 2.4% of circumcised boys and in 20.1% of uncircumcised boys.

### Classification

According to Guidelines on Paediatric Urology (March 2013) [4] there are five widely used classification systems according to the site, episode, severity,

symptoms and complicating factors. For acute treatment, site and severity are most important.

### Classification according to site

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder with general signs and symptoms including dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (>38°C), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

### Classification according to episode

**First infection:** the first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage. Anatomical evaluation is recommended (see below).

**Recurrent infection** can be divided into unresolved and persistent infection. In **unresolved infection**, initial therapy is inadequate for elimination of bacterial growth in the urinary tract [inadequate therapy, inadequate antimicrobial urinary concentration (poor renal concentration/gastrointestinal malabsorption), and infection involving multiple organisms with differing antimicrobial susceptibilities]. **Persistent infection** is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae in papillary necrosis, urachal cyst, urethral diverticulum, periurethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas).

The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

**Reinfection:** each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is E. coli, which occurs in many different serotypes. Therefore, recurrent E. coli UTI does not equate to infection with the same organism.

### Classification according to severity

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI.

In severe UTI, infection is related to the presence of fever of >39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

### Classification according to symptoms

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response.

In symptomatic bacteriuria, symptoms associated with UTI include irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

### Classification according to complicating factors

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal urinary tract. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of their bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract.

In complicated UTI, all neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent from their location. Functional obstruction often results from lower urinary tract dysfunction of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux. Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary

### History

The history and clinical course of a UTI vary with the patient's age and the specific diagnosis. No one specific sign or symptom can be used to identify UTI in infants and children.

Combinations of findings, including a prior history of UTI, circumcision in boys, and, in older children, typical symptoms such as frequency, abdominal or suprapubic discomfort, and dysuria, should be taken into account when making a decision to evaluate for UTI. Guidelines from the American Academy of Pediatrics recommend considering the diagnosis of UTI in patients aged 2 months to 2 years with unexplained fever.

When UTI is diagnosed in a child, an attempt should be made to identify any risk factors for the UTI. These include recent broad-spectrum antibiotic therapy, an anatomic anomaly, voiding dysfunction, and constipation.

### Signs and Symptoms of Urinary Tract Infection in Children

• Syndrome of intoxication – fever, malaise, anorexia, growth failure.

• Painful syndrome – pains in abdomen or lumbar region (palpation of abdomen, positive Pasternatskiy symptom – jerk on lumbar region).

• Syndrome of disuria – frequent and painful micturitions, incontinence.

### Urinary tract signs and symptoms

Dysuria
Frequency
Dribbling/hesitancy
Enuresis after successful toilet training
Malodorous urine
Hematuria
Squatting
Abdominal/suprapubic pain

### Systemic signs and symptoms

Fever
Vomiting/diarrhea
Flank/back pain

### Children aged 0–2 months

Neonates and infants up to age 2 months who have pyelonephritis usually do not have symptoms localized to the urinary tract. UTI is discovered as part of an evaluation for neonatal sepsis.

Neonates with UTI may display the following symptoms:

- Jaundice
- Fever
- Failure to thrive
- Poor feeding
- Vomiting
- Irritability

### Infants and children aged 2 months to 2 years

The febrile infant or child who has no other site of infection to explain the fever, even in the absence of systemic symptoms, should be assessed for the likelihood of pyelonephritis (upper UTI). Most episodes of UTI during the first year of life are pyelonephritis.

Febrile infants younger than 2 months constitute an important subset of children who may present with fever without a localizing source. The workup of fever in these infants should always include evaluation for UTI.

Infants with UTI may display the following symptoms:

- Poor feeding
- Fever
- Vomiting
- Strong-smelling urine
- Abdominal pain
- Irritability

As with young infants, the majority of infants and young children in this age range who have pyelonephritis also lack symptoms localized to the urinary tract. However, some children aged 1-2 years may present with voiding symptoms suggestive of cystitis, with crying on urination or only a foul odor to the urine in the absence of clinically significant fever (temperature <38°C).

Infants and young children of this age may also have only a history of unexplained fever (ie, rectal or tympanic membrane temperature of >38°C). Some infants with pyelonephritis in this age range have fever and few other symptoms, whereas others are acutely ill and have a history of irritability, decreased oral intake, abdominal pain, vomiting, and loose bowel movements. Patients in this age group are at higher risk for renal injury than are older children, possibly because the lack of localizing signs of infection delays the start of antibiotic therapy.

### Children aged 2–6 years

Preschoolers with UTI can display the following symptoms:

- Vomiting
- Abdominal pain
- Fever
- Strong-smelling urine
- Enuresis
- Urinary symptoms (dysuria, urgency, frequency)

Children in this age group with febrile UTI (pyelonephritis) usually have systemic symptoms with loss of appetite, irritability, and abdominal, flank, or back pain. Voiding symptoms may be present or absent.

Children with acute cystitis have voiding symptoms with little or no temperature elevation. Voiding dysfunction may include urgency, frequency, hesitancy, dysuria, or urinary incontinence. Suprapubic or abdominal pain may be present, and the urine sometimes has a strong or foul odor.

### Children older than 6 years and adolescents

School-aged children with UTI can display the following symptoms:

- Fever
- Vomiting, abdominal pain
- Flank/back pain
- Strong-smelling urine
- Urinary symptoms (dysuria, urgency, frequency)
- Enuresis
- Incontinence

Adolescents are more likely to present with typical urinary symptoms (eg, dysuria, urgency, frequency). Adolescent girls with vaginitis or a sexually transmitted infection (STI) may present with similar symptoms. In addition, adolescent girls who are diagnosed with cystitis may have a concurrent vaginitis or STI.

UTI among children in this age range usually affects the lower tract, but pyelonephritis also occurs. Symptoms are similar to those in children aged 2–6 years.

Girls who have pyelonephritis in infancy or early childhood, including those with persistence of vesicoureteral reflux (VUR), usually have cystitis with UTI when they are older. They are also prone to have a recurrence during pregnancy.

### Physical Examination

Infants and younger children with pyelonephritis usually have no localizing findings, but they are febrile and often irritable. Older children with pyelonephritis often have tenderness of the flank or costovertebral angle (Pasternatskiy's symptom), and those with cystitis may have suprapubic tenderness. Hypertension should raise suspicion of hydronephrosis or renal parenchyma disease.

Physical examination findings in pediatric patients with UTI can be summarized as follows:

- Costovertebral angle tenderness
- Abdominal tenderness to palpation
- Suprapubic tenderness to palpation
- Palpable bladder
- Dribbling, poor stream, or straining to void

Examine the external genitalia for signs of irritation, pinworms, vaginitis, trauma, or sexual abuse.

### Laboratory Studies

#### Urinalysis

Urine must be collected with proper technique to be useful for diagnosing cystitis or pyelonephritis. Suprapubic bladder aspiration should be performed in uncircumcised male patients in whom the urethral meatus is not visible, as well

as in infants with periurethral irritation. Bladder catheterization is the appropriate technique for obtaining a urine sample in most infants and young children. A clean-catch, midstream urine sample may be obtained in children who can cooperate and void on request. A specimen collected by using sterile bag may be used for urinalysis but not urine culture.

There are three methods that are commonly used for urinalysis:

1. Dipsticks.

These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria requires approximately 4 h in the bladder. However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) [5].

A urine specimen that is positive for nitrite, leukocyte esterase, or blood may indicate UTI.

2. Microscopy.

This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of 5 white blood cells (WBCs) per high-power field (25 WBC/μL). In uncentrifuged urine, >10 WBC/μL has been demonstrated to be sensitive for UTI and this could perform well in clinical situations. Microscopic examination of an unspun sample that contains more than 10 WBCs per high-powered field or any bacteria is highly predictive of a positive urine culture. RBC or WBC casts suggest underlying renal parenchymal disease. Epithelial cells suggest skin contamination. A normal result from urinalysis does not exclude pyelonephritis.

3. Flow imaging analysis technology.

This is being used increasingly to classify particles in uncentrifuged urine specimens. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods.

### Urine culture

After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is recommended. It is unclear what represents a significant UTI. In severe UTI, $>10^5$ colony-forming units/mL (CFU/mL) can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [6]. The classical definition of $>10^5$ CFU/mL of voided urine is still used to define a significant UTI. The

recent American Academy of Pediatric Guidelines on Urinary tract İnfection suggest that the diagnosis should be on the basis of the presence of both pyuria and at least 50 000 CFU. However, some studies have shown that, in voided specimens, $<10^4$ organisms may indicate a significant UTI [7]. If urine is obtained by catheterisation, 1,000–50,000 CFU/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

**Criteria for UTI in children**
**(adapted from the EAU guideline on Urological Infections [8])**

Urine specimen from suprapubic bladder puncture – any number of CFU/mL (at least 10 identical colonies)
Urine specimen from bladder catheterization – >1,000–50,000 CFU/mL
Urine specimen from midstream void – $>10^4$ CFU/mL with symptoms
$>10^5$ CFU/mL without symptoms

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by Mycobacterium tuberculosis or Chlamydia trachomatis.

Urine cultures must be obtained in all children with suspected pyelonephritis. Treatment should not be commenced on the basis of urinalysis results, and normal urinalysis findings do no exclude an infection. Acute pyelonephritis may be present even if urine cultures demonstrate no growth.

A clean-catch urine specimen with more than 100,000 colony-forming units (CFUs) of a single organism is considered diagnostic of a UTI. Organisms, such as *Lactobacillus, Staphylococcus,* or *Corynebacterium* species may not be clinically relevant.

Cultures showing more than 100,000 CFUs of a single organism obtained by means of transurethral catheterization demonstrate is 95% sensitive and 99% specific for UTI. Specimens growing $10^4$ CFUs may be consistent with infection, but the test should be repeated if infection is not likely and if treatment has not yet commenced.

Cultures from bagged urine specimens are useful only if no growth is observed. Bagged urine specimens result in a false-positive rate of 85%. Before treatment is started on the basis of results from a bagged-specimen test, a catheterized or suprapubic specimen should be obtained.

Structural abnormalities of the urinary tract may be associated with infections secondary to multiple organisms or unusual gram-negative bacteria, such as *Pseudomonas aeruginosa.*

### Electrolyte measurements

Some patients may have abnormalities, which may be secondary to vomiting or diarrhea. In cases of recurrent or chronic infection, renal scarring may lead to renal failure.

Secondary pseudohypoaldosteronism may develop, with impaired renal tubular function, in infants with pyelonephritis. Mild hyponatremia and hyperkalemia may be present. Infants with underlying urinary-tract anomalies have an increased risk of this electrolyte imbalance, which resolves when the infection is treated.

**Renal function testing:** An increased BUN and/or creatinine level should raise the suspicion for hydronephrosis or renal parenchymal disease.

### Determination of inflammatory markers

An elevated WBC count is nonspecific and does not help in distinguishing lower UTI from upper UTI.

In the presence of a febrile UTI, a erythrocyte sedimentation rate (ESR) of more than 30 mm/h is highly predictive of acute pyelonephritis.

**C-reactive protein (CRP)** levels are correlated with parenchymal defects on dimercaptosuccinic acid (DMSA) scanning. Elevated CRP concentrations are sensitive but nonspecific markers of renal parenchymal involvement in the febrile infant and child with UTI. CRP values may be used to distinguish bladder colonization from acute pyelonephritis in a febrile child with bacteriuria and a neurogenic bladder.

### Serum procalcitonin

Procalcitonin is an acute inflammatory marker with a sensitivity of 70–95% and a specificity that approaches 90% for renal involvement compared with results of DMSA scan in infants and children with febrile UTI. Although less sensitive than CRP, procalcitonin is more specific for the diagnosis of acute pyelonephritis. Procalcitonin values are better correlated with long-term renal scarring than CRP.

Procalcitonin levels near 0.5 ng/mL may not consistently correlate with acute pyelonephritis. As procalcitonin levels increase, the severity of renal lesions on DMSA increases.

Higher levels of procalcitonin predict VUR in infants and children at the onset of pyelonephritis.

**Serum and urinary interleukin (IL)-6 and IL-8** are correlated with renal involvement in infants and children with UTI with high sensitivity (81–88%) and acceptable specificity (78–83%). These markers are not reliable in neonates with suspected acute pyelonephritis.

### Imaging Studies

Imaging is the basis of diagnosis and management of VUR. The standard imaging tests include renal and bladder ultrasonography (US), voiding cystourethrography **(**VCUG) and nuclear renal scans.

### Radiography

Radiographic studies are generally not indicated to diagnose acute pyelonephritis.

Studies may be indicated if the child's condition does not respond to treatment as expected and if colonization must be distinguished from infection in the patient with chronic bacteriuria.

Guidelines from the American Academy of Pediatrics recommend imaging after first febrile UTIs in infants and young children to identify abnormalities that may predispose them to recurrent infection or renal scarring [9].

### Renal ultrasonography

In children who have not had ultrasonography performed in the prenatal period, this study may be useful to exclude congenital malformations but is otherwise not useful in the evaluation of acute pyelonephritis.

This study is useful to determine the size and shape of the kidneys but is generally poor for visualizing nondilated ureters. Renal ultrasonography does not provide information regarding renal function.

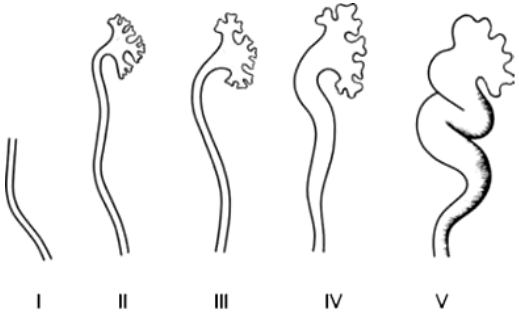
Renal ultrasonography has low sensitivity (50%) in detecting acute pyelonephritis, although focal abnormalities on ultrasonography, combined with a CRP level of more than 70 mg/L may be predictive of renal scarring.

Findings on power Doppler ultrasonography were recently correlated with DMSA findings of acute pyelonephritis.

Renal ultrasonography is useful in the diagnosis of urolithiasis, hydronephrosis, hydroureter, ureteroceles, and bladder distention.

### Voiding cystourethrography (VCUG)

The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [10, 11] (*Picture 3*).




**Picture 3.** Grading system for VUR on VCUG, according to the International Reflux Study Committee

VCUG is useful for visualizing the urethral and bladder anatomy and for the detecting VUR.

VCUG may be performed after 3–4 days of therapy to ensure that bladder irritability has resolved and that the urine is sterilized.

The voiding phase is needed to evaluate for VUR and posterior urethral valves.

Performance of VCUG after a first febrile UTI may be indicated if renal and bladder ultrasonography reveal hydronephrosis, scarring, obstructive uropathy, or masses or if complex medical conditions are associated with the UTI. Informed consent and preferences of the patient's parents or caregivers are considered.

Children who respond to treatment for a UTI but afterwards demonstrate an abnormal voiding pattern may need to undergo an evaluation for voiding dysfunction. This evaluation may include standard VCUG.

VCUG is also recommended after a second episode of febrile UTI. There is some concern, however, that without VCUG after the first documented febrile UTI, some cases of significant reflux disease will be missed.

**Grading system for VUR on VCUG, according to the International Reflux Study Committee [10]**

**Grade I** – Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation

**Grade II** – Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices

**Grade III** – Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices

**Grade IV** – Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible

**Grade V** – Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

### Nuclear cystography

This study is good for evaluating the bladder and detecting VUR. However, it does not permit adequate evaluation of the urethra and is therefore not used for an initial evaluation of the urologic anatomy.

Cystography has only about 1% of radiation dose of fluoroscopic study.

Cystography may be used for serial follow-up studies.

### Nuclear cortical scanning

Dimercaptosuccinic acid (DMSA) is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. DMSA is taken up by proximal renal tubular cells and is a good indicator of renal paren-

chyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. DMSA scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up. DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis. Children with a normal DMSA scan during acute UTI have a low risk of renal damage.

Nuclear cortical scanning depicts tubular damage and scarring. It provides information regarding the general size of the kidneys; however, it does not provide detailed information regarding the collecting system. DMSA scanning is not necessary to evaluate or follow up most episodes of acute pyelonephritis.

This study most frequently involves the use of technetium-99m DMSA to depict renal cortical scarring. The volume of initial defect is useful in predicting the development of renal scars.

Follow-up DMSA scans performed more than 6 months after acute pyelonephritis resolves are useful to detect permanent renal scarring. Studies performed less than 6 months after acute pyelonephritis may reveal residua of the original infection rather than permanent scars.

DMSA scans can help in determining the cause of fever in children with chronic bacteriuria, such as patients with spinal-cord injury and those who undergo clean intermittent catheterization.

In a recent meta-analysis of DMSA literature by region, the incidence of renal scarring following acute pyelonephritis varied by region, from 26.5% in Australia to 49% in Asia. In terms of renal units, the incidence of acquired renal cortical scarring varied by region, from 16.7% in the Middle East to 58.4% in Asia. When combined by VUR status, children and renal units with refluxing ureters exhibited an increased risk of renal scarring (odds ratios 2.8 and 3.7, respectively).

DMSA as a sensitivity of more than 90% in detecting changes that are suggestive of acute pyelonephritis.

Radiation exposure to the patient undergoing this procedure is low.

**MRI**

Gadolinium-enhanced MRIs are correlated with DMSA scans in detecting renal parenchymal defects and is effective in distinguishing acute inflammation from scars.

MRI is superior to nuclear scintigraphy in distinguishing acute inflammation from chronic scars.

MR cystography may be useful in evaluating VUR.

Sedation is generally required.

### CT

Enhanced CT may be useful in distinguishing acute pyelonephritis from other causes of fever.

Increased radiation exposure makes CT a less favorable study in children, especially because ultrasonography is generally adequate in defining the anatomic structure.

## Management of UTIs

### General principles of upper UTIs treatment

The aims of treatment are to:

- Eliminate symptoms and eradicate bacteriuria
- Prevent renal scarring
- Prevent recurrent UTIs
- Correct any associated urological lesions

Bed rest is indicated during the fever period and 3–4 days more.

In acute period it is expedient to give milk-vegetable diet with moderate limitation of protein (1,5–2 g/kg) and salt (to 2–3 g). Diet limitations depend on salt in the urine sediment, its acidity.

Good fluid intake to increase urine flow and decrease in intoxication and perspiration's loss. Daily quantity of liquid 1,5 times exceeds the age requirements.

Children with a high risk of serious illness and/or aged younger than 3 months should be referred immediately to secondary care.

Do not delay treatment if the sample cannot be obtained and the infant or child is at high risk of serious illness.

Carefully assess the degree of toxicity, dehydration and ability to maintain oral fluid intake. Encourage fluids, avoid or correct constipation, and encourage full voiding.

Initial antibiotic therapy should be based on age, clinical severity, location of infection, presence of structural abnormalities, and allergy to certain antibiotics. Treatment generally begins with a broad-spectrum antibiotic, but it may need to be changed based on the results of urine culture and sensitivity testing.

Hospitalization is suggested for symptomatic young infants (less than three months of age) and all children with clinical evidence of acute severe pyelonephritis (high fever, toxic appearance, severe flank pain).

### Administration route

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged <2 months, parenteral antibiotic therapy is recommended. Electrolyte disorders with hyponatremia and hyperkalaemia can occur in these cases.

Combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or respectively a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporines against common uropathogens; enterococcus gap is closed with Ampillicin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective [12, 13].

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity testing of the isolated uropathogen [14]. Especially in infancy, not all available antibiotics are approved by the national health authorities. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI.

### Duration of therapy

Adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (1-3 days) are inferior to those of 7–14-day courses. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA (dimercaptosuccinic acid) scan. Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual 2–4 days intravenous therapy followed by oral treatment. Similar data have been shown for amoxicillin-clavulanate, however, these antibiotics are associated with increasing rates of resistance. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised.

In complicated UTI, uropathogens other than E. coli, such as Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, enterococci and staphylococci, are more often to be anticipated. Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubic cystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy.

Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially vesicorenal reflux or urinary obstruction (megaureter). Prolonged intravenous antibiotic treatment is sufficient in most

cases, and intravenous and oral therapy tailored to the pathogen identified in culture is recommended.

**Antimicrobial agents** for treatment of urinary tract infections in infants and children are reproduced in *table 1*.

**Table 1** – Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children

| Chemotherapeutics | Daily dosage | Application |
|---|---|---|
| Parenteral cephalosporins | | |
| Group 3a, e.g. cefotaxime | 100–200 mg/kg<br>(Adolesc.: 3–6 g) | i.v. in 2-3 D |
| Group 3b, e.g. ceftazidime | 100–150 mg/kg<br>(Adolesc.: 2–6 g) | i.v. in 2-3 D |
| Ceftriaxone | 75 mg/kg | i.v. in 1 D |
| Oral cephalosporins | | |
| Group 3, e.g. ceftibuten | 9 mg/kg<br>(Adolesc.: 0,4 g) | p.o. in 1-2 D |
| Group 3, e.g. cefixime | 8–12 mg/kg<br>(Adolesc.: 0,4 g) | p.o. in 1–2 D |
| Group 2, e.g. cefpodoxime proxetil | 8–10 mg/kg<br>(Adolesc.: 0,4 g) | p.o. in 1–2 D |
| Group 2, e.g. cefuroximaxetil | 20–30 mg/kg<br>(Adolesc.: 0,5–1 g) | p.o. in 2D |
| Group 1, e.g. cefaclor | 50–100 mg/kg<br>(Adolesc.: 1,5–4 g) | p.o. in 3 D<br>p.o. in 2–3 D |
| Trimethoprim or<br>Trimethoprim/sulfamethoxazole | 5–6 mg/kg<br>5–6 mg/kg (TMP-Anteil)<br>(Adolesc.: 320 mg) | p.o. in 2 D<br>p.o. in 2 D |
| Ampicillin<br>Ampicillin and Amoxicillin are not eligible for calculated therapy | 100-200 mg/kgKG<br>(Adolesc.: 3-6 g) | i.v. in 3 D<br>i.v. in 3–4 D |
| Amoxicillin | 50–100 mg/kg<br>(Adolesc.: 1,5–6 g) | p.o. in 2–3 D[1]<br>p.o. in 2–3 D |
| Amoxicillin/clavulanic acid<br>(parenteral) | 60–100 mg/kg<br>(Adolesc.: 3,6–6,6 g) | i.v. in 3 D<br>i.v. in 3 D |
| Amoxicillin/clavulanic acid (oral) | 45–60 mg/kg<br>(Amoxicillin-fraction)<br>(Adolesc.: 1500 + 375 mg) | p.o. in 3 D<br>p.o.in 3 D |
| Piperacillin | 300 mg/kg | i.v. in 3-4 D |
| Tobramycin (Drug monitoring) | 5 mg/kg<br>(Adolesc.: 3–5 mg/kg, max. 0,4 g) | i.v. in 1 D |
| Gentamicin | 5 mg/kg<br>(Adolesc.: 3–5 mg/kg, max. 0,4 g) | i.v. in 1 D |

| Chemotherapeutics | Daily dosage | Application |
|---|---|---|
| Ciprofloxacin<br>Approved in most<br>European countries<br>as second- or third<br>line medication for<br>complicated UTIs,<br>„reserve-antibiotic“! | Children and adolesc.<br>(1–17 years of age):<br>20–30 mg/kg (max. D:<br>400 mg) (parenterally)<br>Children and adolesc.<br>(1–7 years of age):<br>20–40 mg/kg<br>(max. D 750 mg) (orally) | i.v. in 3 D<br><br><br><br>p.o. in 2 D |
| Nitrofurantoin<br>Contraindicated in the case of<br>renal insufficiency | 3–5 mg | p.o. in 2 D |

[1] – Infants 2 D, children 1–12 ys. 3 D.

Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection (by the European Association of Urology, 2009) are in the table 2.

**Table 2** – Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection (by the European Association of Urology, 2009)

| Diagnosis | Proposal | Application | Duration of therapy |
|---|---|---|---|
| Pyelonephritis during the first 0–6 months of life | Ceftazidime + Ampicillin or Aminoglycoside + Ampicillin | 3–7 days parenterally, for at least 2 days after defervescence, then oral therapy<br>In newborns: parenteral therapy for 7-14 days, then oral therapy | 10 (–14) days<br>Newborns 14–21 days |
| Uncomplicated pyelonephritis after 6 months of age | Cephalosporin group 3 | Orally (initially parenterally, if necessary) | (7–)10 days |
| Complicated pyelonephritis/ urosepsis (all ages) | Ceftazidime + Ampicillin or Aminoglycoside +Ampicillin | 7 days parenterally, then oral therapy | 10–14 days |

The choice of antibiotic should be determined by local guidelines. The antitbiotic may need to be adjusted according to the MSU results.

With successful treatment, urine usually becomes sterile after 24 h, and leukocyturia normally disappears within 3–4 days. Normalisation of body temperature can be expected within 24–48 h after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate ultrasound examination is recommended in these cases.

### Treatment of cystitis

**The first episode:**

- Uroantiseptics (trimethoprim/sulfamethoxazole 5–6 mg/kgbw/TMP-fraction p.p. in 3 D; nitrofurantoin 3–5 mg/kgbw p.o. in 2 D) – 5 days

**or**

- Antibiotics (oral cephalosporin 1-3 generation: cefaclor 50 (-100) mg/kgbw p.o. in 2–3 D, cephalexin 50 mg/kgbw p.o. in 3–4 D, cefuroxime 20–30 mg/kgbw p.o. in 2 D, cefixim 8 mg/kgbw p.o. in 1–2 D; Amoxicillin/clavulanic acid 37.5–75 mg/kgbw (Amoxicillin-fraction) p.o. in 3 D) – 3 days

**Recurrence** (consultation of urologist, gynecologist; VCUG, exclusion of urogenital infections):

- Uroantiseptics (trimethoprim/sulfamethoxazole; nitrofurantoin – 7 days

**or**

- Antibiotics (oral cephalosporin 2-3 generation: cefuroxim, cefixim, amoxicillin/clavulanic acid ) – 5 days

### Prevention

A urine culture should be obtained three to seven days after the completion of treatment to exclude relapse. Prophylaxis is recommended for all children younger than five years of age with vesicoureteral reflux (who are not surgical candidates) or other structural abnormalities and in children who have had three documented UTIs in one year.

Relief of voiding dysfunction, good hygiene, wiping from front to back after micturition in girls, avoiding constipation, bubble baths, chemical irritants and tight clothing are sensible recommendations.

### Chemoprophylaxis

Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage.

Prophylaxis: 1/3–1/4 dose of uroantiseptics before bedtime for 1–6 month

**Drugs for antibacterial prophylaxis** – substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.
Trimethoprim 1 mg/kgbw/d (Limitations until 6 weeks of age)
Nitrofurantoin 1 mg/kgbw/d (Limitations until 3 months of age)
Cefaclor 10 mg/kgbw/d (No age limitations)
Cefixim 2 mg/kgbw/d (Limitations in preterms and newborns)
Ceftibuten 2 mg/kgbw/d
Cefuroximaxetil 5 mg/kgbw/d

## Other therapy of UTI in children

**Analgetic antipyretic** are used to relieve burning, spasticity, and pain during voiding caused by UTIs.
**Antispastic therapy** is prescribed in painful syndrome.
**Treatment of predisposing factors**:

- Stone or obstructive lesions should be managed surgically
- Mild to moderate degrees of VUR need for medical treatment (long term antibiotic therapy, physiotherapy, vitamins) or resolve spontaneously with increasing age. Severe VUR should be managed surgically.

## Prognosis

Most children recover quickly and completely with antibiotic treatment. Recurrence of UTI is more likely in:

- Younger children, ie aged less than 6 months.
- Girls compared with boys.
- VUR grade 3–5, compared with reflux grade 1–2, or no reflux.
- Dysfunctional voiding syndrome; this is an abnormality of emptying, due either to a small-capacity, unstable bladder or a large-capacity, poorly emptying bladder.

Mortality related to UTI is exceedingly rare in otherwise healthy children in developed countries.

Cystitis may cause voiding symptoms and require antibiotics, but it is not associated with long-term, deleterious kidney damage. The voiding symptoms are usually transient, clearing within 24-48 hours of effective treatment.

Morbidity associated with pyelonephritis is characterized by systemic symptoms, such as fever, abdominal pain, vomiting, and dehydration. Bacteremia and clinical sepsis may occur.

Children with pyelonephritis may develop focal inflammation of the kidney (focal pyelonephritis) or renal abscess. Any inflammation of the renal parenchyma may lead to scar formation. Approximately 10-30% of children with UTI develop some renal scarring; however, the degree of scarring required for the development of long-term sequelae is unknown.

Long-term complications of pyelonephritis are hypertension, impaired renal function, and end-stage renal disease.

Dehydration is the most common acute complication of UTI in the pediatric population. Intravenous fluid replacement is necessary in more severe cases.

In developed countries, kidney damage with long-term complications as a consequence of UTI has become less common than it was in the early 20th century, when pyelonephritis was a frequent cause of hypertension and end-stage renal disease in young women. This change is probably a result of improved overall healthcare and close follow-up of children after an episode of pyelonephritis. Currently, these complications are most commonly encountered in infants with congenital renal damage.

## Control questions

**1.** What is the normal level of white blood cells in the urinalysis?

*A. Up to 1–2 in each high powered field.*
*B. Up 3–4 in each high powered field.*
*C. Up to 5–6 in each high powered field.*
*D. Up to 10 in each high powered field.*
*E. None.*

**2.** What is the normal level of white blood cells in urine sample by Nechiporenko?

*A.* $<1\times10^6$*/l.*
*B.* $<4\times10^6$*/l.*
*C.* $<6\times10^6$*/l.*
*D.* $<10\times10^6$*/l.*
*E.* $>10\times10^6$*/l.*

**3.** What level of bacteriuria is significant for cystitis (midstream clean catch sample)?

*A.* $>10^{2-3}$ *CFU/ml.*
*B.* $>10^{3-4}$ *CFU/ml.*
*C.* $<10^{3-4}$ *CFU/ml.*
*D.* $<10^{2-3}$ *CFU/ml.*
*E.* $>10^{5-6}$ *CFU/ml.*

**4.** What level of bacteriuria is significant for pyelonephritis (midstream clean catch sample)?

*A.* $>10^{2-3}$ *CFU/ml.*
*B.* $>10^{3-4}$ *CFU/ml.*
*C.* $>10^{4-5}$ *CFU/ml.*
*D.* $<10^{2-3}$ *CFU/ml.*
*E.* $>10^{5-6}$*CFU/ml.*

**6.** What per cent of primary urine is reabsorbed in the renal tubules?

*A. 68–69%. B. 78–79%. C. 88–89%. D. 98–99%. E. 58–59%.*

**7.** The most common manifestation in infants with urinary tract infection is:

*A. Fever.*
*B. Dysuria.*
*C. Frequency.*
*D. Costovertebral angle tenderness.*
*E. Incontinence.*

**8.** What bacterial pathogen can be the cause of pyelonephritis?

*A. Escherichia coli.*
*B. Klebsiella species.*
*C. Proteus species.*
*D. Enterococcus species.*
*E. All of the above.*

**9.** What bacterial pathogen is the most frequent cause of pyelonephritis?

*A. Escherichia coli.*
*B. Klebsiella.*
*C. Proteus.*
*D. Enterococcus.*
*E. Pseudomonas aeruginosa.*

**10.** The presence of renal parenchymal scarring due to vesicoureteral reflux is best determined by

*A. Intravenous pyelography.*
*B. Renal ultrasonography.*
*C. Voiding cystourethrogram (vcug).*
*D. Ct scan.*
*E. Dmsa scan (scintigraphy).*

**11.** What is the most frequent way (route) of contamination in pyelonephritis?

*A. oral.*
*B. hematogenous.*
*C. lymphogenous.*
*D. droplet.*
*E. ascending.*

**12.** What investigation should be prescribed for detection of vesicoureteral reflux?

*A. voiding cystourethrogram (VCUG).*
*B. Urine test.*
*C. Blood test.*
*D. renal ultrasonography.*
*E. CT scan.*

**13.** A girl of 8 years old was admitted to the hospital with complaints of pain in the abdomen, weakness, high fever, frequent and painful micturitions. Temperature was 38,5°C. Pasternatsky's test was positive. What is the most appropriate diagnosis?

*A. Acute cystitis.*
*B. Acute glomerulonephritis.*
*C. Acute interstitial nephritis.*
*D. Acute pyelonephritis.*
*E. Acute cholecystitis.*

**14.** A 6-year-old girl complains of pain in the back, weakness, high fever, frequent and painful micturitions. Pasternatski's sing is positive. The most appropriate prescription is:

*A. Penicillin.*
*B. Prednosolone.*
*C. Aspirin.*
*D. Drotaverinum.*
*E. Ceftriaxon.*

**15.** The imaging study of choice for the first urinary tract infection in an 18-month-old during the hospitalization is

*A. None of the below.*
*B. Intravenous urography.*
*C. Computed tomography.*
*D. Voiding cystourethrogram (vcug).*
*E. Renal ultrasonography.*

**16.** A girl of 8 years old was admitted to the hospital with complaints of pain in the abdomen, weakness, high fever, frequent and painful micturitions. Pasternatsky's test is positive. Last year girl had the same symptoms. What is the most appropriate diagnosis?

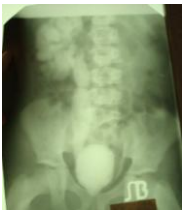
*A. Chronic cystitis.*
*B. Acute glomerulonephritis.*
*C. Acute interstitial nephritis.*
*D. Chronic pyelonephritis.*
*E. Chronic cholecystitis.*

**17.** What is the antibiotic of choice for prophylaxis of pyelonephritis?

*A. Bicillin.*
*B. Nitrofurantoin.*
*C. Gentamycine.*
*D. Amoxicillin.*
*E. Ceftriaxon.*

**18.** What degree of VUR on VCUG?

A. 1.
B. 2.
C. 3.
D. 4.
E. 5.



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*Навчальне видання*

# МОДУЛЬ 1
# ЗМІСТОВИЙ МОДУЛЬ 6
# ТЕМА 17
# ІНФЕКЦІЇ СЕЧОВОГО ТРАКТУ У ДІТЕЙ

***Методичні вказівки для студентів***

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# MODULE 1
# SUBSTANTIAL MODULE 6

# THEME 17
# URUNARY TRACT INFECTIONS IN CHILDREN

***Practical policies for students***