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Recommendations on diagnostics and treatment of urinary tract infections in children

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Considering the highest prevalence of urinary tract infection (UTI) among renal pathology in children, it is particularly important to detect the disease timely, provide adequate antibiotic treatment and, if necessary, carry out anti-relapse treatment. It is known, that recurrent UTI is a risk factor for the progression of kidney damage with the development of kidney failure. The clinical recommendations, presented for diagnosis and management of UTI, are based on the principles of evidence, and will allow enhancing the work of pediatricians and pediatric nephrologists.

Keywords: *urinary tract infection, etiology, clinical manifestations, diagnostics, leukocyturia, bacteriuria, examination, treatment, антибактериальная therapy, preventive measures, children.*
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DEFINITION

Urinary tract infection (UTI) **—** the growth of bacteria in the urinary tract.

Bacteriuria — the presence of bacteria in urine [more than 10^5 colony forming units (CFU) per 1 ml of urine] extracted from the urinary bladder.

Asymptomatic bacteriuria is bacteriuria, which is discovered at dispensary or targeted examination in a child without any complaints and clinical symptoms of the diseases of the urinary system.

Acute pyelonephritis — an inflammatory disease of the renal parenchyma and renal pelvis, which arose because of a bacterial infection.

Acute cystitis — an inflammatory disease of the urinary bladder, a disease of bacterial.

Chronic pyelonephritis — a kidney disease manifested by fibrosis and deformation of pelvicalyceal system, being a result of repeated attacks of IMP infection. Usually it occurs on the background of anatomical abnormalities of urinary tract or obstruction.

Vesicoureteral reflux (VUR) **—** retrograde urine flow from the urinary bladder into the ureter.

Reflux nephropathy — focal or diffuse sclerosis of the renal parenchyma, which is caused by vesicoureteral reflux, leads to intrarenal reflux, repeated attacks of pyelonephritis and renal tissue sclerosis.

Urosepsis — generalized non-specific infectious disease that develops, being a result of penetration of various microorganisms and their toxins from the organs of the urinary system into the urinary tract into the blood channels.

ICD-10 CODES

N10 Acute tubulointerstitial nephritis.
N11 Chronic tubulointerstitial nephritis.
N11.0 Nonobstructive chronic pyelonephritis, associated with reflux.
N11.1 Chronic obstructive pyelonephritis.
N11.8 Other chronic tubulointerstitial nephritis.
N11.9 Chronic tubulointerstitial nephritis, unspecified.
N13.6 Abscess of kidney and perinephric fiber.
N30.0 Acute cystitis.
N30.1 Interstitial cystitis (chronic).
N39.0 Urinary tract infection without the detected localization.

EPIDEMIOLOGY

The prevalence of UTI in children is about 18 cases per 1000 children. The incidence of UTI depends on age and sex, and the most frequent category suffering from the disease are children of the first year of life. In infants and young children, UTI — the most common heavy bacterial infection, it occurs in 10-15% of hospitalized febrile patients of this age. In infants below 3 months of age, UTI is more common in boys, at an older age — in girls. In the early school years — at 7,8% of girls and 1,6% of boys. With age, after suffering the first occurrence of UTI, the relative risk of relapse increases.

The relapse frequency:

- in girls:
  - in 30% during a year after the first occurrence;
  - in 50% during 5 years after the first occurrence;
- in boys:
  - in 15−20% during a year after the first occurrence.

ETIOPATHOGENESIS

Among the agents of urinary tract infections in children gram-negative bacteria prevails, about 90% are infected with bacteria *Escherichia coli*. Gram-positive bacteria are mainly represented by staphylococci and enterococci (5-7%). In addition, nosocomial infection strains are worth to be mentioned: *Klebsiella, Serratia* and *Pseudomonas spp*. In newborn infants, a relatively frequent cause of urinary tract infections are streptococci of groups A and B. There was a marked increase in detection of Staphylococcus saprophyticus recently, although its role remains controversial.

Currently, more than half of the strains *E. coli* in UTI in children, have become resistant to amoxicillin, however, they retain sensitivity to amoxicillin/clavulanate.

Among multiple factors, contributing to the development of the UTI, the most significant are the biological properties of microorganisms, colonizing the renal tissue, and the abnormalities of urodynamics (vesicoureteral reflux, obstructive uropathy, neurogenic urinary bladder dysfunction).

The most frequent way for infection to spread is considered ascending pathway. The reservoir of uropathogenic bacteria are the rectum, the perineum, the lower urinary tract.

The anatomical features of the female urinary tract (urethra is short and wide, the proximity of the anorectal region) cause a greater frequency of occurrence and recurrence of UTI in girls and young women.

In case of the ascending pathway of UTI spread, after overcoming the barrier of vesicoureteral by the bacteria, their rapid reproduction with endotoxin release occurs. In response, local immunity of the microorganism starts activating: activation of macrophages, lymphocytes, endothelial cells, resulting in generating inflammatory cytokines (IL 1, IL 2, IL 6, tumor necrosis factor), lysosomal enzymes, inflammatory mediators; the activation of lipid peroxidation, which leads to damage of renal tissue, primarily, tubules.

Hematogenous pathway of the infection of the urinary tract is rare; it is mainly common for neonatal period, during the development of septicemia in infants, especially in the presence of immune defects. This pathway also occurs if there is an infection with *Actinomyces species*, *Brucella spp.*, *Mycobacterium tuberculosis*.

THE CLINICAL PICTURE

For newborns and infants with UTI high fever is common; vomiting occurs often; diarrhea, body weight loss, low-grade fever are less often; disease is commonly not accompanied by dysuria.

In older children, the major symptoms of UTI should include temperature increases (usually up to febrile figures) without catarrhal symptoms, vomiting, diarrhea, pain in abdomen and/or lumbar region, sharp smell of urine, dysuric manifestations (too frequent and/or painful urination, daytime and nighttime urinary incontinence, urgency to urinate).

In purulent kidney disease, a positive symptom of Pasternatskiy occurs (morbidity at tapotement or pressing a finger between the base of the 12th rib and spine — in young children).

DIAGNOSTICS

The diagnosis of urinary tract infection is most likely during leukocyturia > 25 in 1 mkl or > 10 in the event of bacteriuria > 100 000 microbial units/ml when checking urine sterility (**2b**). Isolated pyuria, bacteriuria or positive nitrate test in children under 6 months are not reliable signs of the urinary tract infection **(3a**). Clinical analysis of urine with counting the number of leukocytes, erythrocytes and the nitrate detection (**2b, B**) is recommended as a diagnostic method.

Furthermore, leukocytosis (> 15×10^9/l), elevated levels of C-reactive proteins ≥ 60 mg/l and procalcitonin ≥ 2 ng/ml indicate a high likelihood of a bacterial infection of renal localization.

The levels of reliability and quality grading of recommendations are presented in Table 1 and 2. Differential-diagnostic criteria of acute cystitis and acute pyelonephritis are given in Table 3.

Table 1. Confidence level

Level	Type of data
1a	A meta-analysis of randomized controlled research (RCRs)
1b	The data obtained from the results of one RCR
2a	The evidence obtained from meta-analyzes of research without randomization
2b	At least one well-conducted quasi-experimental research
3	Well-conducted non-experimental studies - comparative, correlation or "case-control"
4	Expert consensus opinion or clinical experience of recognized authority

Table 2. Recommendations quality grade

Evidence grade		Recommendations base	Interpretation
A	High	Large double-blind, placebo-controlled researches, as well as data obtained from the meta-analysis of several RCRs	We are sure that the true effect corresponds to the supposed
B	Medium	Small randomized and controlled	The true effect is close to the

		researches, in which the statistical data are built on a small number of patients	supposed, although differences are possible
C	Low	Non-randomized clinical researches on a limited number of patients	The true effect can significantly differ from the supposed
D	Very low	Development of a consensus by a group of experts on a specific issue	The supposed effect is very unclear and in majority of cases is far from the truth

Table 3. Differential-diagnostic criteria of acute cystitis and acute pyelonephritis

Symptom	Cystitis	Pyelonephritis
Temperature raise over 38°C	Not typical	Typical
Intoxication	Not typical (in young children)	Typical
Dysuria	Typical	Not typical
Pain in abdomen/lumbus	Not typical	Typical
Leukocytosis (neutrophilic)	Not typical	Typical
Erythrocyte sedimentation rate	Unchanged	Increased
Proteinuria	No	Small
Hematuria	40−50%	20−30%
Macrohematuria	20−25%	No
Leukocyturia	Typical	Typical
Concentration kidney function	Preserved	Reduced
Increased kidney size (by ultrasound examination)	No	Sometimes observed
Thickening of urinary bladder wall (by ultrasound examination)	Sometimes observed	No

Imaging diagnostics

1. *Ultrasound diagnosis*

It is the most affordable and common technique that allows to assess the size of the kidneys, pelvicalyceal system condition, the volume and condition of the urinary bladder wall, to suspect the presence of structural abnormalities of the urinary system (expansion pelvicalyceal system, ureteral stenosis, etc.), stones. To identify the above reasons, it is necessary to carry out ultrasound examinations during filled urinary bladder, and also after urination act.

Ultrasound is conducted for all children during and after the first episode of urinary tract infection.

2. *Micturating cystography*

It is used to detect VUR and determine its degree, and to identify ureteroceles, diverticulum, posterior urethral valves (**2a, B**). In children with one occurrence of UTI, micturating cystography detects vesicoureteral reflux of 3-5th degree in only 17% of cases, of 1-2nd degree **—** in 22% of children, usually with changes detected by ultrasonography (US) [1].

Indications for cystography:

- all children below 2 years of age after febrile UTI occurrence, in the presence of pathological changes, detected by ultrasonography (increased kidney size, dilatation of the pelvicalyceal system) **—** in remission;
- recurrent UTI

3. *Static nefrostsintigrafiya*

It is conducted not earlier than 6 months after the acute episode of UTI (**2a, B**) using the radiopharmaceutical dimercaptosuccinic acid (Dimercaptosuccinic Acid, DMSA) to identify nephrosclerosis foci.

4. *Dynamic nephroscintigraphy (possibly with voiding probe)*

Is conducted with radiopharmaceutical ^{99m}Ts-Tehnemag to detect vesicoureteral reflux. The examination with voiding probe is performed in children, who can control the process of urination.

5. *Excretory urography, MR-urography*

It is used as an auxiliary method for detection of obstruction, abnormalities of the urinary system development (after exclusion of VUR).

Indications for specialty consultations

Children's gynecologist or andrologist's consultation is necessary, since there may be children, who have dysuria disorders and leukocyturia due to local inflammation of the genitals **—** vulvitis or balanitis. The presence of phimosis (**2a, B**) can predispose the development of VUR infection.

Screening

- Clinical urine analysis (leukocyturia detection, hematuria) is prescribed to children during fever with no symptoms of the upper respiratory tract disorders.
- Ultrasound of the kidneys and urinary bladder is prescribed to all children of the first year of life.

EXAMPLES OF DIAGNOSES

1. Acute pyelonephritis, active stage. Renal functions are preserved.
2. Urinary tract infection, recurrent course, active stage. Renal functions are preserved.
3. Reflux nephropathy. Secondary chronic pyelonephritis. Remission. Renal functions are preserved.
4. Acute cystitis, active stage. Renal functions are preserved.
5. Urinary tract infection (the first episode).

TREATMENT

1. Emergency prescription of antibacterial drugs (table 4).
2. Focusing on the sensitivity of microorganisms (**1b, A**).
3. The timely detection and correction of urodynamics disorders.
4. Long-term antimicrobial prophylaxis at VUR and recurrent UTI (**2a, B**).
5. Control of intestinal tract functional ability.
6. Reducing the dose of antibacterial drug, depending on creatinine clearance.

Table 4. The range of antibacterial drugs, applied for the treatment of urinary tract infection in hospitalized patients

Drug (INN)	ATC code	Daily dosage*	Dosage frequency (*per os*)
Amoxicillin + Clavulanic acid	J01CR02	50 mg/kg per day (based on moxicillin)	3 times per day
Cefixime	J01DD08	8 mg/kg per day	2 times per day
Cefuroxime axetil	J01DC02	50−7 mg/kg per day	2 times per day
Ceftibuten	J01DD14	9 mg/kg per day	1 times per day
Co-trimoxazole	J01EE01	10 mg/kg per day (based on sulfamethoxazole)	2−4 times per day
Furazidin	J01XE	3−5 mg/kg per day	3−4 times per day

Note. * **—** it should be remembered that in case of the reduction of endogenous creatinine clearance less than 50 ml/min, the dose of the drug should be reduced by half!

Table 5. Antibacterial drugs for parenteral administration

Drug (INN)	ATC code	Daily dose*	Dosage frequency
Amoxicillin + Clavulanic acid	J01CR02	90 mg/kg per day	3 times per day
Ceftriaxone	J01DD04	50−80 mg/kg per day	1 times per day
Cefotaxime	J01DD01	150 mg/kg per day	4 times per day
Cefazolin	J01DB04	50 mg/kg per day	3 times per day

Note. * **—** it should be remembered that in case of the reduction of the glomerular filtration rate less than 50 ml/min, the dose of the drug should be reduced by half!

In hospitalized patients, particularly in infants, who are difficult to administer the drug internally, antibiotic therapy is commonly started with parenteral route of administration of the drug during the first three days (table 5) with subsequent transition to oral administration. In the absence of apparent intoxication and the stable ability of the child to receive the drug orally, oral drug administration is possible since the first day (**2a, B**).

Aminoglycosides (***amikacin*** at the dose of 20 mg/kg per day once a day, ***tobramycin*** at the dose of 5 mg/kg per day three times a day, ***gentamicin*** at the dose of 5-7,5 mg/kg per day three times a day), carbapenems can be used as reserve drugs, as well as in combined therapy during urosepsis. ***Ticarcillin/clavulanate*** (250 mg/kg per day) or ***ceftazidime*** (100 mg/kg per day) + ***tobramycin*** (6 mg/kg per day) can be used during pseudomonas infection, in special refractory cases – fluoroquinolones[1]. Treatment effectiveness is assessed after 24-48 hours according to the clinical symptoms and the results of urine examination. If the treatment is ineffective, anatomical defects or kidney abscess should be suspected [2].

Antibacterial therapy usually eliminates the infection during 7-10 days, regardless of its location. In longer courses, flora resistance is developing [3]. Antibiotic administration during 3-5 days is sufficient (**Ib, A**) in children with cystitis. Antibacterial therapy less than 3 days (1a, A) is not recommended.

PREVENTATIVE MEASURES (PRIMARY)

- Regularly voiding of the urinary bladder and bowel.
- Sufficient fluid intake.
- Hygiene of the external genitalia.

Indications for preventative treatment (2a, B):

- presence of vesicoureteral reflux of 2-5 degree;
- recurrent UTI;
- severe abnormalities of the urinary tract development, up to surgical correction.

The duration of the preventative treatment is determined individually: usually at least 6 months.

Drugs, used for prolonged antimicrobial preventative treatment, are shown in table 6.

Phytotherapy with bactericidal action can be additionally applied, for instance, Kanefron H drug (**D**).

[1] Application in children **—** with the permission of Local Ethics Committee of the medical organization, given the informed consent of the parents/legal representatives and the child over the age of 14.

Table 6. Drugs, administered for long-term antimicrobial prophylactic

Drug (INN)	ATC code	Daily dose*	Dosage frequency
Furazidinum	J01XE	1 mg/kg	One time before sleep
Co-trimoxazole	J01EE01	2 mg/kg (based on sulfamethoxazole)	One time before sleep
Amoxicillin + Clavulanic acid	J01CR02	10 mg/kg	One time before sleep

PATIENT MANAGEMENT AND REHABILITATION MEASURES

1. In case of recurrent IMP episodes (more than 2 — in girls, more than 1 — in boys), an examination is recommended to exclude VUR (**2b, B**).
2. In the first 3 months of observation in acute pyelonephritis and after the exacerbation of chronic pyelonephritis, the clinical analysis of urine is taken once in 10 days, during 1-3 years — monthly, afterwards — once every 3 months.
3. Urine culture is performed in case of leukocyturia > 10 in p/zr. and/or during unmotivated temperature rise without catarrhal symptoms.
4. Urine probe according to Zimnitsky, determining the creatinine level in blood, is performed once a year.
5. Ultrasound examination of the kidneys and urinary bladder — once a year.
6. Repeated instrumental examination (cystography, radioisotope nephroscintigraphy) are performed once in 1-2 years in chronic pyelonephritis with frequent exacerbations and detected VUR.
7. Vaccination is carried out within the framework of the National Calendar of vaccination in remission of UTI.

Indications for children with urinary tract infection for hospitalization in a specialized hospital (1b, A)

1. Young children (less than 2 years).
2. Symptoms of intoxication.
3. Inability to perform oral rehydration in presence of signs of dehydration.
4. Bacteremia and septicemia.
5. Recurrent UTI, to avoid its secondary phase and the selection of adequate antirecurrent treatment.

The duration of hospital stay in UTI is 10-14 days. In the absence of the indications above, provision of medical care for children with urinary tract infection may be carried out in outpatient conditions or at a specialized day hospital.

FORECAST

The vast majority of cases of acute urinary tract infection ends in recovery. Localized renal scarring is detected in 10-20% of patients, after pyelonephritis, especially in case of recurrent infection and the presence of vesicoureteral reflux. If VUR is detected at a young age (less than 2 years old), cicatricial changes in kidney are found in 24% after 5 years, in older children — in 13% of cases. Thus, more active diagnosis and treatment at an early age reduce the risk of progression to chronic renal failure stage. Arterial hypertension develops in 10% of children with reflux nephropathy [2].

Conflict of interest

The authors of this article have indicated they have no conflict of interest to report.

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