

Acute pyelonephritis (pediatrics)

Infections of the uropoietic tract are among the most frequent bacterial infections of childhood. In some children, they can leave permanent consequences with a gradual decline in renal function and the transition to uremia, the development of hypertension and complications in pregnancy. The biggest problem then is IMC in infancy, when it is necessary to identify risk factors (obstruction, VUR) and, conversely, to exclude children with a low risk of developing consequences, so that invasive examinations can be reduced to a minimum.

Terminology/Classification

IMC

- **non-specific bacterial infection of the tubulointerstitial apparatus of the kidneys and mucous membranes of the hollow system of the uropoietic tract**

Acute urinary tract infections can be classified as an infection affecting the renal parenchyma, i.e. **acute pyelonephritis**, and as an infection limited to the lower urinary tract, i.e. **acute lower urinary tract infection**. (in practice most often referred to as acute cystitis). This classification is of practical importance, because kidney infection means the risk of scarring = scarring and requires more aggressive therapy on the part of the pediatrician.

- **acute pyelonephritis** = the presence of bacteria in the renal tissue together with significant bacteriuria in the urine.

After the 5th year of life, it is usually manifested by a syndrome of high temperatures, pain in the lumbar region, dysuria, bacteriuria, leukocyturia and often hematuria, before the 5th year of life the symptoms are uncharacteristic.

- **acute lower urinary tract infection** = bacterial/viral inflammation of the bladder and urethra.

TT usually < 38 °C, stranguria, pollakisuria

About 10–20% of children with symptomatic IMC fail to be classified into the two groups mentioned above. We therefore call such infections unclassifiable or unspecified. For practical reasons, we approach these children as if they had acute pyelonephritis.

- **Asymptomatic bacteriuria** = repeatedly positive bacteriuria in a child who has no other signs of IMC, we often catch it during preventive examinations.

Today, both acute and chronic pyelonephritis are considered secondary capture of bacteria in kidneys damaged by tubulointerstitial nephritis, caused by various causes: obstruction, congenital anomalies of the uropoietic tract, VUR, urolithiasis, disorders of the innervation of the bladder and urinary tracts, immunodeficiency, immunosuppressive therapy, diabetes mellitus, pregnancy, previous ATB therapy, especially with synthetic penicillins.

- **Pyelonephritic renal scarring** = focal or generalized renal damage in the DMSA image.

Occurrence

- IMC is the second most common bacterial infection in children, after respiratory infections,
- approx. 3-5% of girls and 1-2% of boys experience IMC in childhood,
- most pyelonephritis occurs in infancy, boys predominate in the first months of life,
- most cystitis is in preschool/school age with a clear predominance of girls.

IMC is often the cause of an unclear febrile condition, especially in children under 3 years of age. A high percentage of urinary infections (acute pyelonephritis) in infancy still remain undiagnosed. If they are diagnosed with pyelonephritis later in life, pyelonephritic scars are usually already present in the kidneys.

Etiology

- most microorganisms causing urinary infections are gram-negative bacteria, originating from fecal or periurethral flora,
- the causative agent of most IMC is *Escherichia coli*, which causes 80-90% of primary infections in children,
- *Proteus* bacteria occur in approximately 30% of boys with uncomplicated lower urinary tract infections,
- *Staphylococcus saprophyticus* is detected in about the same percentage of adolescents of both sexes with acute IMC,
- in children with malformations or dysfunction of the urinary tract, the causative agents of infections are usually other pathogens – *Enterococcus*, *Pseudomonas aeruginosa*, *Klebsiella*, *Staphylococcus aureus*,

Streptococcus B (GBS), rare causes of IMC in children are *Salmonella* , *Shigella* and *Campylobacter* .

If unusual pathogens are found in the urine, we must specifically look for anatomical anomalies of the urinary tract and conditions associated with immunodeficiency. Some *E. coli* serogroups are more common urinary pathogens than others—these uropathogenic strains include *E. Coli* serogroups O1, O2, O4, O6, O7, O8, O18, and O75.

Pathogenesis

Bacteria enter the urinary tract via **hematogenous** or **ascending** routes . The hematogenous route is assumed only in newborns and small infants. In the other age categories, IMC is most often caused by an ascending route, when pathogenic bacteria come from the intestine. The intensity of the inflammatory response is stronger if the causative pathogen has fimbrial adhesions on its surface, because the endotoxin lipopolysaccharide of the bacteria can be better applied there. The most serious form of infection in the uropoietic tract is **pyelonephritis**, as it can lead to permanent kidney damage. Pyelonephritis begins with the contact of pathogenic bacteria with the host's immune system - proinflammatory mediators are flushed out with an overall effect - the result is a massive inflammatory reaction of the entire organism. IL-6 causes fevers and induces an acute phase reaction (FW, CRP, leukocytosis). Polymorphonuclear leukocytes (they are attracted to the site of infection by IL-8) are one of the first defense barriers that the body uses to fight infection. The interesting thing is that the disorder of their function (neutropenia, inhibition of migration) prevents the formation of renal scars. Thanks to migration, polymorphonuclear cells come into contact with pathogenic bacteria and kill them after phagocytosis. Active oxygen molecules are an effective but double-edged weapon here. It acts non-selectively, destroying bacteria as well as kidney tubular cells, because urine does not contain the enzyme superoxide dismutase SOD, which inactivates oxygen radicals. The result of the entire inflammatory cascade is the aggregation of neutrophils, damage to the endothelium of vessels, vasoconstriction, edema and subsequent ischemia - a similar condition occurs in the kidneys as in ischemia-reperfusion damage.

Host factors promoting the emergence of IMC

- bacterial colonization of the periurethral area.

It is the most important factor in the pathogenesis of IMC. In boys, in the first 6 months of life, the presence of preputium is associated with richer periurethral bacterial colonization and a higher probability of infection. Evidence of this is the lower incidence of IMC in circumcised boys. In girls, the short urethra and its intimate contact with the vaginal and perianal area are risk factors for IMC (pathogens can easily enter the bladder).

- VUR,
- obstructive uropathy/malformation of the uropoietic tract – distal urethral stenosis in girls, posterior urethral valves in boys, hydronephrosis , megaureter, urolithiasis,
- neurogenic bladder dysfunction,
- disorders of the non-specific defense of the bladder mucosa.

Properties of IMC-inducing bacteria

- bacterial adherence.

Adherence of bacteria to uroepithelial cells is a basic condition for the development of infection in the urinary tract. *E. Coli* adhesions are mediated by fimbriae (the most important are P-fimbriae, which are related to strains causing pyelonephritis). Hemolysin formation has been found to increase the nephropathogenicity of *E. Coli* strains by allowing them to obtain iron from erythrocytes.

- cell membrane of bacteria.

Lipopolysaccharides are particularly important because they represent O-antigens (they induce the formation of specific antibodies).

Overview of *E. Coli* virulence factors

- O-antigens (lipopolysaccharides) – induce a humoral immune response,
- K-antigens – adhesive properties,
- H-antigens (flagella) – enable bacteria to move and stimulate chemotaxis,
- Hemolysins (bacterial enzymes) – induce tissue damage, increase the bioavailability of iron for bacterial growth,
- Fimbriae – mediate bacterial adherence to uroepithelial cells.

Host defense mechanisms

The urinary tract has several barriers above the urethra that help prevent infection. The first of them is the drainage mechanism , i.e. regular emptying of the bladder. If done correctly, the bladder will empty completely and the bacteria will be washed away in the urine. The second barrier is the transitional epithelium of the bladder, which is covered with a glycoprotein mucus layer and has bactericidal properties. The third barrier is the **ureterovesical junction** , which works as a one-way valve. However, this antireflux mechanism is often insufficient in childhood.

Clinic

- Fever is often the only symptom of acute pyelonephritis in infants and young children,
- the fever begins suddenly, it can be septic in nature, but it can also occur with subfebrile or unchanged temperature (febrile may be completely absent during the first month of life),
- paleness appears, in infants, loss of appetite, vomiting, diarrhea, tendency to dehydration, icterus, convulsions, somnolence or meningismus ,
- prolonged bacteriuria may lead to failure to thrive,
- anamnesticly, we look for anomalies of the uropoietic tract in the family, for boys in infancy we are interested in information about the flow of urine, its fluidity and duration of micturition (strictures, urethral valves),

For an atypical clinical picture, IMC must be ruled out in infants and toddlers at any temperature and failure to thrive.

- newborns have little ability to prevent the dissemination of bacteria => with the simultaneous occurrence of urinary tract anomalies, pyelonephritis has a septic course,
- in older children, acute pyelonephritis begins suddenly with high fever, chills, dysuria, headache and abdominal pain - pain in the lumbar region is typical (the doctor taps = tapottement) in the area of the costovertebral angle, the child often detects a painful reaction.

Complications

The most serious complication of a kidney infection is scarring. Kidney damage from inflammation most often occurs during the period of kidney growth, usually in infancy. The formation of scars in infants is most often with a late diagnosis of acute pyelonephritis. Scarring is found in 10-20% of patients who have experienced pyelonephritis. Risk factors for scarring:

- low age,
- late started therapy (> 72 hours),
- VUR,
- obstruction,
- recurrent infections,
- bladder emptying disorders,
- urolithiasis.

In children with bilateral kidney damage, GF is often reduced and the risk of its progressive reduction is high. Currently, 10-20% of children with end-stage renal disease have a primary diagnosis of urinary tract infection, often with VUR. We observe the development of hypertension in about 10% of children and young adults with felux nephropathy. The risk of hypertension is proportional to the extent of kidney damage. Girls with a tendency to recurrent infections have an increased risk of developing a new infection during pregnancy - women with renal scarring have a significant rise in blood pressure during pregnancy .

Diagnostics

Urine examination

urine chemistry and sediment

leukocyturia

- The best IMC screening marker (from this point of view, initially collecting urine in a urine bag/collection bag is sufficient),
- usually we find a full field of leukocytes, the criterion for arbitration is already a value > 10 leu in the field of view,
- pathognomonic for IMC is the presence of leukoclasts,
- the finding of leukocyte casts is reliable evidence of pyelonephritis.

hematuria

- In pyelonephritis we find different degrees of microscopic hematuria,
- cystitis is characterized by high erythrocyturia -> macroscopic HU.

proteinuria

- In IMC we find variable proteinuria,
- has a tubular and postrenal character,
- rarely exceeds values > 0.5 g/24 h.

leukocyte esterases

- With IMC, we demonstrate their elevation,
- it is a detection of leukocyturia using the paper method (Cytur test, Leukophan),
- sensitivity and specificity are around 90%.

Urine pH

- An alkaline urine pH > 7.0 is indicative of IMC.

nitrites

- Pathophysiologically, it is the conversion of physiologically present nitrates into nitrites=nitrites through the action of enterobacteria,
- with IMC we prove their positivity,
- have a high sensitivity for IMC.

IL-6 in urine

- We demonstrate its increased amount in urine in acute pyelonephritis,
- the decrease to the norm comes within 14 days,
- a slower decrease is found in patients with VUR and obstructions.

quantitative bacteriuria

- The basic diagnostic criterion for infection in the urinary tract is the presence of significant=significant bacteriuria.

The biggest problems with the diagnosis of IMC are in infants and toddlers, where there is a high risk of urine contamination from the periurethral (preputial, labial) area. On the other hand, not diagnosing IMC in a child is associated with a high risk of progressive kidney damage. Therefore, the quality of urine collection for culture examination is of decisive importance.

urine collection options

suprapubic puncture

- We use a black needle, puncture in the midline approx. 2 cm above the symphysis, proceed to a depth of approx. 2 cm, aseptic procedure - disinfection of the abdominal wall, sterile gloves,
- gold standard,
- essential in boys with conglutination or phimosis ,
- high-quality filling of the bladder is necessary => appropriate ultrasound check,
- complications rare (macrohematuria).

bladder catheterization

- We use a feeding tube for newborns, enough mesocaine gel, aseptic procedure - genital disinfection, sterile gloves,
- suitable alternative to suprapubic puncture,
- a large filling of the bladder is not necessary.

medium current draw

- Wash the genitals with clean water, open the labia for girls, pull back the foreskin for boys,
- in infants and toddlers as an emergency method, since the sensitivity is only 80% when taking 1 sample, or three samples with the same developer's card with identical sensitivity are necessary so that the validity corresponds to the previous two methods.

quantitative bacteriuria evaluation criteria

midstream

- significant bacteriuria - above 10⁵
- suspected/borderline bacteriuria - 10⁴ - 10⁵
- insignificant bacteriuria - under 10⁴

Nowadays, the diagnostic significance of the so-called low count bacteriuria, i.e. values of 10³ in the presence of clinical symptomatology (a change in the biological properties of the bacteria) is being considered.

catheterization

- significant bacteriuria - above 10⁴
- suspected/borderline bacteriuria - 10³ - 10⁴
- insignificant bacteriuria - under 10³

suprapubic puncture

- any finding is significant

After collection, the urine must be inoculated onto the soil within two hours, as the number of bacteria in the urine increases geometrically at room temperature. If this is not possible, the urine must be stored in a refrigerator at a temperature of +4 °C (with this storage, the number of bacteria does not change for approx. 24 hours). In the outpatient clinic, it is then most suitable to take a special culture soil on a glass slide - the dip-slide method.

Inflammatory markers

The clinical syndrome of acute pyelonephritis is a reflection of the host's acute inflammatory response to bacterial infection. For a febrile response to occur, the immune system producing pyrogens – TNF (tumor necrosis factor), IL-1 and IL-6 – needs to come into contact with microorganisms. This occurs when the bacteria enter the kidneys - therefore, a febrile response is considered the primary sign of renal involvement in a urinary tract infection.

acute phase proteins

CRP

CRP is produced in hepatocytes after their stimulation by IL-6. The serum concentration of CRP increases 10-100-fold within a few hours after the onset of infection and is rapidly corrected with successful treatment. The CRP concentration is therefore used not only to determine the severity of an acute infection, but also to monitor the effectiveness of treatment. Values > 40-50 are significant for bacterial infection, values > 100 are often given as a criterion for parenteral ATB application.

fibrinogen /FW

During the acute phase of the response, fibrinogen is produced in the liver following IL-6 and TNF stimulation. A change in the erythrocyte sedimentation rate is an indirect indicator of fibrinogen metabolism.

procalcitonin , IL-6

In the resting stage, they have almost zero values, their value rises within two hours after the beginning of the bacterial infection. Due to their financial demands, these examinations are reserved for ICUs and premature wards.

leukocytes

Leukocytosis

Leukocytosis > 12,000 is a sign of bacterial infection. Values > 20,000 together with CRP > 100 are an indication for parenteral ATB therapy.

neutrophilia/left shift

They represent another clue to the differentiation of bacterial inflammation.

antibody coated bacteria = ACB test (antibody coated bacteria)

Antibody-coated bacteria often indicate a kidney infection. However, a clear correlation with pyelonephritis was not confirmed in children. Urinary infection also activates an immune response against host antigens, e.g. Tamm-Horsfal glycoprotein. However, this antibody response is also detected in febrile conditions of non-renal origin.

Clinical criteria of acute pyelonephritis (according to Prof. Jodal)

- TT > 38
- CRP > 20
- FW > 25
- always present significant bacteriuria

Display methods

UZV

- we detect the presence of structural or functional anomalies that predispose the patient to infection or maintain infection in the uropoietic tract
- extremely dependent on the erudition of the examiner and the quality of the instrument
- **UZV B-mode**
 - we demonstrate enlargement of the affected kidney (according to Dinkel's graph), thickening of the pelvis, hyperechogenicity of the renal parenchyma
- **Power doppler** ultrasound
 - "takes" all streams
 - the pathological finding is hypoperfusion

DMSA = static scintigraphy

- is currently the most sensitive method for the diagnosis and localization of acute pyelonephritis
- during acute pyelonephritis, inflammation rapidly causes tubular dysfunction and DMSA uptake by proximal renal tubule cells is reduced at the site of inflammation/scarring
- in acute pyelonephritis, to prove the diagnosis, an examination must be performed within 5-7 days from the start of ATB administration - a positive finding proving acute pyelonephritis is diffuse changes in one kidney, any focal changes or approximation of functions below the ratio of 45% x 55%
- approx. 6 months after acute pyelonephritis, changes on DMSA indicate the formation of scars (scarring)
- the normal distribution of the radiopharmaceutical is up to a ratio of 45% x 55%

helical CT

- the advantage is the low radiation load, the disadvantage is the low availability of examinations
- sensitivity approaches DMSA

MAG 3 = dynamic scintigraphy

- performed in case of suspicion of a malfunction of the drainage function of individual parts of the draining urinary tract
- simultaneous use of furosemide excludes an anatomical lesion - obstruction
- note: when using glucoheptonate, we can simultaneously perform dynamic scintigraphy and then static scintigraphy

MCUG

- used to prove VUR and posterior urethral valves
- performed routinely after every proven pyelonephritis in children under 1 year (we are considering the indication for children 1-6 years old - yes for toddler age, rather no for preschool age), in children > 6 years old we perform MCUG in the indication after acute pyelonephritis only with proven changes on ultrasound = dilatation of the urinary tract or with a positive DMSA scan
- we perform with an interval of about 6 weeks after infection
- repeated (cyclical) filling is suitable - VUR card only when filling again
- it is advisable to capture the phase of micturition - proof of active VUR
- in boys, a lateral projection is also necessary - urethral valves

Therapy

Preschool age patients should be hospitalized.

ATB

For empiric treatment, we choose ATB resistant to beta-lactamase, i.e. cephalosporins II. generation or potentiated aminopenicillins, the alternative to empiric treatment is then aminoglycosides, ev. cephalosporins III. generation. For resistant strains, we choose ATB - cephalosporin II combinations. generation (III generation) + aminoglycoside. ATB is used immediately after an adequate collection of urine for culture, even if pyelonephritis is suspected. Indications for parenteral administration of ATB:

- newborns/infants
- septic condition
- vomiting
- delayed start of therapy/required change of ATB
- CRP > 100
- leu > 20,000

With adequate treatment, we expect urine to be sterilized within 24 hours of ATB administration, persistence of bacteriuria means bacterial resistance or the presence of a serious anatomical abnormality of the uropoietic tract. Symptoms of inflammation persist for a longer time even with adequate treatment - fever 2-3 days, leukocyturia 4-5 days, CRP 4-5 days, FW 2-3 weeks. We administer ATB for 10-14 days, followed by chemoprophylaxis in one daily dose at night until MCUG is performed or for 4-6 weeks.

chemoprophylaxis

- Cotrimoxazole 2-2.5 mg/kg
- Nitrofurantoin 2-2.5 mg/kg
- Trimethoprim 2-2.5 mg/kg

Complementary therapy

antipyretics

- we prefer ibuprofen, which according to some studies reduces the incidence of renal scarring

adequate hydration

- we try to hydrate the patient sufficiently, if necessary, with an infusion of crystalloids
- consistent hydration reduces the osmolality of the kidney medulla - deterioration of the conditions for the capture and multiplication of bacteria, especially gram-negative

prevention genital douching

- proper post-defecation hygiene

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Source

- MD HAVRÁNEK, Jiří: *Acute pyelonephritis*