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Urinary tract infections in children in the era of growing antimicrobial resistance – recommendations of the Polish Society of Paediatric Nephrology

Zakażenia układu moczowego u dzieci w dobie narastającej lekooporności bakterii – zalecenia Polskiego Towarzystwa Nefrologii Dziecięcej

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Abstract

Introduction and objective: Urinary tract infections can recur in children, and due to their potential long-term consequences, they require appropriate diagnosis and prompt treatment. Although *Escherichia coli* is the most common aetiology, an increase in infections with drug-resistant strains has been observed. The aim of this study was to develop current diagnostic and treatment recommendations in the era of increasing microbial resistance. **Materials and methods:** The recommendations are based on updated guidelines developed by the experts of the Polish Society of Paediatric Nephrology and a literature review. **Results:** Because the symptoms of urinary tract infection are often non-specific, urinalysis and urine culture should be performed in children presenting with fever without an identifiable cause. Correct method of urine collection and interpretation of the results are crucial for therapeutic decisions. Treatment should be continued for 7–14 days for upper and 3–5 days for lower urinary tract infections; the choice of the narrowest-spectrum antimicrobial should be based on bacterial susceptibility. Antibiotic prophylaxis is limited and recommended in children with grade III–V vesicoureteral reflux. Non-pharmacological management should include treatment of bladder and bowel dysfunction. Ultrasound is recommended for all children up to 24 months of age. Indications for voiding cystourethrography are limited to cases with ultrasound abnormalities, recurrent and septic infections. **Conclusion:** The paper provides up-to-date, practical recommendations for the diagnosis and management of urinary tract infections in children in the era of increasing microbial resistance and restricted indications for invasive radiological investigations.

Keywords: urinary tract infection, recommendations, antibiotic resistance, bacteriuria, urine culture

Streszczenie

Wprowadzenie i cel: Zakażenia układu moczowego u dzieci mogą mieć charakter nawrotowy, a ze względu na potencjalne odległe konsekwencje wymagają właściwej diagnostyki i szybkiego leczenia. Najczęstszym czynnikiem etiologicznym zakażenia układu moczowego jest *Escherichia coli*, ale obserwuje się wzrost częstości zakażeń innymi bakteriami, wśród nich – szczepami lekoopornymi. Celem pracy było sformułowanie aktualnych zaleceń diagnostyczno-leczniczych wobec narastającej lekooporności patogenów wywołujących infekcje dróg moczowych. **Materiał i metody:** Rekomendacje są oparte na uaktualnionej wersji zaleceń opracowanych przez ekspertów Polskiego Towarzystwa Nefrologii Dziecięcej oraz na przeglądzie piśmiennictwa. **Wyniki:** Z uwagi na często niespecyficzne objawy zakażenia dróg moczowych dzieci gorączkujące bez uchwytnej przyczyny wymagają diagnostyki z uwzględnieniem badania moczu i posiewu moczu. Właściwa metoda pobrania moczu do badań i prawidłowa interpretacja wyników są kluczowe dla decyzji terapeutycznych. Leczenie

zakażeń górnych dróg moczowych powinno trwać 7–14 dni, a dolnych – 3–5 dni; należy wybierać antybiotyki o jak najwęższym spektrum działania, bazując na wrażliwości bakterii. Zastosowanie przewlekłej profilaktyki antybiotykowej, z uwagi na ryzyko selekcji szczepów opornych i niejednoznaczny wpływ na odległe rokowanie, jest ograniczone i zalecane u dzieci z odpływem pęcherzowo-moczowodowym III–V stopnia. Postępowanie niefarmakologiczne powinno obejmować leczenie czynnościowych zaburzeń wydalania moczu i stolca. Zaleca się wykonanie badania ultrasonograficznego u wszystkich dzieci z zakażeniem układu moczowego w wieku do 24 miesięcy. Wskazania do cystouretrografii mikcyjnej są ograniczone do przypadków, w których stwierdzono nieprawidłowości w ultrasonografii, zakażenia nawrotowe i zakażenia o przebiegu septycznym. **Wnioski:** Praca zawiera aktualne praktyczne rekomendacje dotyczące diagnostyki i leczenia zakażeń układu moczowego u dzieci w dobie narastającej antybiotykooporności bakterii i ograniczania wskazań do inwazyjnych badań radiologicznych.

Słowa kluczowe: zakażenie układu moczowego, zalecenia, antybiotykooporność, bakteriuria, posiew moczu

INTRODUCTION

Urinary tract infections (UTIs) are among the most common infections in childhood. They affect both children with and without urinary congenital defects. In the first year of life, UTIs are more common in boys, while later on, they are more likely to be diagnosed in girls[1]. Since younger children with UTIs usually present with non-specific symptoms, diagnosis can sometimes be challenging, with the risk of generalisation of the disease. Prompt diagnosis and treatment are therefore essential. Delayed diagnosis and treatment of UTI, or unnecessary antibiotic therapy may also result from incorrect urine collection for bacteriological testing and misinterpretation of results, hence the importance of knowledge of the diagnostic and treatment algorithms for suspected UTI. UTIs tend to recur in some children. It is believed that renal scars develop as a result of recurrent febrile UTIs, leading to organ dysfunction and posing a risk of hypertension, although the relationship between renal scarring and UTI episodes is still under investigation[2,3]. Avoiding recurrent UTIs is addressed by identifying and attempting to eliminate risk factors.

Although gram-negative bacteria, mainly *Escherichia coli* (*E. coli*), remain the most common aetiological agent of UTIs in children, the emergence of strains resistant to standard antibiotics has been increasingly observed in recent years. This has prompted updating of the current guidelines on the choice of antimicrobial, treatment duration, and indications for long-term prophylaxis of UTIs. The emergence of multidrug-resistant bacterial strains has significantly limited the indications for long-term antibiotic prophylaxis. It has also led to a modification of most treatment regimens for UTIs: reduced length of therapy and the use of antibiotics with the narrowest possible spectrum of action to reduce the selection of resistant strains. The indications for antibacterial prophylaxis prior to urinary tract diagnostic workup involving bladder catheterisation have also been significantly reduced.

AIM OF THE STUDY

The aim of the study was to present current recommendations for the diagnosis and treatment of paediatric UTIs, including indications for long-term antimicrobial prophylaxis in view of the growing antimicrobial resistance.

MATERIALS AND METHODS

The recommendations presented here are based on an updated version of the guidelines for the management of paediatric patients with UTIs developed by experts from the Polish Society of Paediatric Nephrology (Polskie Towarzystwo Nefrologii Dziecięcej, PTNFD), as well as on a literature review of Medline, Embase and Cochrane Library databases. Updated recommendations of national scientific societies (e.g. North American and Italian), research institutes (including the UK National Institute for Health and Clinical Excellence, NICE) and the European Society for Paediatric Urology (ESPU), were included in the study. Additionally, the position of microbiology experts included in the recommendations of the Polish National Programme for the Protection of Antibiotics has been taken into account in the recommendations on the treatment and prevention of UTIs. Based on studies with a high level of clinical credibility, the PTNFD expert panel developed recommendations categorised by the strength of recommendation and quality of evidence.

DIAGNOSIS OF URINARY TRACT INFECTIONS

UTIs develop as a result of an imbalance between the body's defence capacity and pathogenic virulence. Symptoms of paediatric UTIs depend on the patient's age and the site of infection. It is generally not possible to determine the site of infection in newborns and infants. In children aged ≥2 years, medical history, physical examination and urine laboratory tests usually allow the infection to be classified into one of the following categories: lower urinary tract infection (LUTI), upper urinary tract infection, and asymptomatic bacteriuria (AB).

Medical history

In the youngest children, fever may be the only evident sign of urinary tract infection[1,4,5]. Children with fever ≥39°C,

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especially one persisting for 24–48 hours, are more likely to be diagnosed with UTI than children with lower body temperatures[1,6–8]. Therefore, it is recommended to consider the diagnosis of UTI and to collect urine for testing in febrile children under 5 years of age without other identified causes of fever. Regardless of age, UTI should be suspected in children with fever and identified risk factors for UTI (Tab. 1). Since normal urinary outflow is one of the key defence mechanisms of the urinary tract, congenital urinary defects, such as obstructive and reflux uropathy, as well as bladder and bowel dysfunction are the main risk factors for UTIs[9–13]. A history of micturition including bladder retention, urine stream, urine dripping and constipation is important (Tab. 1). Attention should be also paid to previous antimicrobial treatment. Symptoms of UTI by age are summarised in Tab. 2.

Physical examination

Physical examination of a child with suspected UTI is essential for reaching a correct diagnosis, assessing risk factors for infection and interpreting diagnostic findings. A thorough external genitourinary, sacral and abdominal assessment, including potential enlargement of the kidneys and bladder, retention of faecal masses and pain on palpation, are necessary.

Urinalysis

Urine tests (strip tests, microscopic and microbiological examination) are recommended before initiating antimicrobial treatment (Tab. 3). Urine culture is not necessary in adolescents with symptoms of LUTI without a history of recurrent UTI. Although manual assessment of centrifuged urine sediment remains the gold standard, the widely used flow cytometry and automated microscopy show comparable sensitivity and specificity. Due to their sensitivity and specificity for both leukocyte esterase and nitrite, urine strip tests are employed as a preliminary screening tool[14]. If the result is positive, doubtful or inconsistent with the child's clinical condition, microscopic verification is required.

Leukocyturia indicates inflammation of the urinary tract; however, the absence of leukocytes in urine sediment does not exclude UTI. No leukocyturia is found in approximately 10% of patients with UTI caused by pathogens other than *E. coli*, such as *Klebsiella* spp., *Pseudomonas aeruginosa* (*P. aeruginosa*), *Enterococcus* spp.[15].The urine nitrite test has a high specificity (98%), but low sensitivity (50%) in UTI[15]. False negative result may be obtained in the case of infection with bacteria that do not reduce nitrate to nitrite, such as *P. aeruginosa*, *Enterococcus* spp.,

Risk factors for UTIs
Medical history of UTI
Congenital urinary defect impeding the free flow of urine or vesicoureteral reflux (obstructive or outflow uropathy)
Abnormal ultrasound image indicating the presence of an reflux or obstructive urinary tract defect
Positive family history of congenital urinary defects
Positive family history of UTI
Bladder catheterisation
Micturition disorders (urinary incontinence, frequent or infrequent micturition, urgency)
Constipation, faecal incontinence
Urolithiasis and conditions predisposing to urolithiasis (e.g. hypercalciuria)
Sexual activity in girls
Improper hygiene of perineum
UTI – urinary tract infection.

Tab. 1. Risk factors for UTIs according to PTNFD recommendations

	2–12 months	**>12 months**
Acute pyelonephritis	Fever Poor feeding Vomiting No weight gain Irritability and crying during micturition Excessive drowsiness Change in urinary color, transparency and odor	Fever Nausea and vomiting Abdominal pain Pain in the lumbar region Malaise
Cystitis	Non-specific symptoms Poor feeding Irritability and crying during micturition Change in urinary color, transparency and odor	Dysuria Urination disorders Change in urinary color, transparency and odor

Tab. 2. Symptoms of UTI depending on the patient's age and the site of infection

UTI diagnosis in children	**Strength of recommendation**
UTI should be suspected and urine tests should be performed in all children ≤5 years who present with fever without an identifiable cause and in children with symptoms suggestive of UTI or with risk factors for UTI	AI
Physical examination of a child with suspected UTI should include an assessment of the external urogenital organs	AI
The following urine tests are recommended for children with suspected UTI: • strip tests • microscopic examination • microbiological examination	BII
The following methods of urine collection are recommended in children: • For urinalysis – any method • For microbiology (directly into a sterile container): – midstream – bladder catheterisation – suprapubic aspiration Urine should be collected after thorough cleansing of the urethral opening area	BI
Urine collected for testing may be stored for no longer than 4 hours	CII
Significant bacteriuria is defined as: • 10^4 CFU/mL in catheterisation sample • 10^3 CFU/mL in suprapubic aspiration sample • $\geq 10^5$ CFU/mL in a midstream urine sample	BII
CFU – colony-forming unit; **UTI** – urinary tract infection.	

Tab. 3. Diagnosis of UTIs – PTNFD recommendations

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or *Staphylococcus saprophyticus*, frequent bladder emptying (e.g. in the youngest children), or low dietary nitrate intake[14,16].

PTNFD recommends obtaining urine sample for bacteriological testing from spontaneous midstream urine collection. When this is not possible, collection of a urine sample by bladder catheterisation is suggested. Suprapubic bladder puncture is performed in exceptional cases due to greater trauma for the child. Depending on urine collection method, the risk of contamination of the urine sample is 1% with suprapubic puncture, 10% with catheterisation and 26% with midstream collection[17]. Thorough cleansing of the external genitourinary area is important to avoid sample contamination and to obtain a reliable result; it reduces the risk of false positives and, consequently, unnecessary treatment. The urine sample for bacteriological testing should be submitted immediately to the laboratory. Urine can be stored at 4°C for no longer than 4 hours prior to testing[18,19] (longer storage is only possible if transport medium is used).

A positive urine culture should be interpreted with reference to urinalysis and the overall clinical picture. According to PTNFD, the following findings should be considered as significant bacteriuria:

- 10^4 CFU/mL in catheterisation sample;
- 10^3 CFU/mL in suprapubic aspiration sample;
- $\geq 10^5$ CFU/mL in a midstream urine sample.

Upper urinary tract infection (acute pyelonephritis, AP)

AP is an acute inflammatory process involving the renal pelvis and interstitium. Infants and younger children present with fever, usually >39°C, restlessness or apathy, poor feeding, anorexia and vomiting. Fever, chills, abdominal and back pain or tenderness in the lumbar region are typical symptoms in older children (Tab. 2). Blood tests, including leukocytosis, C-reactive protein (CRP) and procalcitonin (PCT), can be helpful in determining the site of infection, although they have relatively low sensitivity and/or specificity[20–24]. A meta-analysis of clinical trials found PCT to be the most sensitive marker of renal parenchymal involvement, although neutrocyte count >60% and serum CRP >40 mg/L were risk factors for renal scarring[25–27]. Renal parenchymal involvement may be confirmed by Doppler ultrasound (US) or DMSA scan (dimercaptosuccinic acid scintigraphy); however, scintigraphy is not used for this purpose in clinical practice[2,28].

Lower urinary tract infection (cystitis)

Cystitis is an inflammation of the urinary bladder characterised by the presence of typical symptoms, such as urinary frequency, urgency, pain during micturition, low micturition volume, enuresis, urinary leakage, suprapubic pain, malodorous urine, and sometimes haematuria[28,29]. Infants and children aged <24 months with lower urinary tract infection present with non-specific symptoms, such as irritability, poor feeding or discomfort with urination (Tab. 2). Lower urinary tract infections are usually not accompanied by fever.

Asymptomatic bacteriuria

AB is defined as the presence of high urine bacterial titres not accompanied by a urinary inflammatory response[28,30]. It can be either transient or persist for a prolonged period of time. The prevalence of AB is estimated to be 0.37% in boys and 0.47% in girls[31]. AB is more common in uncircumcised boys in the first year of life, in girls with urinary and bowel disorders, and in children with neurogenic bladder. According to some studies, AB may have a defensive role and protect against symptomatic UTI, with microbes causing AB becoming non-virulent over time[5,32]. According to current research, small amounts of bacteria of the natural urinary microbiome, referred to as urobiome, whose composition depends on age and sex, are isolated from the urinary tract in healthy individuals. These typically include strains of *Lactobacillus*, *Prevotella*, *Corynebacterium*, *Gardnerella* and *Shigella*[33]. The composition of urobiome changes in patients undergoing immunosuppressive treatment and urinary tract catheterisation, those with urinary stasis, diabetes mellitus, and after antibiotic therapy. Attempts to eradicate AB adversely affect the composition of urobiome, compromising protection against symptomatic UTI[33]. Therefore, PTNFD does not recommend urine screening or treatment for AB. In catheterised patients, the risk of AB increases with the length of time the catheter remains in the bladder; however, if the catheter is maintained for no more than 30 days, most patients do not develop symptomatic UTI[34].

TREATMENT OF URINARY TRACT INFECTIONS

The choice of treatment for a child with UTI depends on the age of the patient, the severity of the symptoms, as well as physical examination and laboratory findings.

Empirical treatment

The youngest children (≤3 months) should be treated in a hospital setting due to the high risk of generalised infection. Additionally, infants with UTI often present with gastrointestinal symptoms, which generates difficulties with oral antibiotic therapy and makes it necessary to administer the antibiotic parenterally. In infants >3 months of age and older children, the choice of treatment for AP depends on the clinical condition, with an option of oral, intravenous or sequential (i.e. initially by the intravenous route and then by the oral route) therapy. Oral therapy can be considered when the risk of generalised infection is low.

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Treatment begins with empirical antibiotic therapy. The choice of drug and route of administration should take into account the child's age and clinical condition, the severity of the inflammatory lesions and previous medical history, including congenital urinary tract defects. Recent antimicrobial use and local resistance of pathogens to antibiotics are also important. The spectrum of empirical antibiotic therapy should cover the most likely culprit pathogen, taking into account Gram-negative bacilli (including *E. coli*) and typical strains of Gram-positive cocci. The chosen antimicrobial should reach high levels in the urine with the least possible impact on renal function. The PTNFD recommendations for age-adjusted antibiotic therapy in paediatric UTI are listed in Tab. 4. The inclusion of amoxicillin/clavulanic acid as empirical therapy in UTI requires confirmation of local susceptibility of cultured pathogens due to the reported increasing bacterial resistance resulting from the frequent use of these drugs in respiratory tract infections[35]. The proportion of isolated drug-resistant strains is increasing in children with recurrent UTI and in children with a history of urological treatment[36–39]. Empirical therapy should be individualised in such cases; importantly, the inclusion of higher-generation antimicrobials is acceptable here.

Once the result of the urine culture taken before treatment onset has been obtained, antibiotic therapy should be reviewed, selecting an antimicrobial with the narrowest spectrum of action. Targeted treatment includes de-escalation therapy, i.e. the use of a broad-spectrum antibiotic during the empirical phase, which, after obtaining bacteriological findings, is switched to an agent with good activity against the isolated microorganism, but with the narrowest possible spectrum of action.

Treatment of UTIs	Strength of recommendation
Hospital admission and parenteral antibiotic therapy are suggested in all children with UTI who are under 3 months of age In children with AP aged ≥3 months, the treatment method depends on the patient's general condition and it should include oral, intravenous or sequential therapy It is suggested to consider outpatient treatment and oral therapy in patients with a low risk of severe disease (sepsis)	BII
If AP is suspected, it is recommended to collect urine for urinalysis and culture, and then administer an empirically selected antibiotic After obtaining a urine culture, it is recommended to review the treatment and switch to an agent with the narrowest spectrum	AI
The following agents are recommended for empirical treatment of AP in children up to 3 months of age: • third generation cephalosporin or • ampicillin-aminoglycoside	AI
First-line antimicrobials in the empirical treatment of AP in children aged ≥3 months include: • 2nd or 3rd generation cephalosporin • amoxicillin/clavulanic acid (with confirmed sensitivity) • ciprofloxacin (in accordance with the restrictions set out in SmPC)	AI
Parenteral treatment is recommended for children aged ≥3 months when clinically justified, depending on the local resistance of strains: • 2nd or 3rd generation cephalosporin • amoxicillin/clavulanic acid (with confirmed sensitivity) • ciprofloxacin (in accordance with the restrictions set out in SmPC) • aminoglycoside (amikacin, gentamicin) It is recommended to switch to an oral antibiotic no earlier than 48 hours after treatment initiation (sequential treatment).	AI
It is recommended that treatment of upper urinary tract infections, either oral, intravenous or sequential, be continued for 7–14 days	AI
The following agents are recommended as first choice in the empirical treatment of lower urinary tract infections: • furazidine • nitrofurantoin • co-trimoxazole, trimethoprim • fosfomycin (girls >12 years of age)	BI
Treatment of lower urinary tract infections should be continued for 3–5 days	CI
AP – acute pyelonephritis; **UTI** – urinary tract infection.	

Tab. 4. Treatment of UTIs – PTNFD recommendations

Targeted treatment

PTNFD recommends that oral, intravenous or sequential treatment of upper urinary tract infections be continued for 7–14 days. Antibiotic therapy should be initiated within 48 hours of the onset of fever, as delayed treatment increases the risk of renal scarring[40,41].

In children aged >3 months, oral antimicrobial therapy is preferred if clinically possible. Oral antibiotics have been shown to be as effective in UTIs as parenteral therapy, which requires hospitalisation[42,43]. In a justified clinical situation, e.g. when a generalised infection is suspected or when the child's age or vomiting makes oral administration impossible, parenteral therapy is recommended according to PTNFD guidelines (Tab. 4). No sooner than 48 hours after the onset of therapy, if the child's condition allows it, the parenteral route can be switched to oral (sequential therapy). Sequential therapy is psychologically and pharmacoeconomically beneficial as it reduces the length of the patient's hospital stay and minimises the number of invasive medical procedures.

PTNFD suggests 7–10 days of antibiotic therapy for uncomplicated AP. Complications of AP in the form of renal abscesses or xanthogranulomatous pyelonephritis require prolonged antibiotic therapy and surgical treatment in some cases. Microbiological analyses of pathogens causing UTI in children still indicate broad susceptibility to second- and third-generation cephalosporins, carbapenems, amikacin, gentamicin and ciprofloxacin, although in recent years there has been rapidly growing resistance to fluoroquinolones and a higher incidence of bacteria resistant to amoxicillin/clavulanic acid and β-lactamase-producing bacteria (extended spectrum beta-lactamases, ESBLs)[13]. The choice of antibiotic should therefore be based on local susceptibility profiles of bacterial flora[36,37,44,45]. Children

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diagnosed with congenital urinary tract defects, who are frequently hospitalised, and children who have undergone urinary tract instrumentation are at significantly higher risk of developing infections caused by bacteria other than *E. coli* (*Enterococcus* spp., *Pseudomonas* spp., *Klebsiella* spp., *Staphylococcus* spp.) or infections with ESBL-producing strains[36–39]. Third-generation cephalosporins and carbapenems or amikacin are used in these patients[46]. According to the recommendations of the Polish National Programme for the Protection of Antibiotics, antibiotics with the narrowest possible spectrum of action should be used in targeted treatment[47].

The drugs recommended by PTNFD for the targeted treatment of lower urinary tract infection in children (see Tab. 4) should be used for 3–5 days.

DIAGNOSIS AND TREATMENT OF URINARY TRACT INFECTIONS IN SPECIAL CLINICAL SITUATIONS

Recurrent urinary tract infections

Recurrent UTI is defined as ≥2 episodes of upper UTI, or 1 episode of upper and ≥1 episode of lower UTI, or ≥3 episodes of lower UTI[28]. Risk factors for recurrent UTI include congenital defects of the urinary tract, such as vesicoureteral reflux (VUR), as well as urinary stasis and urinary and faecal dysfunctions. Recurrent UTIs affect 8–30% of children, more often those with a history of UTI in the first year of life[48]. The risk of recurrence due to drug-resistant bacteria is higher in children put on chronic antibiotic prophylaxis and in those hospitalised within three months prior to recurrent UTI[3,49,50]. Pathogens other than *E. coli*, including ESBL and *P. aeruginosa*, are significantly more likely to cause recurrent UTIs[51].

As set out in PTNFD recommendations, the choice of antibiotic for recurrent UTI should be dictated by the local resistance of pathogens. All children with recurrent UTI should be assessed for risk factors for recurrence and, if possible, attempts should be made to eliminate these risk factors. Chronic antimicrobial prophylaxis should be considered in selected cases.

Bacteriuria in patients prior to a potentially traumatic urinary tract intervention

Asymptomatic bacteriuria is more common in children with urogenital abnormalities or neurogenic bladder. Patients with AB who undergo endoscopic urological procedures are at risk of damage to the urinary tract mucosa during the procedure and secondary infectious complications. Therefore, PTNFD recommends urine bacteriological examination before a potentially traumatising urinary tract instrumentation and, if AB is confirmed, administering two doses of a targeted antibiotic: 30–60 minutes before and immediately after the procedure.

Asymptomatic urinary tract infections caused by *Pseudomonas aeruginosa*

P. aeruginosa is a Gram-negative bacterium intrinsically resistant to the most commonly used antimicrobials, which is characterised by biofilm formation and acquisition of antibiotic resistance. Asymptomatic *P. aeruginosa* bacteriuria is more common in patients with congenital urinary defects and neurogenic bladder and in children with a history of multiple hospital admissions. Due to its natural characteristics, complete eradication is generally not possible. AB treatment may therefore contribute to the resistance of *P. aeruginosa* strains rather than its eradication[52–54]. PTNFD does not recommend antibiotic therapy in patients with asymptomatic bacteriuria or asymptomatic UTIs caused by *P. aeruginosa*. Clinical symptoms of UTI are an indication for initiating antibiotic therapy. Treatment should also be initiated in patients scheduled for urinary tract instrumentation or surgery.

Asymptomatic urinary tract infections in chronically catheterised patients

Patients with neurogenic bladder treated with clean intermittent catheterisation often present with leukocyturia, which is generally not caused by clinically significant UTI[53,55,56]. Also, AB or asymptomatic infection, affecting up to 70% of children in this group, are not risk factors for renal damage[57,58]. A catheter-associated urinary tract infection (CAUTI) should be suspected and targeted treatment is needed only in symptomatic patients (fever ≥38°C and pain in the lumbar or pelvic region) with abnormal urinalysis and positive urine culture[52–54]. It is also indicated in the case of planned urinary instrumentation or surgery. PTNFD does not recommend routine antimicrobial prophylaxis to prevent CAUTI, whether it is a one-time or long-term bladder catheterisation.

PREVENTION OF URINARY TRACT INFECTIONS IN CHILDREN

Functional urinary and bowel disorders

Functional urinary and bowel disorders are now considered an important risk factor for recurrent UTIs. They are estimated to occur in up to 30-50% of children with first UTI episode[59]. They are characterised by urinary and/or faecal incontinence/retention in previously fully toilet trained children and who have no anatomical or neurological abnormalities. Functional disorders are diagnosed based on a thorough history of constipation and symptoms of voiding dysfunction, such as urgency, urinary frequency or incontinence, following a seven-day assessment of bowel rhythm using the Bristol Stool Chart and a 48-hour bladder diary, as well as an ultrasound assessment of post-micturition urinary retention[60,61]. An extended diagnosis,

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including uroflowmetry, urodynamic testing or specific diagnostic imaging, is indicated in selected cases. Behavioural and pharmacological treatment of functional urinary and bowel disorders is an essential element of UTI prevention in children.

Indications for antibiotic prophylaxis

Chronic antibiotic prophylaxis was a common practice in children with recurrent UTIs or confirmed congenital urinary defects for many years as it was believed to protect against renal scarring. Nowadays, in view of the increasing resistance of pathogens and the results of new randomised trials, the purposefulness and efficacy of UTI prophylaxis are debatable. A Swedish reflux trial showed that among children with grade III–IV VUR, only girls aged >12 months benefited from antibiotic prophylaxis, with no benefit observed in the boy group[62]. The PRIVENT trial showed a 6% reduction in the risk of UTI during prophylaxis in children with VUR, but no effect of this treatment on renal scarring was demonstrated[63]. The RIVUR study showed 11.9% reduction in the risk of recurrent UTI, but the intention-to-treat analysis concluded that 8 patients should receive prophylaxis for 2 years to avoid 1 episode of UTI[64]. In the PREDICT study, a small but statistically significant benefit of antibiotic prophylaxis in the prevention of UTI was observed in a group of infants with grade III–V VUR without previous episodes of UTI, with an intention-to-treat analysis indicating that preventing 1 episode required 2-year prophylaxis in 7 patients[3]. There was no effect of prophylactic treatment on renal scar formation during the 2-year follow-up. At the same time, 64% of children not receiving prophylaxis did not experience any episode of UTI. It seems that it is mainly female infants with high-grade VUR that benefit from prophylactic treatment[3,62].

Importantly, all studies found growing pathogen resistance to the antibiotics used in the prevention of UTI and a higher incidence of infections caused by bacteria other than *E. coli*, such as *P. aeruginosa*. Therefore, according to PTNFD, the decision to initiate antibiotic prophylaxis for UTI should be made by a nephrologist after careful evaluation of the potential benefits and risks, and implementation of all non-pharmacological methods. The decision to continue prophylactic treatment should be reviewed every 6 months. In view of the cited studies, PTNFD recommends pharmacological prophylaxis of UTI in children with grade III–V VUR. Despite the 6–10% risk of UTI in children with a prenatally suspected urinary tract malformation, these patients have not been shown to benefit from prophylactic antibiotic therapy[65–69]. Although PTNFD does not recommend pharmacological prophylaxis of UTI in children with a prenatally suspected urinary tract defect, such patients should be monitored for urinary tract infections until the diagnostic process of the defect is completed. Children diagnosed with megaureter are at higher risk of UTI[70]. A prospective study in children with prenatally diagnosed hydronephrosis showed that ureteral dilatation ≥7 mm was associated with a threefold higher risk of UTI. In such cases, there was a statistically significant benefit of antibiotic prophylaxis to prevent UTI[71].

The choice of drug for the prevention of UTI should be based on the local susceptibility profiles of *E. coli* strains. Typically, nitrofurantoin or furasidine, trimethoprim/sulfamethoxazole, amoxicillin or cefuroxime axetil, given as a single dose, are first-line treatment. A slower build-up of bacterial resistance has been observed during prophylactic use of nitrofurantoin[72].

DIAGNOSTIC IMAGING

Ultrasonography

Despite its low sensitivity in diagnosing VUR and renal scarring, ultrasound helps detect serious urinary tract abnormalities that require intervention and UTI complications in the form of renal and perirenal abscesses. PTNFD recommends urinary ultrasound in all children under 24 months of age diagnosed with the first episode of UTI, and in children >24 months of age diagnosed with AP or atypical UTI, with risk factors for recurrence, and in the event of recurrence. According to some published recommendations, ultrasound should be performed after the acute symptoms of UTI have resolved to minimise the impact of urinary inflammation on ultrasound imaging, as well as in the case of fever persisting beyond 72 hours after the onset of antibiotic therapy[42].

Micturition cystourethrography

Voiding cystourethrography (VCUG), as the method of choice in the diagnosis of VUR, a risk factor for renal scarring, has been widely used in the diagnosis of children with a history of VUR for years. VCUG requires bladder catheterisation and involves patient irradiation with a dose of 0.03 to 0.3 mSv. In addition to VUR, it can detect obstructive uropathies, as well as abnormalities of the urethra (such as posterior urethral valves), bladder and ureter. Renal scarring is now also thought to occur in children without VUR, which has limited the indications for VCUG. The trend towards less frequent use of chronic antibiotic prophylaxis, especially in children with low-grade VUR, and the restriction of indications for surgical treatment of VUR have also contributed to the change in indications for VCUG [62].

The likelihood of VUR in children who have undergone UTI is higher in the case of an abnormal urinary ultrasound, UTI caused by pathogens other than *E. coli* and UTI with fever >39°C. VUR should be excluded in patients with recurrent febrile UTI, irrespective of the child's age. PTNFD therefore recommends that VCUG be performed in any child with a history of UTI in whom urinary ultrasound scan may suggest VUR or other urinary tract abnormalities,

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as well as in children with recurrent UTI and those with a history of septic UTI (Tab. 5).

DMSA renal scintigraphy

DMSA renal scintigraphy can be used to diagnose acute inflammation of the renal interstitium during AP or to detect renal scarring. As already mentioned, due to its invasiveness, the associated exposure to irradiation doses of 0.3 to 1 mSv and the availability of a less invasive ultrasound technique, also with Doppler option, DMSA scanning is not recommended in acute UTI. This diagnostic modality is currently mainly used to assess renal scarring. It has been shown that 15% of children with renal lesions on DMSA scan during an acute episode of UTI present with renal scarring 4 months after the infection[73]. Ultrasound and DMSA renal scintigraphy should be considered as complementary imaging modalities in children with suspected renal parenchymal injury[74]. In particular, DMSA renal scintigraphy is indicated to confirm the diagnosis in cases of scarring visible on ultrasound and in children with clinical signs of renal damage in the form of albuminuria/proteinuria and hypertension.

PTNFD recommendations on the indications for a DMSA scan in children are summarised in Tab. 5. Renal scintigraphy should be performed 4–6 months after an AP episode.

CONCLUSIONS

The growing resistance to antimicrobials used in recent years and the latest research findings on the long-term follow-up of children with UTIs prompted some changes in the diagnostic and therapeutic strategies. Although the choice of an antimicrobial to treat UTI should be based on established treatment regimens, local bacterial resistance should be also considered in children with recurrent infections, as well as a history of multiple admissions and urological procedures. Current treatment algorithms suggest the use of agents with the narrowest possible spectrum and shorter antibiotic therapy. Due to both the lack of proven benefits of chronic antibiotic prophylaxis in terms of renal scarring and the risk of selection of drug-resistant strains, PTNFD recommends limiting chronic pharmacological prophylaxis of UTI only to selected cases. Treatment of functional urinary and bowel disorders is a recognised preventive measure. Treatment of asymptomatic bacteriuria is not recommended due to its potentially protective effects against infection with more virulent pathogens and due to the risk of developing drug resistance. The recommendations on diagnostic imaging in children with UTI allow for ultrasound in all patients up to 24 months of age, but limit the indications for VCUG, which should be used in the event of urinary tract abnormalities detected on ultrasound and in children with recurrent or septic infections.

Indications for diagnostic imaging		Strength of recommendation
US	• First UTI in a child aged ≤24 months • AP in a child aged >24 months • Atypical UTI in a child aged >24 months • First UTI in a child >24 months with risk factors for recurrent UTI • Recurrent UTIs	C1
VCUG	• Urinary tract US image suggesting VUR or other urinary tract abnormalities • Recurrent UTIs • Septic UTI	B1
DMSA scan	• Recurrent AP • Grade III–V VUR • US or clinical findings suggestive of renal scarring	C1
AP – acute pyelonephritis; **DMSA** – dimercaptosuccinic acid; **VCUG** – voiding cystourethrography; **VUR** – vesicoureteral reflux; **US** – ultrasound.		

Tab. 5. Diagnostic imaging in children with urinary tract infections – PTNFD recommendations

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: IZ, AJ, KKP, PSi, PSk, MT, AŻ, AMW. Collection, recording and/or compilation of data: IZ, AJ, KKP, PSi, PSk, MT, AŻ, AMW. Analysis and interpretation of data: IZ. Writing of manuscript: IZ. Critical review of manuscript: AJ, KKP, PSi, PSk, MT, AŻ, AMW. Final approval of manuscript: AJ, KKP, PSi, PSk, MT, AŻ, AMW.

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