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Urinary Tract Infections in Children

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Abstract

Urinary tract infections are one of the most common bacterial infections in children. It may cause severe complications in both acute and chronic periods. *Escherichia coli* is the most common microorganism that causes urinary tract infections in children. Recurrent urinary tract infection is a significant risk factor for kidney scarring. Early diagnosis and appropriate treatment of urinary tract infection, as well as determination of risk factors and prevention of recurrent urinary tract infections, should be the most critical goals in managing children with urinary tract infections.

Keywords: Urinary tract infections, children, urosepsis

Introduction

Until antibiotics were discovered in the mid-20th century, urinary tract infections (UTI) were a major life-threatening health problem. In an article published by Kenny JF et al.[1] in 1966, it was reported that 8 out of 11 infants hospitalized for *E. coli*-related pyelonephritis developed septicemia, and four of them died. Fortunately, urinary tract infections are not so severe in children today, but it remains a significant problem. Although death due to urinary tract infection is rare today, urinary tract infection may cause complications such as urosepsis, renal abscess and acute kidney damage in the acute period, chronic renal failure, proteinuria, and hypertension in the chronic period due to renal scarring. It is reported that 10-40% of children with pyelonephritis have renal scarring.[2-4] Therefore, urinary tract infections need to be diagnosed early, treated appropriately, and closely monitored.

Epidemiology

Urinary tract infections are the second most common bacterial infection in children. It was determined that 8.4 % of girls and 1.7 % of boys had urinary tract infections at least once in the first seven years of life. It has been found that a second UTI

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develops in 30% of children with urinary tract infections. Urinary tract infections affect boys and girls equally in the first year of life but are more common in girls after one year.[5-8] Risk factors that facilitate the occurrence of urinary tract infection are given in **Table 1**.[9]

Etiopathogenesis

Escherichia coli is the most common microorganism that causes urinary tract infections in children. Other enteric Gram-negative bacteria causing UTI are *Klebsiella*, *Pseudomonas*, *Proteus*, *Enterobacter*, and *Citrobacter spp*. Some Gram-positive organisms can also cause UTI, such as *Staphylococcus saprophyticus*, *Enterococcus spp*, and *Staphylococcus aureus*. The vast majority of microorganisms that cause urinary tract infections originate from fecal flora that crosses from the perineum to the urethra and infect the bladder.[9] Bacterial virulence characteristics and impairments in host defense are the most critical factors in the occurrence of urinary tract infections. Virulence factors that make the microorganism uropathogenic are among the most important factors in the occurrence of urinary tract infection. These factors vary with different types of UTI. P-fimbriae, found in *E. coli*, helps bacteria attach to the uroepithelial cell and thus keep the bacteria in the urinary tract despite urine flow. Other virulence factors include hemolysin, O antigen, capsule K phenotypes, siderophores. Some strains of bacteria such as *Klebsiella* and *Pseudomonas* do not have such properties, so they need impaired host defenses to cause infection. Host defense factors that play a role in the pathogenesis of urinary tract infection include systemic or local anatomical or functional problems. Urinary flow is an important host defense factor in the urinary tract. It has been reported that anatomical disorders that prevent urinary flow, such as obstructive uropathies and severe vesicoureteral reflux (VUR), facilitate urinary tract infections. In these cases, the risk of urinary tract infection increases. Some functional abnormalities, such as bladder and/or bowel dysfunction, can disrupt the local defense system and facilitate the formation of urinary tract infection. The risk of urinary tract infection may increase in systemic immunodeficiency or immune suppression, especially in cases of systemic immunodeficiencies, such as impairment of Toll-like receptors or abnormal production of antibacterial peptides (eg cathelicidines and α-defensins).[10,11]

Highlights

- Urinary tract infections are one of the most common bacterial infections in childhood and the most common cause is *Eshericia coli*.
- The diagnosis is based on the detection of significant bacteriuria in the urine sample with clinical suspicion.
- Taking a proper urine sample is important for diagnosis. Especially in young children, catheterization or suprapubic aspiration methods are recommended to obtain urine samples.
- Early diagnosis and appropriate treatment can prevent renal scar development.
- Predisposing factors (especially bladder and bowel dysfunction) should be investigated in children with recurrent urinary tract infections.

Table 1.
Risk factors that facilitate the occurrence of urinary tract infection

• Bowel and bladder dysfunction
• Urinary tract abnormalities
Structural
- Vesicoureteral reflux, posterior urethral valves, prune belly syndrome, ureteropelvic /ureterovesical junction obstruction, megaureter, polycystic kidney disease
Functional
- Neurogenic bladder
• Indwelling catheter
• Immunosuppressed status
• Neonates
• Uncircumcised boys

Clinical features

Urinary tract infections can generally be presented in three different clinical presentations: Acute pyelonephritis, acute cystitis, and asymptomatic bacteriuria.

Acute pyelonephritis reflects infection of the kidney parenchyma and pelvis. Patients usually present with high fever (may rise to 39-40°C) and systemic symptoms such as nausea, vomiting, anorexia, flank, or abdominal pain. Acute cystitis refers to bladder infection and is the most common form of UTI. In this clinical situation, complaints and findings are generally localized in the lower urinary system rather than systemic. Dysuria, frequent urination, a feeling of urgency, pain in the lower abdomen are the most common complaints. Generally, there is no fever, or it may be mild (rarely up to 38°C). Asymptomatic bacteriuria is the asymptomatic presence of bacteria in the urine without significant pyuria. Children often show symptoms of bladder dysfunction.[9,10]

Urinary tract infections are clinically defined in two different types as simple or complicated. Complicated urinary tract infection describes urinary tract infection occurring in the presence of risk factors such as structural or functional urinary tract abnormalities, indwelling devices, stones, and immunosuppression. On the other hand, any risk factor does not accompany urinary tract infection in the simple urinary tract infection type.[9] Defining simple or complicated UTI is essential in terms of treatment and follow-up planning.

It is important to determine whether it is the first urinary tract infection or recurrent urinary tract infection in the child diagnosed with urinary tract infection.[9] If a child has had two or more urinary tract infections, a recurrent urinary tract infection is mentioned. Recurrent urinary tract infection is important because it has been reported in different studies that recurrent UTI is a risk factor for kidney scarring. The risk of kidney scarring increases as the number of repeats increases.[9,10]

It has been suggested that some factors facilitate the occurrence of urinary tract infection or the recurrence of urinary tract infection. These risk factors include age (3-5 years, typical toilet training age), Caucasian race,

high-grade VUR, female gender, bowel, and bladder dysfunction. For example, it has been reported that the presence of vesicoureteral reflux is a predisposing factor for the occurrence of urinary tract infection, and the rate of recurrence of urinary tract infection increases as the degree of vesicoureteral reflux increases. As mentioned above, children with urinary tract infections should be evaluated for the presence of risk factors since urinary tract infection, especially recurrent urinary tract infection, may cause renal scar formation.[8-10]

Is renal scarring important?

It is well known that renal scarring leads to three crucial chronic problems. These are reduced kidney function, hypertension, and pregnancy complications.[10] Toffolo et al.[12] analyzed long-term follow-up data from 19 studies involving 3148 pediatric patients with urinary tract infections. Although heterogeneous results, the prevalence of decrease in renal functions was determined as 0-56%, the prevalence of hypertension as 1.2-35%, and pregnancy complications such as hypertension, proteinuria, or preeclampsia were detected in 12% of pregnancies.[12] Gebäck et al.[13] evaluated adult women's kidney function with childhood urinary tract infections in their study. They found that women with no renal scar in infancy had stable GFR.

In contrast, those with bilateral scarring in infancy had a significant decrease in their GFR and commented that individuals with bilateral scarring have a chance of developing clinically significant chronic kidney disease. In another study, Gebäck et al.[14] evaluated ambulatory blood pressure measurements of adult women with childhood urinary tract infections after 35 years of follow-up. They found a higher rate of systolic blood pressure in the group with scarring in childhood.

Diagnosis

There are two main goals when diagnosing a urinary tract infection: early diagnosis and avoiding unnecessary antibiotic use. The clinical diagnosis of UTI is based on the presence of symptoms and the demonstration of bacteriuria in the urine. Bacteriuria is a mandatory finding for the diagnosis of UTI.[9,10,16] UTI symptoms can range from asymptomatic to a severely ill child with a high fever and secondary bacteremia.[2] It is not always easy to diagnose a urinary tract infection. Symptoms can be nonspecific, especially in young children. Therefore, it is an important problem for clinicians to consider a UTI and which patient will be screened for urine. The first step in the diagnosis of urinary tract infection is suspicion. Also, the presence of risk factors can be considered to predict the probability of UTI in febrile infants and young children (2-24 months). The presence of more than 2 of the following risk factors in baby girls increases the likelihood of UTI by more than 2%: Caucasian, age less than 12 months, fever more than 48 hours, no other source of fever, fever of 39°C or higher. The presence of more than 3 of the following risk factors in circumcised baby boys increases the likelihood of UTI by more than 2%: Non-black race, fever for more than 24 hours, no other source of fever, fever of 39°C or higher.[9]

The American Academy of Pediatrics (AAP) and other guidelines recommend that the diagnosis of UTI be made according to the presence of pyuria and significant bacteriuria. Pyuria is defined as the presence of 10 or more white blood cells per mm^3 or five or more white cells per high power area (HPF). The presence of leukocyte esterase in the stick test also indicates pyuria. The definition of significant bacteriuria varies according to the method of collection of the urine sample. Isolation of a single uropathogen greater than 50,000 colony forming unit (CFU) per ml in urine culture sample collected by catheterization or suprapubic aspiration, or more than 100,000 CFU per ml in urine culture sample collected by the midstream method or bag, is considered to be significant bacteriuria according to the AAP guidelines.[15]

In the study conducted by Shaikh et al.[16] clinical and laboratory findings were evaluated to confirm the diagnosis of urinary tract infection. While malodorous urine, uncircumcised boy, presence of previous UTI, and fever of unknown origin were determined as the most important clinical findings indicating urinary tract infection, nitrite test positivity, leukocyte esterase test positivity, and presence of pyuria were determined as the most important laboratory findings.[16]

A calculator (UTICalc) that can assist clinicians has been developed to estimate UTI probability in children younger than two years old. This online calculator (https://uticalc.pitt.edu) was designed using clinical findings that most likely indicate urinary tract infection.[17] Ebell et al.[18] proposed a guideline (The DUTY Clinical Decision Rules) to facilitate UTI diagnosis in emergency services and primary health care, using the most common clinical and laboratory findings indicating UTI.

Laboratory findings are more prominent in diagnosing urinary tract infection, and urine analysis and urine culture must be performed. The urine collection method is important for urine tests. How to obtain the appropriate urine sample may be related to the child's age and clinical condition. The urine sample can be obtained through a bag, clean catch, midstream voiding urine, catheter, or suprapubic aspiration. It is generally not recommended to diagnose a UTI based on a urine sample taken from a bag placed in the perineum. Because there is a high probability of contamination in bag urine samples, they should exclude UTI but not diagnose UTI. If a UTI is suspected based on the bag sample, a repeat urine sample should be collected by urinary catheterization or suprapubic aspiration (SPA).[15,19,20] Instead of collecting urine with a bag, a clean urine sample can be collected from the perineum (clean-catch) using suprapubic and sacral stimulation procedures. Culture results obtained with this collection method should also be interpreted carefully. When bacterial growth is detected in the urine culture, the urine culture should be repeated, preferably with a catheter or SPA urine sample.[15,21]

In the diagnosis of urinary tract infection, a urine examination is done in two steps. After the urine sample is taken, it is divided into two parts. While one part is reserved for urine culture, the other part is used for urine analysis. In urine analysis, especially nitrite test, leukocyte esterase test, presence of leukocyte in microscopic examination (pyuria), and bacteria presence in Gram staining are investigated.

The urinary nitrite test is highly specific for UTI but may not always be positive in the presence of UTI by low sensitivity (50%).[23] It can take up to 4 hours for organisms to degrade nitrate to nitrite, so urine must wait in the bladder for a while. Especially in patients who urinate frequently, there may not be enough time for the nitrite test to be positive. Besides, not all uropathogenic bacteria have urease enzymes and do not produce nitrite.[10]

Leukocyte esterase positivity indicates the presence of leukocytes in the urine. Pyuria is identified by urinalysis (UA): greater than or equal to 10 white blood count (WBC)/mm^3 or greater than or equal to 5 WBC per high-powered field (HPF).[9] Leukocyte esterase positivity or pyuria are findings suggestive of urinary tract infection. Nitrite positivity with leukocyte esterase positivity in the stick test has 93% sensitivity and 72% specificity for UTI. Leukocyturia (pyuria) / leukocyte esterase positivity is found in most children with UTI. AAP considers pyuria or leukocyte esterase positivity as a prerequisite for diagnosing UTI.[9,10,15] However, in the urine of 10% of children with UTI, especially in cases of UTI caused by non-*E. coli* organisms, leukocytes are absent, or leukocyte esterase may be negative. Children with UTI caused by *Enterococcus spp*, *Klebsiella* spp, and *Pseudomonas aeruginosa* may have a lower incidence of pyuria than children with *E. coli* with UTI.[22,23] Although it is a basis or a prerequisite for the diagnosis of UTI, the presence of LE is not specific for UTI, and both the sensitivity and specificity of the test are low. Sterile pyuria may occur in the urine without UTI in cases of Kawasaki disease, glomerulonephritis, acute interstitial nephritis, appendicitis, and intense exercise.[9] Although not widely used in practice, Gram staining in a fresh, non-centrifuged urine sample is considered a reliable test for identifying UTI.[22] The association of bacteriuria and pyuria in microscopy has a positive predictive value of 84% for UTI.[9]

The gold standard for diagnosing urinary tract infection in children is to show bacteriuria in the urine sample.[9,10] There are some problems in detecting and identifying significant bacteriuria in children. Contamination of the urine sample with preputial or vaginal flora is the most important problem in urine samples taken with bags. In one study, simultaneous bladder puncture and urine samples with clear-voided urine or bag were compared, and the contamination rate was found to be 25%.[24,25] Collecting urine samples with a catheter significantly increases the diagnostic accuracy compared to bag urine cultures. Suprapubic bladder puncture gives the most accurate culture result, but it is an invasive method. Many centers or guidelines recommend using a catheter or suprapubic aspiration for urine sampling, especially in young children. There are also differences in the definition of bacteriuria.[15,26-28] Different guidelines for collecting urine samples and identifying significant bacteriuria in children with UTI are given in **Table 2**.

Definition of the significant bacteriuria threshold value may differ between guidelines. 10^5 CFU/ml is usually accepted as the threshold value for significant bacteriuria in urine samples collected by urination or bag. The American Academy of Pediatrics (AAP) recommends using a cut-off value of 5×10^4/CFU/mL for specimens collected with a catheter. However, in many countries, 10^4 CFU/mL is accepted as the threshold for significant bacteriuria.[15] It is recommended to consider the threshold value of 10000 CFU/mL in urine samples taken by catheter from infants at risk of UTI with fever and pyuria. However, in young children with proven UTIs, it has been shown that approximately 20% of their urine cultures have bacterial colonies lower than the commonly used threshold of 10^5 CFU/MI.[10,29] A recent study conducted in Japan suggested using 10^3 bacterial colonies in urine culture taken by catheter in infants younger than four months as a threshold for diagnosing upper urinary tract infection.[30] However, it should be noted that lowering the threshold value can reduce false-negative results but increase the number of false-positive results.

Blood tests are not diagnostic in the diagnosis of urinary tract infection. However, measuring complete blood count and acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be helpful in the diagnosis of acute pyelonephritis. An increase in leukocytosis, CRP, and ESR may indicate pyelonephritis. Procalcitonin has been suggested as a helpful marker in the diagnosis of pyelonephritis recently. A meta-analysis conducted by Shaikh et al.[32] in 2020 was analyzed the diagnostic value of CRP, ESR, and procalcitonin levels in UTI. In this study, it was interpreted that ESR was not helpful enough to differentiate pyelonephritis and cystitis. A CRP level below 20 mg/dl was useful in excluding that procalcitonin was more beneficial for the diagnosis of pyelonephritis.[31] In another study, a cut-off value of 1.0 ng/ml of procalcitonin is predictive of acute pyelonephritis in young children.

Table 2.
Comparison of different guidelines for collecting urine samples and identifying significant bacteriuria in children with UTI

	NICE[27]	AAP 2011[15]	EAU/ESPU[28]	Okarska-Napierała M et al.[26]
Urine collection in non-toilet-trained children	Clean catch mid-stream void Alternatively: collection bag	Bladder catheterization or SPA (relates to children aged < 2 years)	Clean catch, midstream void, bladder catheterization or SPA for diagnosis Collection bag only as a method of exclusion	Bladder catheterization or clean catch mid-stream void Collection bag only as a method of exclusion
Significant bacteriuria	No identification	Catheterization: 5x104 CFU/ml	Clean-catch urine, midstream, catheterization: 103 -104 CFU/ml SPA: any growth of bacteria	Catheterization: ≥ 103 CFU/ml Clean voided urine: >104 CFU/ml with symptoms or > 105 without symptoms SPA: any growth of bacteria

SPA: Suprapubic aspiration, CFU: Colony-forming unit, NICE: National Institute for Health and Care Excellence, AAP: The American Academy of Pediatrics, EAU/ESPU: European Association of Urology /European Society for Paediatric Urology

Imaging

The primary rationale for imaging in children with UTI is to identify genitourinary abnormalities that require additional evaluation or treatment rather than a diagnosis of urinary tract infection. For this purpose, the first recommended radiological research method is urinary ultrasonography. Ultrasonography (US) is an easy-to-do, simple, non-invasive method that is not exposed to radiation and can be found everywhere. However, there may be differences in interpretation among radiologists. The American Academy of Pediatrics recommends performing renal-bladder US after the first febrile UTI for all children aged 2-24 months.[15] National Institute for Health and Care Excellence (NICE) recommends kidney-bladder US for infants younger than six months and children older than six months with atypical or TIA.[27] Atypical UTI includes severe illness, poor urinary flow, abdominal or bladder mass, elevated creatinine, septicemia, infection with a non-*E. coli* organism, and inability to respond to antibiotics within 48 hours. Recurrent UTI is defined as two or more upper UTI or one upper UTI with at least one lower UTI or at least three lower UTI.[27] The American Academy of Pediatrics guideline recommends that ultrasonography be administered after UTI treatment rather than during acute infection.[15] Acute infection can alter the size and echogenicity of the renal parenchyma, which causes temporary hydronephrosis. So that leads to erroneous interpretations. However, the European Association of Urology (EAU)/European Society for Paediatric Urology (ESPU) guidelines advise renal and bladder ultrasound within 24 h advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract.[28] Miller et al.[9] also recommend an ultrasound of the kidney and bladder at 48 hours of treatment to exclude renal abscess or pyonephrosis if the disease is more severe than expected or if there is no clinical improvement despite appropriate treatment.

Scintigraphy is useful not only in the diagnosis of urinary tract infection but also for detecting renal scarring. Tc-99m dimercaptosuccinic acid (DMSA) scan is considered the gold standard method in pyelonephritis. Uptake defect in renal isotope screening is indicative of pyelonephritis. However, most national guidelines do not recommend the routine use of DMSA scans to diagnose pyelonephritis due to the inconvenience, high cost, and radiation exposure.[15,27,28] However, both NICE and APA guidelines recommend DMSA 4-6 months or 6-12 months after acute infection to detect renal scarring.[15,27]

The voiding cystogram is not a primary radiological research method in children with urinary tract infections and should be performed in selected patients. APA recommends voiding cystourethrogram (VCUG) to be performed after the first febrile UTI when kidney-bladder US is abnormal and after the second febrile UTI when US findings are normal.[15] In the United Kingdom (UK), the NICE guideline recommends VCUG for infants with atypical, recurrent UTIs with dilatation on the US and a family history of VUR.[28] Some recommend performing a voiding cystourethrogram in infants with a first febrile UTI and a circumcised boy after the first febrile UTI.[9,28]

Treatment

UTI treatment should be planned considering the symptoms, location and type of UTI, previous medical history of the child, and resistance patterns of uropathogens in the area where the child lives. UTI treatment aims to eliminate infection and prevent urosepsis, relieve acute symptoms such as fever and dysuria, prevent recurrence of UTI, and long-term complications such as hypertension, renal scar, kidney growth, and dysfunction. All children older than two months can be treated on an outpatient basis. Indications for hospitalization and / or parenteral therapy are:[9,10,15,27,28]

- Age <2 months
- The presence of urosepsis
- Immunocompromised patient
- Vomiting or inability to tolerate oral medication
- Inadequate outpatient follow-up
- Non-response to outpatient medication

It is essential to initiate early (within the first 72 hours) and aggressive antibiotic therapy to prevent renal damage. Empirical antimicrobial therapy should be started immediately after urine sample collection. Delay in the treatment of febrile UTI is associated with an increased risk of kidney scarring. It is reported that a delay of more than 48 hours increases the probability of a new scar by 47%.[4]

Empirical antibiotic treatment should be directed against *E. coli*.[9] Local resistance data should guide the agent of choice in empirical treatment. The resistance properties of *E. coli* isolated from pediatric urine samples from 192 hospitals in the United States were evaluated, and 45% ampicillin resistance and 24% trimethoprim and sulfamethoxazole (TMP-SMX) resistance were detected in *E. coli* culture isolates.[33] Cephalosporins and aminoglycosides are the first recommended agents for empirical treatment of UTI in children. Because the resistance rate of *E. coli* is high, amoxicillin and ampicillin are not routinely recommended in empirical antibiotic therapy. If the enterococcal infection is suspected, ampicillin or amoxicillin can be used. But ampicillin or amoxicillin should not be used as monotherapy in these patients.[9] The French study group recommends aminoglycoside therapy in addition to cefotaxime or ceftriaxone in hospitalized children with febrile UTIs, and amikacin or ceftriaxone or cefixime as the first-line agent of choice in outpatient children with febrile UTI.[34] Again, this group recommends amoxicillin-clavulanic acid as the first choice in patients with cystitis until the culture result is obtained.[34]

It is suggested that children older than two months who do not vomit can be adequately treated with oral antibiotics.[9,15,28] Some clinical parameters that affect antibiotic usage form are patient's age, clinical suspicion of urosepsis, impairment in oral feeding, vomiting, diarrhea, and a course of complicated pyelonephritis. Oral antibiotic use is also an option following short-term parenteral antibiotic use. In the study conducted by Hoberman et al.[35] a patient group who received oral cefixime for 14 days was compared with the patient group who received iv cefotaxime + oral cefixime. No difference was found between the groups regarding sterilization of urine, recurrence of infection, and renal

scarring.Neuhaus et al.[36] found that once a day, ceftibuten therapy was equivalent to the treatment with ceftriaxone followed by ceftibuten. Fluoroquinolones (ciprofloxacin) are effective agents for *E. coli* infection, and resistance is rare in children. However, ciprofloxacin should not be used routinely as a first-line agent. The widespread use of fluoroquinolones can lead to increased resistance among other bacteria. The Infectious Diseases Committee of the American Academy of Pediatrics (AAP) recommends ciprofloxacin in *Pseudomonas aeruginosa* infections or UTI caused by resistant Gram-negative bacteria.[15] Oral agents such as nalidixic acid or nitrofurantoin are excreted in urine but cannot reach therapeutic serum concentrations. So they should not be used to treat UTIs in young children, as they may be insufficient to treat pyelonephritis or urosepsis.[15]

Children over three months old, well-hydrated children, and children without urological abnormalities who cannot tolerate oral therapy and are non-toxic can be treated with outpatient parenteral therapy. A single daily dose of gentamicin or ceftriaxone can be administered intramuscularly.[37]

Short-term antimicrobial treatment (3-5 days) is recommended for children with lower UTI and long-term therapy (usually 7-14 days) for children with fever.[9,10,15,27,28,37] Clinical findings improve within 24-48 hours in most patients given appropriate antimicrobial therapy. The most common causes of treatment failure are misdiagnosis, the presence of resistant bacteria, kidney abscesses, and urinary tract malformations.[9,15,28]

In children whose clinical condition does not improve or worsen as expected within 48 hours, antimicrobial therapy should be expanded. In this situation, kidney and bladder ultrasonography should be performed to evaluate the presence of kidney abscesses or surgically correctable abnormalities or obstruction.[15,28,37] If the patient does not respond to therapy or the uropathogen is not sensitive to the preferred antibiotic, urine cultures should be repeated after 48 hours of treatment. However, if the child has the expected clinical response and the uropathogen is sensitive to the antibiotic used for treatment, repeating urine cultures are not routinely required during antimicrobial therapy to document sterilization of the urine.[15,37]

The treatment of asymptomatic bacteriuria is a highly questioned and discussed issue. In a recent meta-analysis including 14 studies of 46806 children, the prevalence of asymptomatic bacteriuria was reported as 0.37% in boys and 0.47% in girls.[38] Asymptomatic bacteriuria may frequently occur in three different patient groups, depending on age and underlying urinary tract malformation: I) Children with genitourinary abnormalities or neurogenic bladder, II) Uncircumcised boys in the first year of life, III) Girls aged 3-10 years with recurrent UTIs.10 Patients in the third group often have symptoms of functional bladder and bowel dysfunction, and symptoms often persist, although bacteriuria is corrected with antibiotics. Controlled studies do not support the treatment of asymptomatic bacteriuria in these children. It has been suggested that asymptomatic bacteriuria may protect against the development of symptomatic UTI, and bacteria that cause asymptomatic bacteriuria may become avirulent over time.[10]

I) Prophylactic antibiotics

Another goal in managing children with urinary tract infections is to try to prevent recurrent acute pyelonephritis attacks and renal scarring. Prophylactic antibiotics in children with recurrent urinary tract infections have been a topic that has been both applied and discussed for many years. Most of the evidence regarding the use of prophylactic antibiotics comes from studies on VUR and recurrent UTI. Garin et al.[39] reported that antibiotic prophylaxis does not have a significant effect on the recurrence of urinary tract infection in children between 3 months and 18 years of age with stage I-III VUR.On the other hand, In the PRIVENT study, Craig et al.[40] found a moderate decrease in urinary tract infection recurrence in patients aged 0-18 years who were treated with TMP-SMX prophylaxis. The Swedish study group investigated the use of prophylactic antibiotics in children aged 1-2 years with high-grade VUR and found different results between girls and boys. While it found a significant decrease in the frequency of urinary tract infections and renal scarring in girls, it did not detect a difference in boys.[41] In RIVUR study, lower infection rates were found in children who received prophylactic antibiotics. The RIVUR study determined that long-term antibiotic prophylaxis reduced the recurrence of UTIs from 27.4% to 14.8% over a 2-year follow-up period. The proportion of isolates resistant to TMP-SMX was higher (63%) in the prophylaxis group than in the placebo group (19%).[42] In contrast, Hari et al.[43] reported that children with VUR who received prophylactic cotrimoxazole had a 3-fold higher chance of recurrent infection than children given a placebo. There is still confusion regarding the use of prophylactic antibiotics. A 2019 Cochrane meta-analysis of nine studies that compared the antibiotic treatment to placebo or received no treatment showed that using prophylactic antibiotics was not beneficial for preventing recurrent UTIs or uptake defects seen in DMSA scans. This analysis highlighted the significantly increased antibiotic resistance to the drug used for prophylaxis.[44] However, Tullus et al.[10] suggest in a recent review that young children with high-grade VUR are likely to benefit from antibiotic prophylaxis. The most crucial problem in long-term prophylactic antibiotic use is the development of antimicrobial resistance to the drug.[45,46] Mattoo et al.[46] found that antibiotic prophylaxis was associated with a 3-fold increase in *E. coli* resistance and suggested that prophylaxis should be used in selected patient groups such as children with VUR, not in every patient. Both AAP and NICE guidelines do not recommend routine antibiotic prophylaxis in children after the first febrile urinary tract infection.[15,27]

II) Probiotics

Probiotics have not been shown to reduce the recurrence of urinary tract infections in randomized studies in children.[47] However, Lee et al.[48] found that the incidence of recurrent urinary tract infection was 8.2% in patients with lactobacillus prophylaxis, 10% in antibiotic prophylaxis, and 20.6% in children who did not receive prophylaxis in their study in which 191 infants with acute pyelonephritis and normal urinary anatomy were included.

III) Cranberry

Data on the use of cranberry juice in the prevention of urinary tract infections are also controversial. A meta-analysis of randomized controlled trials by Jepson et al.[49] reported that cranberry-based products do not reduce recurrent UTIs than placebo. In a study comparing eight clinical UTI studies, a decrease in UTIs and antibiotic use was found in healthy children using cranberry products. Still, the results were contradictory in children with urological abnormalities.[50] It has been suggested that cranberry products can be an effective option to prevent recurrence in children without anatomical abnormalities.[50] The use of cranberry is recommended to avoid recurrent urinary tract infections in the EAU/ESPU's newly updated guidelines.[28]

IV) Circumcision

It has been suggested that circumcision performed immediately after birth reduces the possibility of having an acute pyelonephritis attack in healthy boys by 90%.[51,52] However, the number of children needed to be circumcised to protect one case of acute pyelonephritis was found too high (the number needed to treat is 111).[27,28] Today, routine circumcision is not recommended in healthy children to prevent urinary tract infections, but it is advised in children with major urinary malformations who need general anesthesia for urological reasons.[9,28]

V) Treatment of bladder and bowel dysfunction

It is well known that bladder and bowel dysfunction is a significant risk factor for urinary tract infection in children. If vesicoureteral reflux accompanies bladder and bowel dysfunction, the risk of urinary tract infection increases further.[53] Therefore, it is recommended to investigate and treat bladder and bowel dysfunction in children with recurrent urinary tract infections. [9,10,28]

When should a child with UTI be sent to a nephrologist?

Indications for referral to a pediatric nephrologist or urologist are:[27]

- Recurrent UTI
- In the presence of dilated vesicoureteral reflux (Stage III-V) or obstructive uropathy
- Presence of kidney anomalies
- Impaired kidney function
- High blood pressure
- Presence of bowel and bladder dysfunction resistant to primary care approaches.

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