Urinary tract infections in children with chronic kidney disease

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Abstract

Studies concerning urinary tract infection (UTI) in children with chronic kidney disease (CKD) are scarce. In CKD children a wide variety of underlying predisposing factors for UTI may be considered, such as age, gender, genetic factors, urinary obstruction, bladder, and bowel dysfunction, bladder catheterization, nephrolithiasis, altered local, and systemic immune status, frequent hospitalizations, and sexual activity in adolescents. General rules of UTI management in CKD children are similar to those used in children without CKD. However, there are some important peculiarities. Common symptoms of UTI may be mimicked by conditions typical for CKD (also post-transplant). Results of laboratory tests concerning detection of pathogenic microorganisms and an inflammatory response in the urinary tract may be misleading because of uremic environment. The aim of UTI treatment must involve not only rapid recovery from complaints, elimination of pathogenic microorganisms from urinary tract, prevention of related complications, but also the prevention of further impairment of kidney function. Dosage of drugs should be adjusted to the estimated glomerular filtration (eGFR) rate, calculated from the current serum creatinine and body length according to the Schwartz formula. Nephrotoxic drugs are contraindicated. Treatment of asymptomatic bacteriuria generally is not recommended, however it should be considered in same cases. Studies on pathophysiological mechanisms of UTI in children with different stages of CKD are needed. Future research should also concern optimization of UTI therapy in order to preserve renal function.

Summary of recommendations

1. The general rules of UTI management are similar to those used in children without CKD (LoE: 4; GoR: B).
2. It is important to investigate for specific factors predisposing to UTI in CKD children, especially: congenital anomalies of the kidney and urinary tract, congenital cystic disorders, bladder and bowel dysfunction, metabolic abnormalities and immunocompromising (LoE: 2a; GoR: B).
3. Severe UTI in CKD children may have an adverse influence on the CKD course and enhance kidney function impairment (LoE: 2a; GoR: B).
4. Dosage of drugs cleared renally should be adjusted to the current eGFR rate (LoE: 4; GoR: C).
5. Treatment of asymptomatic bacteriuria – which generally is not recommended in children – should be considered in some patients with primary or secondary immunodeficiency (for example on chronic immunosuppressive therapy after kidney transplant), with VUR and in patients with planned urinary tract instrumentation (LoE: 1b; GoR: A). Treatment of asymptomatic bacteriuria is indicated in pregnant adolescent girls (LoE: 2a; GoR: B).
6. All recommendations are only pieces of advice and each child with both CKD and UTI should be treated individually (LoE: 4; GoR: C).

1 Introduction

Chronic kidney disease (CKD) refers to a state of irreversible kidney damage and/or reduction of kidney function that is associated with progressive loss of function over time. According to KDIGO (Kidney Disease: Improving Global Outcomes) 2012 Clinical Practice Guideline, definition for pediatric CKD is based on fulfilling one of the following criteria:

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1. Glomerular filtration rate (GFR) of less than 60 mL/min per 73 m2 for greater than three months with implications for health regardless of whether other CKD markers are present.
2. GFR greater than 60 mL/min per 1.73 m2 that is accompanied by evidence of structural damage or other markers of functional kidney abnormalities including proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by histology or inferred by imaging [1], [2], [3].

The KDIGO guideline classifies the severity of CKD for patients greater than two years of age into five stages based on GFR as follows:

- G1 – Normal GFR (≥90 mL/min per 1.73 m2);
- G2 – GFR between 60 and 89 mL/min per 1.73 m2;
- G3a – GFR between 45 and 59 mL/min per 1.73 m2;
- GG3b – GFR between 30 and 44 mL/min per 1.73m2;
- G4 – GFR between 15 and 29 mL/min per 1.73 m2;
- G5 – GFR of <15 mL/min per 1.73 m2 (kidney failure, renal insufficiency) [1].

The term CKD replaced the clinical terms chronic renal failure (CRF) and chronic renal insufficiency (CRI). Now “renal failure” (end stage renal disease; ESRD) refers to stage G5, in which patients need renal replacement therapy (RRT): dialysis – hemodialysis (HD) and peritoneal dialysis (PD) – or renal transplantation (RTx).

In clinical practice in children, we make use of estimated GFR (eGFR) according to Schwartz formula. Value of eGFR depends on the child’s height, serum creatinine, and a constant “k”: eGFR = k x height in cm/serum creatinine. A constant k is dependent on the type of laboratory assay used for the determination of serum creatinine. If the serum creatinine is determined by Jaffe reaction, the value of “k” varies with age, and in adolescents, with the sex [4]. If the serum creatinine is determined by enzymatic reaction by isotope dilution mass spectrometry (IDMS), the value of “k” is equal to 0.413 [5]. Children under two years of age normally have a low GFR even when corrected for body surface area [6]. Therefore, in these patients calculated GFR based upon serum creatinine can be compared with normative age-appropriate values to detect kidney impairment [7].

Congenital anomalies of the kidney and urinary tract (CAKUT) and congenital/hereditary cystic disorders are a major cause of pediatric CKD. In older children and adolescents, glomerular diseases are more prevalent [8], [9], [10], [11]. Data concerning epidemiology of pediatric CKD is not precise. The reported number of children with CKD is likely underestimated because earlier stages of CKD are usually asymptomatic and lead to underdiagnosis. In Europe, an estimated median annual incidence of pediatric CKD stage 3 to 5 is 11.9 cases per million of age-related population (pmarp), while the prevalence is ~55–60 pmarp [10]. In Latin America, the incidence of CKD (stage not defined) ranged from 2.8 to 15.8 cases pmarp. The reported annual incidence of children with ESRD receiving RRT was 9.5 cases pmarp in 11 western European countries and Australia and 15.5 cases pmarp in the United States. The prevalence is about 65 pmarp worldwide [8].

Urinary tract infection (UTI) is one of the most common pediatric infections. UTI is estimated to occur in 5–10% of children up to the age of 14. This value increases to 13% in febrile infants. UTI recurs in approximately 30% of children within a year after the initial episode [12], [13]. UTIs vary in severity, depending on the balance between the infecting pathogenic microorganisms and the antimicrobial host defense [14]. There are different UTI classifications. Traditionally, UTIs are classified based on clinical symptoms, laboratory data, and microbiological findings. Based on a presence of symptoms, UTI can be divided into symptomatic and non-symptomatic. Symptomatic UTIs are classified as cystitis, pyelonephritis and urosepsis. Taking into account other clinical criteria such as severity of symptoms and pattern of infection, UTIs are divided into mild, moderate, severe and septic, and into isolated or sporadic, recurrent, relapse, reinfection and chronic, respectively. In “NICE guideline: UTI in children and young people”, a term “atypical UTI” is used [15]. Definition of atypical UTI includes: seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicemia, failure to respond to treatment with suitable antibiotics within 48 hours, and infection with non-*E. coli* organisms.

The most widely used current classification of UTI differentiates upper urinary tract infection

(pyelonephritis, infectious tubulointerstitial nephritis) and lower urinary tract infection (cystitis). The above classification is relevant for the purposes of this chapter.

It is often difficult on clinical grounds to distinguish upper urinary tract infection from lower urinary tract infection, particularly in children younger than two years. UTI in those children should be treated as upper UTI, unless the clinical picture clearly indicates lower UTI.

An association between CKD and UTI in children is complex. On the one hand, up to one half of children with UTI have a structural abnormality of their urinary tract and kidneys [16]. UTI may damage the growing kidney by forming scars, predisposing to hypertension and, sometimes, to renal function impairment. A UTI that involves renal parenchyma leads to an inflammatory reaction with risk of permanent damage [17], [18]. On the other hand, CAKUT is a major cause of CKD in children. In many cases it is accompanied by recurrent/chronic UTIs which may involve kidneys. In children with CKD a wide variety of underlying predisposing factors for UTI may be considered, such as age, gender, genetic factors, urinary obstruction, bladder and bowel dysfunction, bladder catheterization, nephrolithiasis, sexual activity in adolescents, as well as various specific and nonspecific host defense reactions [12], [13]. It is accepted that local and systemic immune status of patients with CKD is altered [19], [20]. Among others, uremic toxins modify the environment and the expression of different virulence factors of microorganisms, as well as the activity of host-specific defense mechanisms. Phagocytosis is restricted. Alteration of granulocyte function, such as impairment of migration, chemotaxis, degranulation and blockade of glucose uptake will potentially promote colonization of the urinary tract. The release of different cytokines and mediator molecules can modify inflammatory response. These processes may be followed by deterioration in renal function. A special group of children with CKD and UTI are children after kidney transplantation (CKD stage 5). In those patients, additional UTI risk factors play an important role. They include, among others, intensive immunosuppression, in most cases prolonged time on dialysis, abnormal or reconstructed lower urinary tract and prolonged use of urinary catheters [21].

This chapter aims at discussing the management of UTI in children with different CKD stages. Because of the fact that the general rules of UTI management are similar to those used in children without CKD, only the most important peculiarities will be emphasized.

2 Methods

A systematic literature search has been performed for the last 10 years in MEDLINE and the Cochrane library with the following key words: “urinary tract infections” and “chronic kidney disease”, “renal insufficiency”, “renal failure”. Limitations were children aged 0–18. Only publications with abstracts have been considered. A total of 167 publications were found. After screening by titles and abstracts only 24 studies have been included in the final analysis. These publications were supplemented by additional articles obtained from their bibliographies published before 2008 but considered as very important on this topic.

The studies were rated according to the level of evidence and the strength of recommendations graded according to a system used in the EAU guidelines modified from the Oxford Centre for Evidence-based Medicine [22].

In addition, guidelines concerning UTI in children and – separately – CKD in children, published by international pediatric and nephrological associations have been taken into consideration. Textbooks also have been reviewed to provide relevant background and context for this analysis.

3 Results

Studies on UTI in children with CKD are scarce. Moreover, CKD is not addressed with particular reference to pediatric UTI in most cases of literature.

The incidence of UTI in children with different stages of CKD is unclear. It is only known that UTI occurs in 15–33% of children after renal transplantation [21]. Because of higher serum creatinine level, UTI in

patients with advanced stages of CKD is considered complicated or atypical UTI [15].

3.1 An association between UTI and CKD in children

An important contribution to the understanding of the role of UTI in children with CKD was made by study of Salo et al. [17]. They assessed relationship between childhood UTI and CKD by reviewing literature and medical records of patients with CKD monitored at Oulu University Hospital in Finland. Of 366 patients with CKD, only three had recurrent UTIs in childhood. The authors concluded that in the absence of serious congenital anomalies, the etiologic fraction of childhood UTIs as a cause of CKD was less than 1%, and that a child with normal kidneys is not at significant risk of developing CKD with recurrent UTIs. In another study, the clinical (preserved kidney function measured by eGFR) and urodynamic (urinary continence) outcomes were evaluated in the cohort of patients (67 children) with a recto-bladder neck fistula [23]. The results showed that recurrent UTIs were an independent predictor only of incontinence, while hydronephrosis, vesico-ureteric reflux (VUR), a solitary kidney, and urethral anomalies were an independent predictor of CKD. In studied children, CKD was likely multifocal in origin, however UTI seemed not to be significant [23]. Analogic observations concern a group of children with posterior urethral valves (PUV). UTIs were not associated with poor renal outcomes, while nadir creatinine and combination of oligohydramnios, renal cortical cysts, and increased renal echogenicity on antenatal ultrasound scan were predictors of final renal function [24], [25], [26], [27], [28]. Also, renal scarring and CKD in children with neurogenic bladder secondary to spina bifida were not connected with UTI, whereas dilatating VUR remained significant [29]. In one long-term follow-up study, risk of deterioration of renal function was investigated in 86 adult women with UTI in childhood [30]. Renal damage was evaluated by ^{99m}Tc-dimercaptosuccinic acid (DMSA) scan and glomerular filtration rate (GFR) by ^{51}Cr-edetic-acid clearance. The results showed that the women had remarkably well preserved renal function. Of those women with renal damage in DMSA, only one had CKD stage 3 and 14 stage 2.

Special groups among CKD children are patients after RTx [31]. Immunosuppressive therapy in conjunction with per- and post-operative instrumentation of the urinary tract, renders renal transplant recipients prone to infectious complications. In addition, RTx recipients often have various co-morbidities such as cardiovascular disease and anomalies of urinary system, further increasing their risk of infections, of which most common are UTI, ranging from 7 to 86% [32], [33], [34]. In the Danish population-based nationwide cohort of patients older than 16 years, RTx recipients had a 72-fold higher risk of first-time hospitalization for pyelonephritis compared to matched population controls [35]. The highest risk of pyelonephritis was observed within the first six months post-transplantation [34], [35], [36]. Transplantation-related recurrent UTIs may be connected with urological abnormalities in pediatric patients. UTI was significantly higher after kidney transplantation (grafts from both living and deceased donors) in patients with lower urinary tract dysfunction (LUTD) such as neurogenic bladder, PUV, when compared with those without LUTD [37], [38], [39]. Infectious complications (UTI, wound infection, pneumonia) and postoperative urinary tract infection incidences were 68% vs. 25.7%, and 60% vs. 11.4% in above groups, respectively [40]. Different results showed Saad et al. [41]. They compared outcomes of living donor renal transplantation in children with ESRD resulting from LUTD vs. other causes. The causes of LUTD were PUV (41.4%), VUR (37.9%), neurogenic bladder (10.3%), prune belly syndrome (3.4%), obstructive megaureter (3.4%) and urethral stricture disease (3.4%). The rates of urinary tract infections were 24 and 12% in groups LUTD and non-LUDS, respectively, but were not significant. Graft survival rates and eGFR were not different in both groups. Authors concluded that one of the keys for successful kidney transplant is optimization of urinary tract for allograft. In LUTD group, 25 of the 29 patients (86.2%) underwent ≥1 surgery. Pre-transplant nephrectomy was performed in 15 of the 29 patients (51.7%), PUV ablation in nine patients (31%) and ileocystoplasty in four patients (13.7%) [41].

In summary, current studies show that vast majority of UTI cases in children doesn't directly lead to CKD for whose occurrence of other factors plays a significant role. However, children with CKD can be susceptible to UTI. Severe UTIs may have an adverse influence on the course of coexisting CKD and enhance the progression of the disease [42].

3.2 Etiology of UTI

Bacterial UTI is most common in children with CKD. UTIs in patients (both adults and children) with CKD stages 3–5 treated conservatively and on HD were mostly caused by *E. coli* (58.3%) and Klebsiella spp. (29.4%). Other bacteria were: *Streptococcus*, Proteus spp., *Pseudomonas aeruginosa* and *Staphylococci* [43], [44].

Such microorganisms as fungi, viruses, parasites and mycoplasma species may also cause UTI, but definitely more seldom. Fungal infections are more common in immunosuppressed patients. The BK polyoma virus can be a pathogen in the pediatric renal transplant population, especially in younger children and in those receiving a kidney from cadaveric donors [45].

3.3 Diagnostic evaluation

Diagnosis of UTI in CKD children and those without CKD generally should follow the same principles. Many clinical aspects of UTI are well characterized and described in detail elsewhere in this book.

However, patients with CKD are complex. Particular attention should be paid to basic renal disease which leads to CKD, stage of CKD and metabolic disorders connected with it [16], [20], [21]. Next important issue is presence of anatomical or functional urinary system abnormalities. Bladder and bowel disorders as factors predisposing to UTI must be discussed with children and/or their parents [46].

Presentation of UTI varies with age. In small children it is impossible to differentiate between lower and upper urinary tract infection, so all UTIs should be treated as pyelonephritis [16]. Children must be carefully examined with particular attention to genitalia, anal area and sacral lumbar region. Common symptoms of UTI may be mimicked by conditions typical for CKD (also post-transplant), e.g. red and white cells in the urine from a urinary stent or because of basic renal diseases, altered urinary frequency due to a small poorly functioning bladder, polyuria due to loss of urinary concentration ability. Immunosuppression may reduce fever.

Laboratory diagnosis of UTI bases on detection of pathogenic microorganisms and an inflammatory response in the urinary tract. Laboratory urine culture is the recommended method for UTI diagnosis [12], [13], [15], [16]. Urine has to be collected under defined conditions and investigated without delay. Some data should be taken into consideration. Urinary leucocyte count is broadly inversely proportional to the urine volume that is why in patients with advanced CKD stages (polyuria) may be low. Urine dilution can also cause misleading reduction in bacterial colony counts. Currently a definition of “significant bacteriuria” depends on the manner of urine sampling and the grade of its density. Some patients with CKD and “significant bacteriuria” may not have true infection [47], [48]. Isolated bacteriuria may be only a symptom of colonization [15], [16], [49]. On the other hand, in some cases a low bacterial colony count may represent true infection [20], [48]. Therefore, in patient with symptoms suggestive of UTI each bacteriuria can be essential, particularly if a single organism is cultured and leucocytes in urine are present.

It should be remembered that some children may need not only bacterial urine culture, but also fungal urine culture or different diagnostic tests for detection of other than bacteria microorganisms which may be causative factors of UTI. If fungal infection is suspected, urine microscopy and cytology may give a more rapid result than culture [32].

Diagnostic process of UTI in CKD children should involve determination of factors, besides CKD, predisposing to UTI. Imaging procedures after the first UTI can be focused on finding severe urinary tract abnormalities, independently on laboratory markers of kidney function and suspected cause of CKD [17]. Ultrasonography is an important primary imaging tool. Other investigations depend on indication. When a child with CKD requires further imaging, a stage of CKD (eGFR) and additional factors that may impair kidney function, for example general anesthesia, contrast agents, dehydration, must be taken into account.

To exclude lower urinary tract dysfunctions, micturition protocols, uroflowmetry, and bladder ultrasound (performed when bladder is filled and after emptying), following by urodynamics, may need to be used (depending e.g. on age and type of CAKUT).

In summary, children with CKD and UTI must be assessed as a whole. In case of UTI suspicion and also in periodic check-ups of CKD children history, physical examination, urine analysis, urine culture and blood tests (CRP, procalcitonin, complete blood count) should be taken into account. Blood culture should be included if systemic symptoms are present.

3.4 Treatment

The general treatment strategies of UTI in children with CKD are based on the same principles as in children with normal renal function [15], [16], [47], [50]. The aims of UTI treatment are: rapid recovery from complaints, elimination of pathogenic microorganisms from urinary tract, prevention of related complications (such as urosepsis, urolithiasis and renal abscess), as well as prevention of further impairment of kidney function. Moreover, elimination – if possible – of factors predisposing to UTI (both anatomical and functional) and prevention of recurrences.

UTI must be recognized and treated during the early stage of the disease. The choice of drugs depends on severity of the symptoms, the causative microorganisms, stage and type of CKD and whether complicating factors are present. Usually, first drug therapy is empirical according to suspected bacteria, known general bacteria drug-sensitivity and local microbial analyses. When clinical response is not observed, the drug should be replaced according to the result of urine culture and information about drug-sensitivity of cultured bacteria.

What is important, special attention needs to be paid when prescribing drugs in advanced stages of CKD. Drug handling (bioavailability, volume of distribution, protein binding, metabolism and renal clearance) can be altered. Some drugs may be cleared by HD and PD. Moreover, in CKD ability to urine concentration (and at the same time drug concentration) may be changed, what is connected with urine volume. Most children with early stages of CKD have normal or increased urine volume. Children with advanced stages of CKD may be polyuric, oliguric or even anuric (on HD and PD). Above pathophysiological facts have implications for proper UTI therapy.

General principles are as follows. In case of impaired renal function dosage of drugs cleared renally should be adjusted to the eGFR rate, which can be calculated from the current serum creatinine and body length according to Schwartz formula [5]. Patients with CKD are often taking multiple medications, thus increasing drug interactions. Nephrotoxic drugs are contraindicated. When they are necessary, they should be used with caution with monitoring of kidney function parameters and wherever possible – drug level in blood. Therapeutic drug monitoring should be performed when administering aminoglycosides and glycopeptides. Nitrofurantoin is not deployed when the eGFR is less than 50% of the norm, because insufficient renal elimination does not allow to achieve very high urinary concentrations [51].

Drug dosage in children with reduced renal function is available in the literature (for example [52]).

The decision for oral or parenteral therapy complies with age, severity of the illness, and prerequisites for oral application. There are no systematic studies relating to specific drug application form in children with CKD. Moreover, children with CAKUT, the main cause of CKD, have been excluded from all randomized studies comparing the equality of an oral therapy to the parental treatment. Thus, decision on oral or intravenous therapy should be taken after analysis of total clinical circumstances.

The optimal duration of antibiotic therapy in children with CKD is not established. John and Kemper recommend 14-day antibiotic therapy in transplant pyelonephritis. Moreover, antifungal prophylaxis is given during high dose antibiotic treatment [21].

There are no data from randomized trials concerning asymptomatic bacteriuria treatment in children with CKD. Generally, treatment of asymptomatic bacteriuria is not recommended in children [15], [16], [47],

[50], [53]. However, some children with primary or secondary immunodeficiencies, including children receiving chronic immunosuppressive therapy (with organ transplants), and patients with planned urinary tract instrumentation are an exception. Moreover, pregnant adolescent girls should also receive treatment [15], [16], [21].

There are no studies relating to antibiotic prophylaxis in children with CKD. Results from randomized studies performed in general population of children with UTI have shown no benefits from antibiotic prophylaxis [13], [16], [44], [54], [55]. However, such management in children with urinary tract abnormalities (for example with VUR) still remains a controversial issue [56], [57]. So, antibiotic prophylaxis or alternative methods for preventing recurrent UTI in CKD children may be considered.

4 Further research

The current knowledge of many aspects of UTI in children with CKD is limited. Epidemiological data is missing. Interactions between uropathogenic microorganisms and immunocompromised patients with CKD are not clear. CKD is not one disease and pediatric CKD population is non-homogenous because of age, developmental processes, kidney growing, many causes and stages of CKD and differentiated courses of the disease. More studies into the pathophysiology of UTI in children with different stages of CKD are necessary. From clinical point of view, it is important to specify which UTI and in what children can influence kidney function negatively. In particular, studies are urgently needed to elucidate and validate host factors and genetic variations predisposing to renal scarring. Diagnosis of UTI in CKD patients is difficult because of overlapping symptoms, so there is a need to determine additional sensitive markers of UTI in this cohort. Next important issues are to establish groups of children with CKD who are particularly susceptible to UTI and/or require aggressive therapy and prophylaxis. Future research should also concern optimization of therapy (the choice of the appropriate drug and form of its application, duration of therapy, etc.). Also prospective multicenter studies on UTI course in CKD children would be helpful in forming future guidelines.

5 Conclusions

Children with CKD are susceptible to UTIs, so they require periodic control tests for the presence of UTI. When UTI is suspected, diagnosis should be confirmed as soon as possible and appropriate treatment should be started immediately. Antibiotics excreted mainly by the kidney require adjustment of the dose depending on the degree of kidney function.

Severe UTI in CKD children may promote an impairment of kidney function, especially in patients with advanced stages of CKD and those with urinary tract abnormalities, such as obstruction, reflux, polycystic disease. Because of long-term character of CKD and its serious prognosis, eliminating of factors predisposing to UTI (both anatomical and functional, like bowel and bladder dysfunction) and prevention of UTI recurrence are of particular importance. Patients with CKD in the course of known congenital urinary system defect must undergo further diagnostics in case of recurrent UTI. Urinary tract reconstruction seems to be essential before kidney transplantation.

CKD children (also adults) must be treated holistically and individually. In many cases they suffer from additional diseases, so relationships between CKD, UTI and comorbidities should be taken into account. Well-performed controlled trials are required for better UTI management in CKD children.

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