

CHAPTER 7.5 Urinary tract infections

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1 Definition

Urinary tract infection (UTI) is a relevant and frequent complication after paediatric kidney transplantation (KTx); febrile UTI must be distinguished from afebrile UTI. Bacteria growth in excess of 10^5 colony forming units/ml in freshly voided urine is abnormal. The method of bladder urine collection is important (invasive, non-invasive) and has been discussed elsewhere; it mainly depends on the age of the patient and the clinical presentation [1]. Other typical additional urinary abnormalities in UTI include leukocyturia, haematuria and nitrituria, often detected by dipstick testing. Testing for inflammatory markers (leukocytosis, CRP, procalcitonin) is important [2].

2 Risk factors

Risk factors for UTI *before kidney transplantation* include anatomical factors (hydronephrosis, posterior urethral valves, vesicoureteral reflux [VUR] and others) and lower urinary tract dysfunction (e.g. neurogenic bladder). Urinary tract malformations are a common cause of end-stage kidney failure in children. This has implications for the diagnostic work-up prior to KTx: in addition to renal ultrasound, MCUG/CEUS (contrast enhanced ultrasonography) and uroflowmetry should be performed and in more complex patients (posterior urethral valves, neurogenic bladder, Prune Belly syndrome and others) urodynamic studies are necessary [2].

After kidney transplantation, secondary VUR into the transplanted kidney in a previously normal urinary tract must be considered a significant risk factor for febrile UTI. Ranchin et al. [3] demonstrated a 58% prevalence of VUR and an

increased rate of UTI. Whether strict anti-reflux surgery can reduce the risk of febrile UTI after renal transplantation has not been studied. Surgical correction of VUR into the kidney graft was shown to reduce the incidence of UTI in a small series, but was associated with obstructive complications [4], particularly in the cohort with associated abnormal bladder anatomy. More recently, Deflux® injection has been performed also in children after KTx, although this appears to be more challenging than in native VUR [5]. Foreign material such as stents, urinary catheters and suture material can cause UTI due to bacterial (and fungal) colonization. Therefore, these devices should only be used for a short time or avoided if possible.

Sex: The rate of UTI in girls is much higher than in boys [6]. Anatomical reasons (e.g. shortened urethra) may be relevant, and sexual activity must be taken into account in female adolescents. *Immunosuppressive therapy* has an impact on defence mechanisms; one study suggested an increased risk in patients on mycophenolate-based regimens [7]. An accumulation of risk factors (e.g. unnecessary catheterisation or manipulation of the urinary tract) should be avoided or at least limited in immunocompromised patients.

3 Clinical presentation

Fever and renal dysfunction are the typical features of febrile UTI after KTx. Some patients may develop symptoms and signs of urosepsis. An acute, concomitant decline in renal function is common during UTI [8], reflecting the inflammatory parenchymal response and the risk of tissue damage to the transplanted kidney (scarring). Acute rejection episodes may be triggered by febrile UTI [9], and also the development of an intrarenal abscess in the graft following UTI has also been described [10].

4 Prevalence

A high prevalence of febrile UTI in children after KTx has been reported in several retrospective studies [2, 7]. They are not limited to the immediate post-transplant period but also occur later, especially in girls [9]. In paediatric studies, the prevalence ranged from 15% to 33%. A higher prevalence of up to 61% has been reported in adults, but some studies have used less stringent inclusion criteria

and for instance included patients with (asymptomatic) afebrile bacteriuria. Pelle et al. demonstrated a prevalence of UTI of 75.1%; 18.7% of these patients developed transplant pyelonephritis [11]. This leads to a higher hospitalisation rate especially in children.

5 Epidemiology

Although *Escherichia coli* remained the most commonly isolated microorganism, as in other studies, it was isolated less frequently than in the general paediatric population, where it is found in up to 80% of UTIs [12]. This may be due to the underlying immunosuppression and colonisation of the urinary tract. Therefore, from a practical point of view, it is important that surveillance urine cultures are performed in every patient at risk to increase awareness of local antibiotic resistance. Particular attention should be paid to patients with lower urinary tract abnormalities and neurogenic bladder requires attention, in order to identify bacteria with multiple resistances (*Pseudomonas* species and *Enterobacter*). In recent years, there has been an increase in UTI with drug-resistant pathogens such as vancomycin-resistant *Enterococcus*, -extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E), carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Enterobacteriaceae*, and carbapenem-resistant *Pseudomonas* species [13, 14].

6 Treatment

Febrile UTI post-transplant on immunosuppressive therapy should be considered as complicated pyelonephritis and be treated aggressively with parenteral antibiotics, at least until clinical improvement and culture results are available. The optimal duration of treatment has not been studied, but most would favour a total (i.e. parenteral followed by oral treatment) of 10–14 days in transplant pyelonephritis [2, 7]. As *Enterococci* and *Pseudomonas* species are more common, we currently use an initial combination of ceftazidime and ampicillin/sulbactam or clavulanate to cover *E. coli*, *Pseudomonas* and *Enterococci*. Others have recommended ampicillin and gentamicin for the same reason [13, 14], but nephrotoxicity of the latter is a concern. Fungal urinary tract infections may occur and require specific treatment; often antifungal prophylaxis is often given during high-dose antibiotic treatment to reduce the risk of this complication. It

is not uncommon for steroid doses to be increased during febrile UTIs to avoid symptoms of adrenal insufficiency.

Afebrile symptomatic UTI may be treated with oral antibiotics unless there are specific risk factors are present (renal dysfunction etc) [2, 13, 14]. Again, treatment should be specific and an oral cephalosporin may be the first choice. Whether asymptomatic UTI need to be treated remains controversial and is often an individual decision. In patients with abnormal bladder anatomy and regular catheterisation, such as those with spina bifida, colonisation is common and symptoms such as dysuria may be absent. There is no evidence or consensus on whether bacterial colonisation in these patients requires treatment, including bladder washing with antibiotics. In our centre, we currently only treat symptomatic patients with abnormal bladder anatomy and bacterial colonisation and do not use antibiotic bladder irrigation.

7 Diagnostic workup and prevention of (febrile) urinary tract infection

Non-invasive investigations include sonography in the acute infection to demonstrate or exclude dilatation of the urinary tract, tissue perfusion and bladder emptying. Diagnosis of vesicoureteral reflux into the graft may be facilitated by conventional radiological cystography (MCUG) or contrast-enhanced ultrasonography. Static dimercaptosuccinic acid scintigraphy (DMSA scan) is an elegant method of documenting renal scarring when performed after 6 months or more after graft pyelonephritis. Patients with voiding dysfunction may require further work-up including uroflowmetry or complex urodynamic studies.

Prevention and prophylaxis of febrile UTI after KTx are important. This includes antibiotic chemoprophylaxis, e.g., with trimethoprim. Most importantly, urotherapy should be offered to candidates with lower urinary tract dysfunction; in severe cases, intermittent catheterisation may be necessary. If vesicoureteral reflux into the graft is present and febrile UTI persists despite conservative measures, surgery or Deflux® injection should be discussed. Probiotics are often used in children after KTx, although there are no controlled trials on their benefits or side effects [16].

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