Approach to Pediatric Patients with UTI in the PICU

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J Pediatr Intensive Care 2016;5:64–68.

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Abstract

Urosepsis and UTI are common causes and comorbidities in children admitted to the pediatric intensive care unit (PICU). Risk factors for morbidity and mortality in pediatric patients include young age (< 2 years old), presence of congenital renal anomalies of the urinary tract, and immunosuppression from transplant (kidney, liver, heart, and bone marrow). Workup of urosepsis focuses on identification of renal anomalies of the urinary tract through ultrasound, X-ray cystourethrogram, urodynamic studies, and CT/MRI. Management consists of appropriate choice in antibiotics, hemodynamic instability, and prevention of acute kidney injury (AKI) with particular recognition that chronic renal failure can be present in all chronically ill children, which is not limited to pediatric patients with congenital anomalies of the kidney urinary tract. This review includes a review of the workup and management of pediatric patients with UTI and urosepsis in both healthy patients and patients with known anomalies of the urinary tract.

Keywords

- UTI
- urosepsis
- renal anomalies
- neurogenic bladder
- renal transplant

Introduction

Urinary tract infection (UTI) is an infection common to both adults and children. However, there are unique features of this infection in children that make the diagnosis, management, and complications of this common problem different and more comprehensive as compared with adults. This review discusses the workup and management of UTI in the pediatric intensive care unit (PICU) regarding identification of renal anomalies, management of complex bladders, and management of kidney-transplant recipients.

UTI is a common source of infection in children admitted to the PICU for fever associated with hemodynamic instability. Making the diagnosis of UTI and identification of the signs and symptoms of shock in a timely intervention is imperative for survival and avoiding complications associated with multiorgan failure.¹ Pediatric patients younger than 3 years typically will present with signs of systemic symptoms that include (but are not limited to) fever, tachycardia, vomiting,

diarrhea, and hypotension. Indeed, the presence of fever alone is a strong indicator that the infection involves the renal parenchyma that leads to renal damage in many cases.^{2,3} In contrast, older children (generally > age 3) are better able to verbalize or communicate their symptoms and will complain or show signs of dysuria, abdominal pain, increased frequency, and urgency symptoms before the onset of developing systemic symptoms. The presence of such systemic symptoms as fever can be argued to be signs of advancing infectious process, so young children in particular are at higher risk for urosepsis, systemic inflammatory response syndrome (SIRS), and complications of UTI.

In a child younger than 3 and patients already on an intermittent catheterization program (ICP), a catheterized sample should be obtained for urine cultures. In older children in whom a clean catch can be obtained reliably, this can be an alternative to catheterizations. It is an unfortunate common occurrence that a child is treated after a urine-bag sample is obtained. Because it was collected “clean catch”

received
December 5, 2014
accepted after revision
January 3, 2015
published online
October 19, 2015

Issue Theme Nephrology in Pediatric
Critical Care; Guest Editors: Eunice John,
MD, Dch, FAAP, and Gokhan Olgun, MD

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Verlag KG, Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0035-1564737>.
ISSN 2146-4618.

or because the parent did not want catheterization to be performed, the urine culture cannot be used diagnostically. For infants and small children, a 5F feeding tube is the most common catheter device used; in toddler-aged children a 6F feeding tube catheter can be used.

Treatment in Urosepsis and Consideration of Renal Function

Timely identification and treatment of a UTI causing sepsis is the key to reducing morbidity, mortality, and complications from UTI. Empiric antibiotic treatment decisions are commonly based on the American Academy of Pediatrics (AAP) and Redbook guidelines and are largely determined by age (e.g., preterm, term), community- versus hospital-acquired infections, and the presence of meningitis in very young infants along with clinical signs and symptoms of urosepsis (→Table 1).^{4,5} Despite the presence of renal dysfunction (AKI [acute kidney injury]) being common in the setting of urosepsis, none of the guidelines take into account renal dysfunction when choosing antimicrobial therapy. This is primarily because this aspect of choosing antimicrobial therapy has not been studied with most studies focused on comorbidities (meningitis) and antibiotic-resistance patterns. However, the presence of AKI or chronic kidney disease, or both, must be considered when making treatment recommendations. Choosing an antibiotic with renal toxicity has the potential to worsen renal function, which may already be compromised by hypotension and SIRS that will increase morbidity, mortality, and complications from UTI in these patients.⁶ Furthermore, it is not enough to just aim for “nontoxic” or avoidance of higher levels as AKI can be seen with medications such as vancomycin or gentamicin even when trough levels stay

in the therapeutic range and are not elevated. There are no recommendations or publications or controlled studies looking at outcomes in patient using nephrotoxic versus non-nephrotoxic antimicrobials in patient with urosepsis that is surprising and is an area of study needed to be explored.

Once the patient is hemodynamically stabilized and cultures are obtained, parenteral antibiotics should be given to febrile patient as the initial mode of therapy. The patient with presumed gram-negative sepsis (e.g., *Escherichia coli*) needs to be monitored closely for initial few hours of antibiotics as lysis of bacteria can result in a SIRS episode and the patient may need additional hemodynamic support during this time. Poorly managed hypotension and shock can lead to AKI, and this problem not only complicates the management in the PICU but is also the leading risk factor for mortality in children.⁷

The decision to place an indwelling catheter in a critically ill patient requires careful thought and consideration. Monitoring urine output in a septic or critically ill patient is a common indication; however, it is important to recognize that this is an additional risk factor for bacterial or fungal infection. For patients on an ICP, it is reasonable to place an indwelling Foley catheter to ensure that any functional urinary tract dysfunction or bladder dysfunction does not further impact the risk of AKI because renal dysfunction is already a risk factor in the presence of hypotension and poor perfusion in the patient with urosepsis. If an indwelling Foley catheter is placed, there needs to be a plan for its removal when urine output is established and renal function is stable.

Most patients with urosepsis improve with a combination of hemodynamic support (fluid boluses, inotropic agents) and antimicrobial therapy in the initial 24 to 48 hours of treatment, but some may worsen. In these cases, if

Table 1 Commonly used parenteral antibiotics for empiric therapy of urosepsis^a

Antibiotic	Dosing for normal renal function
Ampicillin	100–200 mg kg ⁻¹ /24 h divided every 6 h, max 12 g/24 h
Ceftriaxone	75 mg kg ⁻¹ /24 h single daily dose, max 2 g/24 h
Gentamicin	7.5 mg kg ⁻¹ /24 h divided every 8 h, check peaks/troughs
Cefepime	100 mg kg ⁻¹ /24 h divided every 12 h, max 6 g/24 h
Cefazolin	50–100 mg kg ⁻¹ /24 h divided every 8 h, max 6 g/24 h
Cefotaxime	100–200 mg kg ⁻¹ /24 h divided every 8 h, max 12 g/24 h
^b Weight-directed dosing (intravenous [IV])	for gentamicin
Preterm-postnatal (PNA)	< 1,200 g: 4–5 mg/kg/dose every 48 h
	< 7 d ≥1,200 g: 4–5 mg/kg/dose every 36 h or 4 mg/kg dose every 24 h
PNA 8–28 d	< 1,200 g: 4–5 mg/kg/dose every 36 h
	≥1,200 g: 4–5 mg/kg/dose every 24 h
^b Traditional dosing: IV, intramuscular (IM)	for gentamicin
	PNA 0–28 d and < 1,200 g: 2.5 mg/kg/dose every 24 h
	PNA < 7 d and ≥1,200 g: 2.5 mg/kg/dose every 12 h
	PNA ≥ 7 d: 1,200–2,000 g: 2.5 mg/kg/dose every 8–12 h ≥2,000 g: 2.5 mg/kg/dose every 8 h

^aModified table by Abuazza et al.^{4,5}

^bDose based on age and weight.

sensitivities are unknown and the patient is worsening, consider adding a second agent with broader coverage. In addition, obtain imaging to further assess why the patient is not responding to therapy. This can be due to an abscess, obstruction, or non-urinary tract problem. An abdominal ultrasound (limited) is the easiest, quickest, and safest initial approach and should be done first, even if previously performed on initial admission. If a cause for failing to respond to therapy is not elucidated with a renal ultrasound, other testing can be performed. The gold standard for diagnosis of pyelonephritis is a DMSA (dimercaptosuccinic acid) scan; this will also give information about renal scarring. A computed tomographic (CT) scan with contrast will give information about whether an abscess is present. If a CT is ordered, a CT without contrast should be ordered at the same time to look for kidney stones as this can present in a similar way as a UTI or concurrently with a UTI. A Mag-3 scan will indicate whether obstruction from worsening hydronephrosis is present or not.

UTI in Patients in Healthy Infants: Identification of Renal Anomalies

In comparison with adults, risk factors for urosepsis and complications of UTI in pediatric patients include congenital anomalies of the urinary tract, vesicoureteral reflux (VUR), ureteropelvic junction obstruction (UPJ), duplicated collecting system, and posterior urethral valves (PUVs), to name the most common.⁸ Because children have developing immune systems, they are not immunocompetent and so are at greater risk of serious infection leading to urosepsis.⁹

The incidence of identifying renal anomalies as a risk factor for urosepsis is highest in children younger than 2 years, but it can be seen in older children as well. While routine comprehensive prenatal ultrasound is responsible for identifying most congenital anomalies of the kidney and urinary tract prior to birth, this cannot be solely relied on due to mothers who lack prenatal care (that includes a third-trimester comprehensive ultrasound), inadequate communication of prenatal records to pediatricians, or lack of appropriate follow-up and workup in infants identified with hydronephrosis, pelviectasis, and pelvocaliectasis. Therefore the AAP has recommended renal and bladder ultrasounds on all infants younger than 2 years with a febrile, culture-proven UTI. These recommendations state that if hydronephrosis is identified, further workup for VUR or UPJ is needed that may consist of VCUG and/or Lasix renogram. Controversy exists over this recommendation with several studies showing that significant VUR can be seen among infants with a normal renal ultrasound and call into question whether ultrasound serves as an adequate screening tool for renal anomalies.^{10–12} Therefore, in the outpatient or general pediatric wards patient, it is left to the discretion of the pediatrician to obtain further workup and/or refer the child for further consultation with pediatric nephrologist or pediatric urologist following a febrile UTI. Certainly the standard workup for a febrile UTI (beyond renal ultrasound) in any healthy child will show variations of practice between providers.

However, among infants and children with urosepsis or SIRS who are admitted to the PICU, a more comprehensive workup is required due to the severity of their clinical presentation and should include both a renal ultrasound and VCUG. In terms of the timing of the VCUG following the UTI, early studies indicated a high false-positive rate when the VCUG was obtained right after the UTI, so many providers waited a few weeks before obtaining the VCUG. However, more recent studies show that the incidence and severity of VUR is not significantly affected if the VCUG is obtained right after diagnosis of a UTI as compared with waiting several weeks.^{13,14} The decision for initiating prophylactic antibiotics at discharge and prior to or following a VCUG is controversial as well and will vary across provider and practices, and it needs to be determined on a case-by-case basis.

In summary, the workup for a patient with urosepsis should include both a renal ultrasound and, in most cases, a VCUG to look for renal anomalies. Renal ultrasound alone is not sufficient workup in infants and children admitted to the PICU for urosepsis. For older children (> age 10 years) with no prior history UTI and now with urosepsis, the workup will vary on a case-by-case basis.

Urinary Tract Infection and Urosepsis in Patients with Known Renal Anomalies

Infants and children with a known medical history of a congenital anomaly of the urinary tract such as hydronephrosis (pelviectasis and pelvocaliectasis) are at greater risk for UTI and urosepsis regardless of the degree of hydronephrosis. Certainly, patients with high-grade or severe hydronephrosis are considered to be the group having most significant risk of UTI and urosepsis and many of these patients will be on antibiotic prophylaxis that is an important consideration when choosing antimicrobial therapy. Among these patients, further inquiry should be made into recent UTIs with culture results and antibiotics used in the recent past to further narrow antibiotic treatment if a UTI is indeed diagnosed later. If these complex patients have recurrent UTIs with antimicrobial-resistance patterns identified, I would consider double coverage with antimicrobial therapy and choose antibiotics with presumed sensitivity. All patients with a history of congenital anomaly of the urinary tract should receive a renal ultrasound as part of their workup in the PICU because an acute obstruction, or worsening hydronephrosis, may declare itself as a UTI and urosepsis.

Urinary Tract Infection and Urosepsis with Neurogenic Bladder

Among patients with congenital anomalies of the urinary tract or patients with spinal cord disorders associated with neurogenic bladder, it is important to inquire about whether an ICP is in place and/or prophylactic antibiotic are being used. For patients with an ICP, the bladder is no longer sterile, so urine cultures will generally be positive or show mixed organisms, which makes the diagnosis of a UTI as a cause for urosepsis more challenging. Not all urine cultures from patients on ICP should be

treated. Instead, you have to rely on clinical indicators of infection (hematuria, cloudy urine, foul-smelling urine, abdominal pain, fever), or the presence of systemic symptoms, and often the patient or parent will suspect a UTI based on an observed change in appearance of their urine specimens. In addition, the report of “dysuria” is not reliable in a patient on an ICP as the urethra is presumably desensitized with routine catheterizations and possible bacterial colonization. Some patients with dysfunctional bladder may have augmented bladders in addition to their ICP. Because many bladder augmentations utilize gastric tissues that contain mucous-secreting glandular cells, it is not unusual to see mucous and blood-tinged urine samples that are normal findings in these patients.

For patients with complex bladders and urogenital tracts, pediatric nephrologist or pediatric urologist should be consulted for management. The decision to place an indwelling Foley will depend on a whole host of factors that are individualized for each patient. For a patient on a frequent intermittent regimen, it will make sense to place an indwelling Foley but recognizing that an indwelling versus ICP can lead to increased bacterial colonization and risk for bacterial and fungal UTIs as well as sepsis.

Urinary Tract Infection and Urosepsis in Kidney-Transplant Patients

Kidney-transplant patients have several risk factors for UTI, which will vary from patient to patient, and are at higher risk for urosepsis and complications from UTI. First, being immunosuppressed places them at high risk for UTI. Consultation with a pediatric nephrologist is needed to decide whether a reduction in immunosuppression is needed or not in a particular transplant patient with a UTI and this decision is made in a case-by-case basis. Indeed, the symptoms of UTI in a transplant patient can look identical to a severe acute rejection. For critically ill kidney-transplant patients in whom a UTI is confirmed, immunosuppression should be reduced accordingly.

In addition to bacterial UTIs, kidney-transplant patients are at higher risk for opportunistic infections with viral infections. They are most often entertained as a cause when a bacterial cause has been ruled out by negative urine cultures. While several viruses can be the culprit, one particular virus called BK, named so based on the initials of the index patient, is a commonly identified cause for viral infection in immunosuppressed patients, especially kidney-transplant recipients. BK has several clinical manifestations in immunocompromised patients that include hemorrhagic cystitis, ureteral stenosis. And/or nephropathy in the kidney transplant itself that is made by renal biopsy.¹⁵ BK infection is limited to the urinary tract and causes clinical symptoms only in immunosuppressed patients.

Other viral infections such as cytomegalovirus (CMV), adenovirus, and fungal infections also occur in kidney-transplant recipients and should be considered as clinically symptoms would indicate them as a causative infection. Depending on the practice of individual laboratories, quantitative polymerase chain reaction (PCR) for these viruses (including BK) can be done on urine or blood samples. It is important to get quantita-

tive versus qualitative PCR because quantification with a high viral load will indicate infection where as a lower viral load may indicate colonization. There are some kidney-transplant patients who have positive viral PCR at low levels for a long period of time with no apparent clinical infection. Therefore qualitative PCR are not useful in kidney-transplant patients.

A second risk factor for UTI in kidney-transplant patients is the altered anatomy. The kidney transplant is typically placed orthotopically in the pelvis, extraperitoneal location, and is palpable in the right or left lower quadrant. The main kidney transplant renal vein and artery are most often anastomosed to the internal iliac arteries and veins with the transplanted ureter reimplanted into the bladder wall, along with the two native ureters still in place. This positioning of the kidney transplant in close proximity to the bladder may result in mild hydronephrosis, VUR into the transplant, and a high risk for pyelonephritis with a simple cystitis.

In addition, kidney-transplant patients who were oliguric or anuric prior to transplant may have poorly compliant and functioning bladders. After transplant when bladder capacity is suddenly increased from heavy urine production, patients can have recurrent UTIs and pyelonephritis from a poorly compliant and refluxing bladder. Furthermore, a new kidney transplant may represent challenges in toilet training that were placed on hold when these children were oliguric/anuric, which can lead to recurrent UTI. This is a common underlying mechanism for UTI in newly transplanted young pediatric patients. Proper bladder training techniques, anticholinergic medication, intermittent catheterization, and prophylactic antibiotics (oral or intravascular) are treatment approaches used in these patients. Most of these kidney-transplant patients will have resolution of recurrent UTI over time with these treatment strategies.

For most kidney-transplant patients, a UTI often results in a mildly increased serum creatinine above their usual baseline. This typically does not exceed 20%, and the serum creatinine will return to normal with hydration and antibiotic treatment. The presence of shock symptoms and hypotension can cause AKI that may be severe. It is this group of patients, it is important to limit nephrotoxic agents as much as possible and reduce or stop blood pressure medications that can further contribute to hypotension. In addition, it is important to track calcineurin-inhibitor levels daily because clearance of this medication class is altered with reduced kidney function and drug-drug interactions with new antibiotics that have been started.

Kidney-transplant patients diagnosed with a UTI and urosepsis should have a transplant and bladder ultrasound to look for structural causes for their UTI. All kidney-transplant patients should be treated as a “complex UTI” in terms of length of treatment. For kidney-transplant patients on an ICP, the aforementioned recommendations for ICP apply and pediatric nephrologist and urologist should be consulted for bladder management, which will vary from case to case. Recurrent UTI in a kidney transplant is associated with significant damage that may cause irreparable damage and can be associated with a rapid decline in transplant function so this problem needs to be addressed. For recurrent UTI and pyelonephritis, a voiding cystourethrogram (VCUG) should be performed to look for

VUR into the transplant. Urodynamics may also be performed to further identify the causes of recurrent UTI. Nonsurgical and surgical approaches to recurrent UTI in a transplant patient are decided on in a case-by-case basis. Reimplantation of the transplanted ureter is a surgical option for VUR. However, this is not performed unless the patient has failed noninvasive and non-surgical approaches first. This may include bladder training techniques, anticholinergics, prophylactic antibiotics, and possibly an ICP. One popular approach to patients with recurrent UTI on an ICP is to do start gentamicin bladder irrigations in which a small volume of gentamicin (15–30 mL) is instilled into the bladder at night after the last intermittent catheterization. This is less useful among patients with an overnight Foley. In this group of patients you can use gentamicin bladder irrigations during the day right after intermittent catheterizations.

A third risk factor of UTI in kidney-transplant patients is the unusual occurrence of pyelonephritis in the native kidneys. Native kidneys are only removed prior to (or at the time of) transplant if they are causing uncontrolled hypertension, producing copious amounts of urine that cannot be repleted by oral hydration, nephrotic syndrome, recurrent UTI, or concerns for impending malignancy (Denys Drash or Frasier syndrome). For the most part, native kidneys are not surgically removed, and they involute spontaneously after kidney transplant and pose no additional problems. However, on occasion, there can be VUR into the native kidneys. This can easily be evaluated by a VCUg and a decision can be made for medical (ace-inhibitor) or surgical nephrectomy.

Summary of Recommendations

- Infants and small children younger than 2 years with a febrile UTI or urosepsis should have both a renal ultrasound and VCUg. The decision to place a child on prophylactic antibiotics should be made on a case-by-case basis and will depend on severity of urogenital abnormalities seen on imaging, renal function, clinical information, and comfort of the physician and parent with choosing, or not choosing, a long-term antibiotic for 6 months or longer.
- In children older than 2 years who present with a febrile UTI or urosepsis should have a renal ultrasound done and in many cases a VCUg as well, but the decision to perform this test and any additional testing etc (see the following recommendation) needs to be done on a case-by-case basis.
- In any age child in whom hydronephrosis (pelviectasis or pelvocaliectasis) is diagnosed on renal ultrasound, consultation with pediatric nephrologist or pediatric urologist should be made to decide on whether a Lasix renogram is required, additional workup is needed, whether prophylactic antibiotics should be started, and the plan for outpatient follow-up with one or both of these subspecialty services.
- For patients with a known renal anomaly who present with urosepsis should have a renal ultrasound performed, and possibly additional testing per the pediatric nephrologist or pediatric urologist to determine whether there has been worsening of their underlying condition leading to

the present clinic state of urosepsis. Careful attention must be paid to choosing empiric antimicrobial therapy that is susceptible to most recent organism sensitivity pattern, if patients have had a recent UTI in the last several months. Consider double coverage in very ill patients. Also, consider the presence of chronic kidney disease in this group of patients and choosing antimicrobial therapy that is the least renal toxic.

- For immunosuppressed patients with such a kidney transplant, consider opportunistic fungal and viral causes in addition to bacterial causes. Careful attention must be paid to choosing empiric antimicrobial therapy that is susceptible to most recent organism sensitivity pattern, if patients have had a recent UTI in the last several months. Consider double coverage in very ill patients.
- Placement of an indwelling catheter should be done in all patients with an underlying obstructive process or neurogenic bladder who are on an ICP. For all other patients, it should be avoided as much as possible. In all cases, the indwelling catheter should be removed as soon as clinically indicated.

References

- 1 Zawistowski CA. The management of sepsis. *Curr Probl Pediatr Adolesc Health Care* 2013;43(10):285–291
- 2 Pinson AG, Philbrick JT, Lindbeck GH, Schorling JB. Fever in the clinical diagnosis of acute pyelonephritis. *Am J Emerg Med* 1997; 15(2):148–151
- 3 Bachur R. Nonresponders: prolonged fever among infants with urinary tract infections. *Pediatrics* 2000;105(5):E59
- 4 Abuazza G, Nelson CT, Kiessling SG, et al, eds. *Pediatric Nephrology in the ICU*. Berlin Heidelberg, Germany: Springer-Verlag; 2009: Urosepsis, 11:163–170
- 5 Taketomo CK, Hodding JH, Kraus DM. *Pediatric Dosage Handbook*. 19th ed. Hudson, OH: Lexi-Comp; 2012:788
- 6 Thomas ME, Blaine C, Dawney A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int* 2015;87(1):62–73
- 7 Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003;167(5):695–701
- 8 Pohl HG, Belman AB. Congenital anomalies of the urinary tract. *Curr Pediatr Rev* 2014;10(2):123–132
- 9 Quie PG. Antimicrobial defenses in the neonate. *Semin Perinatol* 1990;14(4, Suppl 1):2–9
- 10 Mahant S, Friedman J, MacArthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. *Arch Dis Child* 2002;86(6):419–420
- 11 Arlen AM, Merriman LS, Kirsch JM, et al. Early effect of American Academy of Pediatrics Urinary Tract Infection Guidelines on radiographic imaging and diagnosis of vesicoureteral reflux in the emergency room setting. *J Urol* 2015;193(5, Suppl):1760–1765
- 12 Nelson CP, Johnson EK, Logvinenko T, Chow JS. Ultrasound as a screening test for genitourinary anomalies in children with UTI. *Pediatrics* 2014;133(3):e394–e403
- 13 Doganis D, Mavrikou M, Delis D, Stamoyannou L, Sifas K, Sinaiotis K. Timing of voiding cystourethrography in infants with first time urinary infection. *Pediatr Nephrol* 2009;24(2):319–322
- 14 Mahyar A, Ayazi P, Tarlan S, Moshiri A, Hamidfar M, Barikani A. When is the best time for voiding cystourethrogram in urinary tract infection of children? *Acta Med Iran* 2012;50(7):468–472
- 15 van Aalderen MC, Heutinck KM, Huisman C, ten Berge IJ. BK virus infection in transplant recipients: clinical manifestations, treatment options and the immune response. *Neth J Med* 2012;70(4):172–183