Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants

Angela Lai, MD,* Kyle O. Rove, MD,† Sachin Amin, MD,* Gino J. Vricella, MD,† Douglas E. Coplen, MD†

*Department of Pediatrics, Loyola University Medical Center, Chicago, IL

†Division of Pediatric Urology, Department of Surgery, Washington University School of Medicine and St Louis Children's Hospital, Saint Louis, MO

Education Gaps

1. Data on the criteria for diagnosis and management of urinary tract infections in neonates are limited.
2. The indications for urologic imaging and prophylaxis in neonates are unclear.

Abstract

Urinary tract infections (UTIs) contribute to a significant portion of bacterial infections in neonates and young infants. Criteria for the diagnosis, treatment, and imaging are more established in the 2- to 24-month-old age group. It may not be ideal to apply recommendations from the group older than 2 months to younger patients, because the presentation, risk factors, complications, management, and imaging may not be appropriate for this more vulnerable population. This review provides a summary of the available literature for diagnosis, treatment, and follow-up of a UTI in the neonate or young infant. We review data on imaging to assess for underlying congenital anomalies of the urinary tract. We also provide insight on the use of antibiotic prophylaxis, particularly when vesicoureteral reflux is identified.

Objectives After completing this article, readers should be able to:

1. Review the most common organisms and risk factors for urinary tract infections (UTIs) in the neonatal population.
2. Describe the criteria for diagnosis of UTIs and the appropriate scenario to assess for concurrent infections.
3. Review the management recommendations for neonatal and infant populations.
4. Review current recommendations for imaging and follow-up in infants after their first UTI.
5. Review indications for prophylactic antibiotic therapy after UTIs in early infancy.

AUTHOR DISCLOSURE Drs Lai, Rove, Amin, Vricella, and Coplen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CAP	continuous antibiotic prophylaxis
CFU	colony-forming unit
HPF	high-power field
RBUS	renal bladder ultrasonography
SPA	suprapubic aspiration
UA	urinalysis
UTI	urinary tract infection
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux
WBC	white blood cell

BACKGROUND

Urinary tract infections (UTIs) are the most common bacterial infection in febrile newborns. (1) Studies focused on febrile infants likely underestimate the true prevalence of UTIs in infants because most infants do not present with fever, especially in the neonatal period. (2) Estimated prevalence in infants younger than 2 to 3 months ranges from 4.6% to 13.6%. (3)(4)(5)(6)(7) The reported prevalence in children younger than 24 months is estimated between 7% and 15.4%. (4)(5)(6)

Previously, it was thought that UTIs may be a "sentinel event for an underlying renal anomaly." The quoted incidence of congenital anomalies of the kidney and urinary tract is 0.3 to 1.6 per 1,000 live births. (8) Most studies in children aged 2 to 24 months found that 12% to 30% had renal ultrasonography anomalies, primarily vesicoureteral reflux (VUR), during an evaluation after their first UTI. (9)(10) A few studies that specifically focused on infants in the NICU showed a much smaller incidence of anomalies (3%), perhaps suggesting that in the younger population, the likelihood of congenital anomalies is much smaller, and affected infants may require a more limited evaluation. (11) This review will concentrate primarily on neonatal UTIs in patients without a congenital anomaly, and provide recommendations for an appropriate evaluation to rule out such anomalies.

EPIDEMIOLOGY

Escherichia coli continues to be the most common causative organism for neonatal UTIs, representing up to 80% to 88% of cases (Table 1). (4)(6)(9)(12)(13) *Enterobacter* species and *Klebsiella pneumonia* follow closely behind. Less common pathogens include *Pseudomonas aeruginosa, Enterococcus* species, group B *Streptococcus, Staphylococcus aureus, Citrobacter freundii, Serratia marcescens,* and *Klebsiella oxytoca*. Fungal pathogens, mainly *Candida* species, are predominantly nosocomial in origin. (14) Boys with VUR are more likely to present with the less common pathogens. (4)(9) In the neonatal population, gram-positive pathogens (*Enterococcus faecalis, S aureus,* group B *Streptococcus, Streptococcus pneumoniae*) are rare. Of note, in infants presenting with *E coli* sepsis, galactosemia should be included in the differential diagnosis. (15)

There is a strong male predominance of UTIs in the neonatal and infant population (<3 months of age), which differs significantly from older infants and children. (3)(6)(9) In a prospective multicenter trial of 1,000 febrile infants younger than 60 days, the absence of circumcision increased the risk of UTI by almost 10-fold in boys: 21% in uncircumcised boys versus 2% for circumcised boys versus 5% in girls. (4) These findings are supported by a meta-analysis of a similar patient population and a population-based study in northern California that found that circumcision markedly lowered medical costs and hospital admissions, especially in the first 3 months of age. (5)(16)

White race and ill appearance were previously thought to be risk factors for UTI, but correlation with race has been called into question in more recent studies. (4)(5)(17) Although VUR remains the most common anomaly and has been associated with as many as 20% of neonatal UTIs,

TABLE 1. **Frequencies of Urinary Tract Infection Pathogens in Infant Studies**

REFERENCE	ZORC ET AL, 2005 (4)	ISMAILI ET AL, 2011 (6)	BONADIO AND MAIDA, 2014 (9)	GREENHOW ET AL, 2014 (13)
Age of patients	≤60 days (febrile)	0–3 months	≤ 30 days (febrile)	1 week–3 months
No. of urine cultures	1,025	46	670	823
Organisms				
Escherichia coli	80%	88%	71%	60%
Klebsiella spp	9%	7%	10%	2%
Enterobacter spp	5%	2%	3%	0%
Enterococcus	–	–	10%	2%
Citrobacter spp	4%	–	–	–
Pseudomonas spp	1%	–	1%	–
Other (gram-positive organisms, fungal, etc)	–	2%	5%	26%

there appears to be no difference in risk of UTI based on sex, birthweight, gestational age, or mode of delivery. (9)(18) In contrast, in a study of infants younger than 2 months in a single NICU, the rate of anomalies in patients with a UTI was less than 5%, with the youngest patients and those with *Klebsiella* as a pathogenic organism more likely to have VUR. (9)(18)

Maternal history may also play a role in the risk of neonatal UTI, because maternal history of UTI, premature rupture of membranes, and maternal exposure to antibiotics may all increase the risk for UTI in neonates. (19) Although breastfeeding may be protective for infants against respiratory and gastrointestinal infections, it has not been found to be protective against UTIs in the first 3 months of age. (20) Some studies suggest that vitamin D administration may increase the risk for UTIs in neonates. (20) A summary of predisposing factors for UTIs in infants is provided in Table 2.

The American Academy of Pediatrics (AAP) published guidelines in 2011 (updated in 2016) for febrile infants aged 2 to 24 months with recommended stratifications for UTI evaluation compared with clinical follow-up based on risk of UTI. (10) Low-risk febrile infants could be monitored clinically without testing for UTI while higher-risk infants should have a urine culture or urinalysis (UA) followed by urine culture if abnormal. Neonates, especially premature neonates, are likely at higher risk for UTI and urosepsis based on multiple factors. Increased susceptibility, prolonged hospitalization, multiple interventions, including intravascular catheters, and exposure to multiple antibiotic courses may contribute to a prevalence rate as high as 20% in premature and low-birthweight infants. (21) There are virtually no reports of UTIs in premature infants in the first 24 hours of age. (22) Data exist to suggest that bacterial colonization of the skin, particularly of the prepuce of uncircumcised boys, coupled with higher susceptibility to ascending infection likely contributes to the higher prevalence of UTIs in preterm versus term neonates (16). Hematogenous spread from invasive catheters or other sources appears to be less likely in preterm infants than previously thought. (23)

TABLE 2. **Predisposing Factors for Urinary Tract Infection in Infants**

NEONATAL OR INFANT CHARACTERISTICS
Male (< 3 months)
Uncircumcised
Prematurity
Renal and urinary tract malformation
High temperature (≥102.2°F [≥39°C])
MATERNAL CHARACTERISTICS
History of urinary tract infection
Premature rupture of membranes
Exposure to antibiotics

CLINICAL PRESENTATION

The clinical presentation in the neonate can often be difficult to differentiate from neonatal sepsis due to neurologic immaturity and nonspecific associated symptoms. (14) Poor feeding, lethargy, vomiting, diarrhea, irritability, feeding intolerance, hypothermia, hypoglycemia, abdominal distention, bradycardic events, and prolonged jaundice may all be presenting symptoms in a neonate with a UTI. Prolonged jaundice can be a presenting symptom in both term and preterm neonates. (2) Although the onset of jaundice after 8 days of age has a particular association with UTI, the AAP recommends screening for UTI in all infants with an elevated direct bilirubin concentration. (10) Fever with a high temperature (≥102.2°F [≥39°C]) is associated with a higher incidence of spontaneous bacterial infection compared with a viral illness. (4) However, up to half of infants with a UTI may only have a low-grade temperature or are afebrile, contributing to the difficulty in diagnosis and need for a high index of suspicion in neonates. (9)(21)

The risk of bacteremia associated with a UTI in infants is inversely related to age. One study showed a 5.7% correlation of a positive blood culture with a known UTI. (24) In a comparison of age-matched controls with bacteremic UTI versus nonbacteremic UTI, elevated serum band count (as a percentage of total white blood cell [WBC] count) and microscopic UA with more than 100 WBCs per high-power field (HPF) were more likely in the bacteremic UTI group. (24) In a 20-center retrospective review of older infants (aged 29-60 days) who presented to the emergency department with temperature greater than 100.4°F (38°C) and UTI, adverse events (death, shock, bacterial meningitis, ICU admission, etc) were found in 2.8% and bacteremia occurred in 6.5%. (25) A clinical prediction model identified a cohort at "low risk for adverse events" (not clinically ill and no medical history of high risk) with a peripheral band count of less than 1,250 cells/μL and absolute neutrophil count of greater than or equal to 1,500 cells/μL. (25) Of these low-risk patients, 28 of 862 (3.2%) were bacteremic and none had an adverse event. (25) While this model focused on an older and lower-risk cohort, it is possible that this could be true for low-risk preterm neonates as well. The risk of meningitis is low (0%–6%), (9) which could support potentially avoiding

lumbar punctures in well-appearing neonates with a suspected or laboratory-proven UTI. (26)

DIAGNOSTIC CONFIRMATION

It is often difficult to collect urine in neonates. While suprapubic aspiration (SPA) and urethral catheterization are preferred methods because of the high contamination rates with sterile bag collection, the AAP recommendations for infants aged 2 to 24 months allow for sterile bag collection for an initial UA. If the UA findings are abnormal (positive leukocyte esterase or nitrite test or microscopic analysis results for leukoctyes or bacteria), a catheter or SPA sample should be sent for culture. (10) Applying this recommendation to a younger population may not be ideal, given the lack of reliability of UA in infants and the high false-positive rate of sterile bag collection. (10) Pyuria, defined as more than or equal to 5 WBCs/HPF, predicts less than 50% of infant UTIs. (27) Use of an enhanced UA (hemocytometer cell count and Gram stain on uncentrifuged urine specimens), which defines pyuria as greater than or equal to 10 WBC/μL, has 91% sensitivity and 96% specificity for positive urine cultures. (28) The use of an enhanced UA method with the low-risk criteria proposed by the AAP improves the identification of infants at lower risk for bacteremia; however, enhanced UA is not readily available in most laboratories at this time. (1)

The gold standard for diagnosis is a urine culture that is positive for a single organism. The threshold for a "positive" culture via SPA or sterile catheter collection varies in the literature between: 1) greater than or equal to 10,000 colony-forming units (CFUs) per milliliter of a single organism in addition to pyuria on enhanced UA, and 2) greater than or equal to 50,000 CFU/mL of a single organism (which the AAP recommends for 2- to 24-month-old neonates). (10)(17) While some studies postulate that 10,000 to 50,000 CFU/mL may represent asymptomatic bacteriuria, (17)(28) increasing this threshold to greater than or equal to 100,000 CFU/mL, even for a bag specimen, may have a 7.5% to 20% false-positive rate. (17)(29) Most experts suggest a threshold of greater than or equal to 50,000 CFU/mL of a single organism via SPA or sterile catheterization to make the diagnosis, and incorporating enhanced UA or clinical symptoms may help confirm a diagnosis of UTI. (10)(17) For lower colony counts on a urine culture in a neonate (10,000–50,000 CFU/mL), the authors suggest the following: if more than or equal to 10,000 CFU/mL of any organism(s) is grown on a suprapubic aspirate or a single organism grows on a catheterized specimen, and there are other clinical indicators of infection, concern for a true UTI should be raised. Bagged specimens are discouraged and should not be used for culture because of their high false-positive rates. A bagged specimen sent for culture that returns negative, however, can be reassuring.

Other laboratory findings, such as an elevated C-reactive protein or erythrocyte sedimentation rate, have low sensitivity and specificity. However, a positive urine culture via SPA (>100 CFU/mL) in combination with pyuria on enhanced UA (≥10 WBC/μL), a C-reactive protein level higher than 20 mg/L (190 nmol/L), or an erythrocyte sedimentation rate higher than 30 mm/hour was found to have a specificity of 98% and 97%, respectively, in a population of 162 febrile infants younger than 8 weeks. (3) Serum leukocytosis and positive leukocyte esterase or nitrite on urine dipstick may be helpful as supplemental tests, but are unreliable in the neonatal and infant population because of frequent bladder emptying. (9)(30)

MANAGEMENT

Initial management for a neonate with a UTI is inpatient intravenous broad-spectrum antibiotics—ampicillin and gentamicin or ampicillin and cefotaxime—followed by narrowing the regimen based on organism sensitivity. (6)(12) In the United States, ampicillin resistance in neonatal *E coli* isolates has been reported in up to 75%, with gentamicin resistance reported to be between 12% and 17%. (31) Despite this high resistance to ampicillin, there is a reported 50% clinical response in patients, suggesting discordance between in vitro and in vivo activity or high concentration in the urine. (32) The current diagnostic approach and management for a neonate with a UTI is summarized in the Fig.

Data on outpatient and/or oral treatment are based mostly on older infants, so safety in this younger age group is not yet known. (6) For febrile infants aged 2 to 24 months, the AAP recommends either intravenous or oral antibiotics for 7 to 14 days based on local sensitivity. (10) Empirical treatment is thought to be important because of the high risk for bacteremia in the newborn period associated with UTIs and to prevent renal scarring. However, some more recent studies have shown no statistical difference, but rather a trend toward long-term scarring with oral versus initial intravenous antibiotics followed by oral antibiotics. Non-*E coli* uropathogens appear to be more likely to result in renal scarring. (33) Duration of treatment for infants less than or equal to 60 days of age varies between less than or equal to 4 days and 7 to 14 days, though the majority are treated intravenously for 5 to 7 days. (24)

For treatment of infants younger than 60 days who have a bacteremic UTI, retrospective review of multiple institutions revealed a mean duration of intravenous antibiotics of 6.3 to

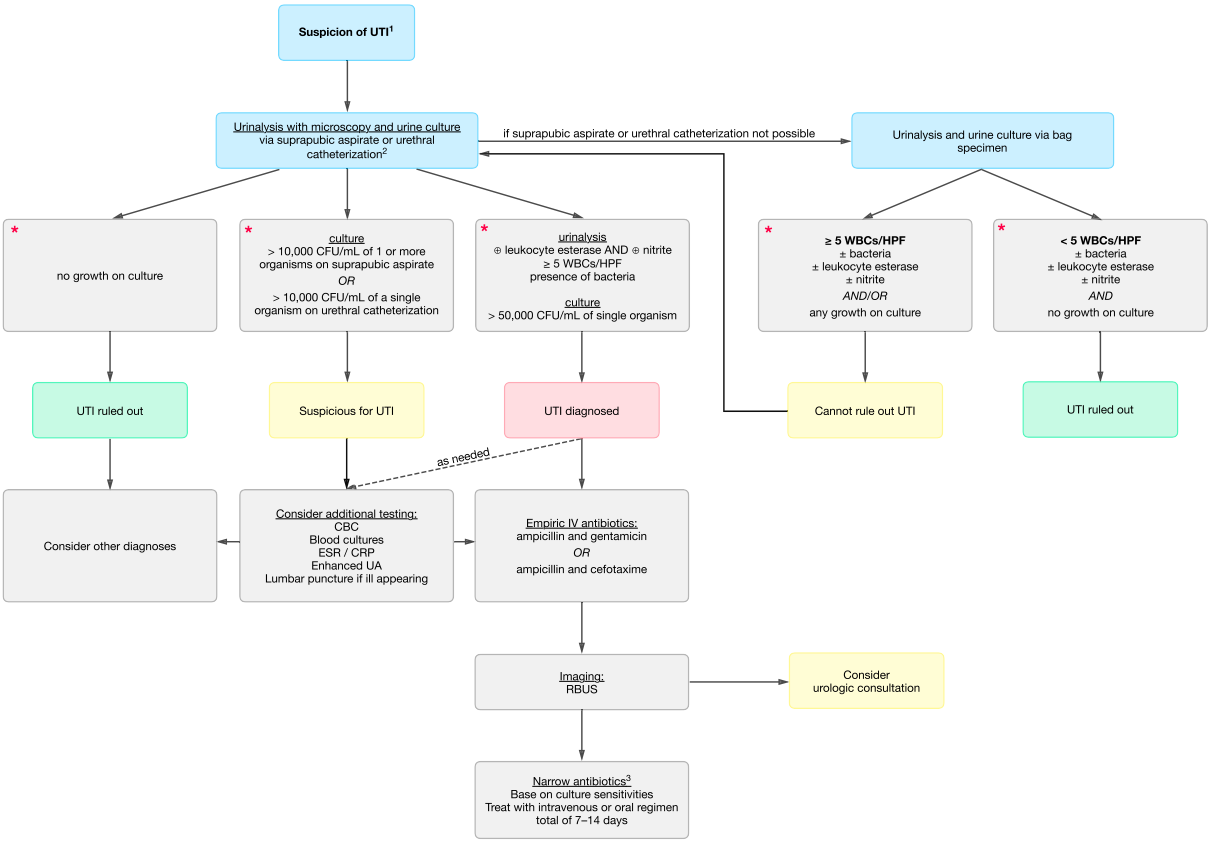

Figure. Flow chart of diagnostic workup for neonate with suspicion for UTI. 1, Clinical signs of illness are fever, hypothermia, lethargy, irritability, feeding intolerance, apneic or bradycardic events, prolonged jaundice, etc. 2, Suprapubic aspiration of bladder or urethral catheterization are preferred method of obtaining urine sample for testing. Bag collection of urine is useful to rule out UTI if testing is negative. 3, Antibiotic course may vary depending on age and severity of illness; may consider transition to oral antibiotics if >3 months of age and otherwise normal laboratory findings and negative cultures. *Interpretation of urinalysis with microscopy and urine culture can be challenging in the context of conflicting information (which is very common). Index of suspicion should go up with congruent, positive findings and similarly, index of suspicion should decrease with incongruent findings.

7.8 days ± 4 days with few relapses. (34) Fever resolves in most patients within 12 to 24 hours. (12) Transition to oral antibiotics after initial intravenous broad-spectrum coverage may be considered in older infants (>3 months) if clinically well with otherwise normal laboratory findings and negative blood or cerebral spinal fluid cultures, because there appears to be no difference in risk for renal scarring. (35) However, the bioavailability, safety, and efficacy of oral antibiotics are unknown in premature infants, so completion of an intravenous course of antibiotics is preferred. Neonates are typically treated for 10 to 14 days, but the gaps in understanding the treatment course with outcomes remain.

MANAGEMENT OF RECURRENT UTIs AND ANTIBIOTIC PROPHYLAXIS

Recurrent UTIs

The treatment and prevention of recurrent UTIs can be challenging and require close coordination among the family, clinical team, and consulting services. The approach is tailored for each individual patient and any identified factors (eg, male, uncircumcised, premature birth, presence of congenital anomalies, prior UTI, clinical circumstances regarding past infection, height of fever). There is no consensus about the definition of recurrent UTIs. However, the treating or consulting physician should be wary of labeling patients with this diagnosis in the absence of strong evidence. In particular, multiple positive urine cultures separated by time and completed treatment represent a bare minimum for UTI to be considered recurrent. The authors do not advise repeating urine cultures during or after treatment of a UTI unless there is clinical suspicion (eg, fever, lethargy, poor oral intake) for recurrence of infection, incomplete treatment, or symptoms. In some circumstances, if a urine culture is repeated, the presence of an ongoing UTI may signify incomplete treatment or newly acquired antibacterial resistance to treatment.

In boys with recurrent UTIs, strong consideration for circumcision should be discussed with the family, particularly in patients younger than 6 months. (36) Uncircumcised boys have at least 50% higher incidence of UTI than circumcised

boys, and circumcision alone can reduce future UTI incidence. (16) There is no strict threshold for which circumcision is offered with regard to recurrent infections. Cultural, religious, and social considerations may weigh on the decision to proceed with circumcision, in addition to other factors such as placement on daily prophylactic antibiotics and the presence of other uncorrected, congenital urologic abnormalities.

Renal bladder ultrasonography (RBUS) is recommended after a diagnosis of a UTI in an infant to rule out new or worsening urinary tract dilation, urolithiasis, or abscess (rare). (37) Repeat RBUS for patients with previous imaging studies should also be strongly considered. As noted earlier, although the risk for concomitant identification of a congenital urologic abnormality is fairly low among neonates with a UTI and even fewer require intervention, the presence of these anomalies can inform future risk and help direct further therapy. Congenital anomalies with a predisposition to urinary stasis or obstruction (eg, posterior urethral valves, ureteropelvic junction obstruction, congenital megaureter, neurogenic bladder) may require surgical intervention to reduce the risk of future infections. As such, urologic consultation is important.

Continuous Antibiotic Prophylaxis

Continuous antibiotic prophylaxis (CAP) is an important component of UTI prevention in patients with congenital anomalies such as VUR, because such prophylaxis has been found to lead to a 50% reduction in future UTIs. (38)(39) Evidence for CAP in the setting of UTI and VUR is generalized from large, randomized controlled trials such as the Swedish Reflux Trial (40) and the RIVUR Study, (39) which showed clear benefits of CAP in the prevention of UTI. The data are generalized to the neonate population because the Swedish Reflux Trial did not include patients younger than 1 year and the RIVUR Study did not include infants younger than 2 months. (39)(40) Support for the broad use of CAP for various congenital anomalies in neonates is of low quality, with better evidence in specific conditions (eg, high-grade hydronephrosis, VUR). (41)

The American Urological Association guidelines do not specifically address the circumstances of premature infants and neonates, but do recommend that patients with a febrile UTI and any grade VUR be placed on CAP. (36) Other clinical and diagnostic circumstances may also warrant CAP in this age group, given their risk for sequelae from UTI (sepsis, bacteremia). In neonates, amoxicillin is typically used for CAP. Alternatives include orally available cephalosporins (eg, cephalexin). Trimethoprim-sulfamethoxazole is avoided in the first 2 months of age in neonates because of the risk of kernicterus. Nitrofurantoin is also avoided in the first month of age because of the risk of hemolytic anemia, particularly in infants with glucose-6-phosphate dehydrogenase deficiency. The authors recommend that if CAP is considered appropriate for a patient, the intended drug of choice should ideally fall within the sensitivities found on any previous cultures of organisms. Use of oral antibiotics that have been approved by the US Food and Drug Administration (FDA) are limited in this population, and this approach may not be possible in patients with a history of drug-resistant organisms. Table 3 provides a summary of common medications used for CAP, dosage, FDA-approved ages and indications, and common adverse effects.

Imaging

While specific guidelines are not available to guide imaging options before age 2 months, some experts have argued that any UTI should be considered pathologic in this age group. Given the potential for recurrent UTIs or sequelae from a UTI in patients with congenital anomalies, imaging is recommended for all neonates diagnosed with an organism-confirmed UTI. The prevalence of congenital urinary tract anomalies in preterm infants and neonates younger than 2 months hospitalized for a UTI remains high, with 35% to 40% having a finding on RBUS. (6)(11) In most cases, mild hydronephrosis is noted. Only 5% of all patients demonstrated more severe pathologies (eg, high-grade hydronephrosis, horseshoe kidney, unilateral renal agenesis, congenital megaureter).

The usefulness of imaging after a diagnosis of a UTI in an infant is predicated on the accuracy of the diagnosis. To minimize cost, false-positive rates, and unnecessary diagnosis of benign phenotypes, the AAP recommends that patients with a UTI at 2 to 24 months of age have imaging only if they develop a second febrile UTI. Because a large proportion of patients who have a UTI at age 2 to 24 months will not develop another, this strategy minimizes overuse of imaging (and subsequent imaging and procedures that tend to follow). However, this strategy may not be appropriate for premature infants and neonates younger than 2 months, but the practitioner should still be wary of overuse and disadvantages of imaging in neonates. To this end, accurate diagnosis of UTI is paramount, and we recommend that clinical suspicion for a UTI be gauged on the strength of the underlying evidence. For example, a bagged urine specimen is considered inadequate for the diagnosis of UTI, because it is associated with a high false-positive rate. A single organism growing 50,000 CFU/mL from an SPA, however, would serve as definitive proof for a UTI in a sick patient.

Ultrasonography is the mainstay of urinary tract imaging in infants and children. Ultrasonography is noninvasive and

TABLE 3. **Common Medications Used for CAP**

MEDICATION	TREATMENT DOSE	CAP DOSE	FDA-APPROVED INDICATIONS	COMMON ADVERSE EFFECTS
Amoxicillin	25–45 mg/kg per day PO divided into 2 doses	15–20 mg/kg daily	Any age, UTI treatment	Cutaneous/allergic reactions, gastrointestinal disturbances
Cephalexin	25–50 mg/kg per day PO divided into 2–4 doses	25 mg/kg daily or divided into 1–2 doses	Any age, UTI treatment	Cutaneous/allergic reactions, gastrointestinal disturbances
Nitrofurantoin	5–7 mg/kg daily divided into 4 doses	1–2 mg/kg daily	>1 month age, UTI treatment or prophylaxis	Hemolytic anemia, gastrointestinal disturbances, interstitial pneumonitis, cutaneous/allergic reactions
TMP	8–10 mg/kg TMP daily divided into 2 doses	2 mg/kg TMP daily	>12 years age, UTI treatment or prophylaxis	Cutaneous/allergic reactions, hematologic toxicity
TMP-sulfamethoxazole	8–10 mg/kg TMP daily divided into 2 doses	2 mg/kg TMP daily	>2 months age, UTI treatment or prophylaxis	Cutaneous/allergic reactions, hematologic toxicity, hepatotoxicity (kernicterus)

CAP=continuous antibiotic prophylaxix; FDA=Food and Drug Administration; PO=orally; TMP=trimethoprim; UTI=urinary tract infection.

avoids ionizing radiation, while providing detailed imaging of the urinary tract. The technique is operator-dependent. Its use in older infants and children with a first UTI has been debated in the past, and current AAP recommendations state that ultrasonography should be performed only after a second UTI. This recommendation is based on studies showing lack of cost-effectiveness and that a majority of older patients (2–24 months) do not have a second UTI or sequelae. (10) Such guidelines have not been established for premature infants or neonates younger than 2 months.

Possible imaging findings that should prompt urologic consultation include:

- Presence of hydronephrosis or hydroureteronephrosis (also referred to varyingly as "pelviectasis" or "calyectasis" by some radiologists)
- A duplex collecting system
- Ureterocele
- Megaureter (dilated, tortuous ureter distally with or without dilation of the collecting system and pelvis at the kidney)
- Posterior urethral valves (dilated posterior urethra as seen on sagittal views of the bladder)
- Renal cysts
- Multicystic dysplastic kidney
- Bladder diverticulum
- Urolithiasis

Newer ultrasound techniques offer the ability to visualize the presence of VUR and even grade it, though this technique is not widely available.

Voiding cystourethrography (VCUG) remains the test of choice for diagnosing VUR and ruling out some other congenital anomalies. A normal finding on RBUS does not necessarily rule out the presence of VUR. (6)(42) Some centers advocate that a VCUG be performed only in the setting of an abnormal RBUS finding, non–*E coli* UTI, or recurrent UTI. We advocate for testing of all premature infants with a UTI, because these patients have an increased likelihood of immature urinary tracts and thus, may be more susceptible to the risks of upper tract infection (see section on sequelae) without proper identification and treatment. (43) One recent study of patients with a UTI at less than 3 months of age noted that the risk of identification of a high-grade VUR was greatest in patients with non–*E coli* UTI and abnormal ultrasound findings (55% with high-grade VUR).

In patients with normal ultrasound findings and non–*E coli* UTI, the risk of identification of high-grade VUR decreased to 26%. (44)

A VCUG should only be performed after treatment of UTI has been completed. (45) If there is a strong suspicion for VUR, the patient may be started on antibiotic prophylaxis after completion of treatment-dose antibiotics to minimize the risk of recurrent UTIs. During a VCUG, a urethral catheter is placed in the bladder, contrast is then instilled into the catheter, and multiple radiographs are obtained of the bladder and urethra. Images are taken of the renal fossae to look for the presence of contrast medium in the upper urinary tracts. Characteristics examined include presence or absence of VUR, associated timing (early, late, voiding), and grade (scale of 1 to 5, with 1 indicating reflux limited to the ureter and 5, severe dilation of the ureters, renal pelvis, and calyces); bladder contour regularity; presence/absence of bladder diverticulae and bladder neck; and posterior urethra configuration (specifically to assess for posterior urethral valves, which would show a dilated posterior urethra, filling defect, and bladder neck with hypertrophy).

Other Imaging Modalities

Magnetic resonance urography and nuclear function testing (Tc-99m mercaptoacetyltriglycine [Mag3], diethylenetriaminepentacetate, or dimercaptosuccinic acid) are not routinely recommended for evaluation of an infant with an isolated UTI. These adjunct, specialized imaging tests may be ordered by consulting services to identify or rule out specific urinary tract abnormalities. Magnetic resonance urography uses nonionizing radiation, but nuclear function testing requires radiation. Nuclear function testing is advocated by some experts to address potential reflux as an initial screen before VCUG ("top-down approach"), but this approach is not widely practiced in North America owing to the lack of availability of the radioactive tracers. (46) Computed tomography is not routinely used to evaluate the urinary tract in neonates or infants, owing to better nonionizing alternatives.

SEQUELAE

Sequelae of UTIs in neonates must be considered, particularly in those with risk factors: prematurity, presence of antenatal hydronephrosis, presence of known congenital urinary tract anomaly such as VUR, non–*E Coli* pathogen, drug-resistant organisms, or recurrent UTIs. Immediate sequelae of a UTI in this population include bacteremia in up to one-third of patients, though more recent studies show that this association may be closer to 5% of patients. (24)(47) Renal growth rates have been shown to be slower in a small cohort (n=22) of patients younger than 1 month with a UTI. Long-term follow-up (mean age, 17 years) showed renal size normalized, but there was size disparity in patients with VUR. (48)

The subsequent development of renal scarring, chronic kidney disease, and hypertension are also of concern in patients with a UTI at an early age. Delay in initiation of treatment for a febrile UTI has been shown in some studies to increase the risk of renal scarring, even in patients without VUR. (49)(50)

There has long been felt to be a strong relationship among UTI, VUR, and the development of renal scarring, which occurs in about 10% of patients with UTI and VUR. (39) However, recently it has been increasingly recognized that VUR and renal dysplasia exist on the same spectrum, and dysplastic kidneys are more likely to harbor or be susceptible to renal scarring. Similarly, such kidneys may already be at risk for poor growth and atrophy, further confounding long-term outcome measures in this patient population, and making it difficult to attribute these outcomes solely to a UTI or other predisposing conditions. (33)(43) Overall, risk of chronic kidney disease or hypertension after a UTI in the neonatal period appears to be low.

CONCLUSION

The estimated prevalence of a UTI in infants younger than 3 months is 4.6% to 13.6% based on limited data. Neonates and young infants often present with nonspecific symptoms that make diagnosis difficult and require a high index of suspicion. The most common pathogen in neonatal UTIs is *E coli*, but the risk factors differ for neonates versus older children. Significant risk factors include male gender, lack of circumcision, prematurity, renal and urinary tract malformation, maternal exposure to antibiotics, and maternal UTI. Suprapubic aspirate, or more often a sterile catheter specimen, is preferred for diagnosis and culture of a single organism, with greater than or equal to 50,000 CFU/mL being the most commonly accepted threshold. However, lower colony counts of a single organism in the setting of strong clinical indicators may also be consistent with a UTI. Pyuria on UA and supplemental testing may help make the initial diagnosis. Bacteremia and meningitis are rare in this population but still represent a significant risk if missed. Empirical treatment with intravenous broad-spectrum antibiotics is preferred, with narrowing based on sensitivities. A 10- to 14-day intravenous course of antibiotics is typical for

neonates, though evidence shows that transition to oral antibiotics may be possible. Imaging with RBUS should be considered for all patients in this age group, with further imaging predicated on patient risk factors. Antibiotic prophylaxis has been shown to be beneficial in preventing recurrent UTIs in patients with VUR, but may be considered in infants with less common congenital urinary tract anomalies in consultation with a specialist.

PARENT RESOURCES

- Preventing urinary tract infections in children: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Prevent-Urinary-Tract-Infections-in-Children.aspx
- Circumcision: https://www.healthychildren.org/English/ages-stages/prenatal/decisions-to-make/Pages/Circumcision.aspx
- Detecting urinary tract infections: https://www.healthychildren.org/English/health-issues/conditions/genitourinary-tract/Pages/Detecting-Urinary-Tract-Infections.aspx

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the causative infectious agents, pathogenesis, and differential diagnosis of urinary tract infections.
- Know the clinical and laboratory features, treatment, and complications of urinary tract infections.

References

1. Herr SM, Wald ER, Pitetti RD, Choi SS. Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics*. 2001;108(4):866–871
2. Garcia FJ, Nager AL. Jaundice as an early diagnostic sign of urinary tract infection in infancy. *Pediatrics*. 2002;109(5):846–851
3. Lin DS, Huang SH, Lin CC, et al. Urinary tract infection in febrile infants younger than eight weeks of age. *Pediatrics*. 2000;105(2):E20
4. Zorc JJ, Levine DA, Platt SL, et al; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Clinical and demographic factors associated with urinary tract infection in young febrile infants. *Pediatrics*. 2005;116(3):644–648
5. Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*. 2008;27(4):302–308
6. Ismaili K, Lolin K, Damry N, Alexander M, Lepage P, Hall M. Febrile urinary tract infections in 0- to 3-month-old infants: a prospective follow-up study. *J Pediatr*. 2011;158(1):91–94
7. Baracco R, Mattoo TK. Diagnosis and management of urinary tract infection and vesicoureteral reflux in the neonate. *Clin Perinatol*. 2014;41(3):633–642
8. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C; EUROSCAN Study Group. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet*. 2005;48(2):131–144
9. Bonadio W, Maida G. Urinary tract infection in outpatient febrile infants younger than 30 days of age: a 10-year evaluation. *Pediatr Infect Dis J*. 2014;33(4):342–344
10. Subcommittee on Urinary Tract Infection. Reaffirmation of AAP clinical practice guideline: the diagnosis and management of the initial urinary tract infection in febrile infants and young children 2-24 months of age. *Pediatrics*. 2016;138(6):e20163026
11. Vachharajani A, Vricella GJ, Najaf T, Coplen DE. Prevalence of upper urinary tract anomalies in hospitalized premature infants with urinary tract infection. *J Perinatol*. 2015;35(5):362–366
12. Dayan PS, Hanson E, Bennett JE, Langsam D, Miller SZ. Clinical course of urinary tract infections in infants younger than 60 days of age. *Pediatr Emerg Care*. 2004;20(2):85–88
13. Greenhow TL, Hung Y-Y, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33(6):595–599
14. Sastre JBL, Aparicio AR, Cotallo GDC, Colomer BF, Hernández MC; Grupo de Hospitales Castrillo. Urinary tract infection in the newborn: clinical and radio imaging studies. *Pediatr Nephrol*. 2007;22(10):1735–1741
15. Levy HL, Sepe SJ, Shih VE, Vawter GF, Klein JO. Sepsis due to *Escherichia coli* in neonates with galactosemia. *N Engl J Med*. 1977;297(15):823–825
16. Schoen EJ, Colby CJ, Ray GT. Newborn circumcision decreases incidence and costs of urinary tract infections during the first year of life. *Pediatrics*. 2000;105(4 Pt 1):789–793
17. Santoro JD, Carroll VG, Steele RW. Diagnosis and management of urinary tract infections in neonates and young infants. *Clin Pediatr (Phila)*. 2013;52(2):111–114
18. Cleper R, Krause I, Eisenstein B, Davidovits M. Prevalence of vesicoureteral reflux in neonatal urinary tract infection. *Clin Pediatr (Phila)*. 2004;43(7):619–625
19. Didier C, Streicher M-P, Chognot D, et al. Late-onset neonatal infections: incidences and pathogens in the era of antenatal antibiotics. *Eur J Pediatr*. 2012;171(4):681–687
20. Katikaneni R, Ponnapakkam T, Ponnapakkam A, Gensure R. Breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76%. *Clin Pediatr (Phila)*. 2009;48(7):750–755
21. Cataldi L, Zaffanello M, Gnarra M, Fanos V; Neonatal Nephrology Study Group, Italian Society of Neonatology. Urinary tract infection in the newborn and the infant: state of the art. *J Matern Fetal Neonatal Med*. 2010;23(suppl 3):90–93
22. Tamim MM, Alesseh H, Aziz H. Analysis of the efficacy of urine culture as part of sepsis evaluation in the premature infant. *Pediatr Infect Dis J*. 2003;22(9):805–808
23. Bauer S, Eliakim A, Pomeranz A, et al. Urinary tract infection in very low birth weight preterm infants. *Pediatr Infect Dis J*. 2003;22(5):426–430

24. Roman HK, Chang PW, Schroeder AR. Diagnosis and management of bacteremic urinary tract infection in infants. *Hosp Pediatr*. 2015;5 (1):1–8

25. Schnadower D, Kuppermann N, Macias CG, et al; American Academy of Pediatrics Pediatric Emergency Medicine Collaborative Research Committee. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126 (6):1074–1083

26. Wallace SS, Brown DN, Cruz AT. Prevalence of concomitant acute bacterial meningitis in neonates with febrile urinary tract infection: a retrospective cross-sectional study. *J Pediatr*. 2017;184:199–203

27. Crain EF, Gershel JC. Urinary tract infections in febrile infants younger than 8 weeks of age. *Pediatrics*. 1990;86(3):363–367

28. Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. *J Pediatr*. 1994;124 (4):513–519

29. Hansson S, Brandström P, Jodal U, Larsson P. Low bacterial counts in infants with urinary tract infection. *J Pediatr*. 1998;132(1):180–182

30. Glissmeyer EW, Korgenski EK, Wilkes J, et al. Dipstick screening for urinary tract infection in febrile infants. *Pediatrics*. 2014;133(5): e1121–e1127

31. Hasvold J, Bradford L, Nelson C, Harrison C, Attar M, Stillwell T. Gentamicin resistance among *Escherichia coli* strains isolated in neonatal sepsis. *J Neonatal Perinatal Med*. 2013;6(2):173–177

32. Williamson JC, Craft DW, Butts JD, Raasch RH. In vitro assessment of urinary isolates of ampicillin-resistant *enterococci*. *Ann Pharmacother*. 2002;36(2):246–250

33. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatr*. 2014;168(10):893–900

34. Lewis-de Los Angeles WW, Thurm C, Hersh AL, et al. Trends in intravenous antibiotic duration for urinary tract infections in young infants. *Pediatrics*. 2017;140(6):e20171021

35. Benador D, Neuhaus TJ, Papazyan JP, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. *Arch Dis Child*. 2001;84 (3):241–246

36. Peters CA, Skoog SJ, Arant BS, et al; American Urological Association. Management and screening of primary vesicoureteral reflux in children. http://www.auanet.org/guidelines/vesicoureteral-reflux-(2010-reviewed-and-validity-confirmed-2017). Accessed March 15, 2018

37. Marks SD, Gordon I, Tullus K. Imaging in childhood urinary tract infections: time to reduce investigations. *Pediatr Nephrol*. 2008;23 (1):9–17

38. Craig JC, Simpson JM, Williams GJ, et al; Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) Investigators. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*. 2009;361(18):1748–1759

39. Hoberman A, Greenfield SP, Mattoo TK, et al; RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370(25):2367–2376 doi: 10.1056/NEJMoa1401811

40. Brandström P, Esbjörner E, Herthelius M, et al. The Swedish reflux trial in children: I, study design and study population characteristics. *J Urol*. 2010;184(1):274–279

41. Braga LH, Mijovic H, Farrokhyar F, Pemberton J, DeMaria J, Lorenzo AJ. Antibiotic prophylaxis for urinary tract infections in antenatal hydronephrosis. *Pediatrics*. 2013;131(1):e251–e261

42. Wallace SS, Zhang W, Mahmood NF, et al. Renal ultrasound for infants younger than 2 months with a febrile urinary tract infection. *AJR Am J Roentgenol*. 2015;205(4):894–898

43. Gleeson FV, Gordon I. Imaging in urinary tract infection. *Arch Dis Child*. 1991;66(11):1282–1283

44. Pauchard J-Y, Chehade H, Kies CZ, Girardin E, Cachat F, Gehri M. Avoidance of voiding cystourethrography in infants younger than 3 months with *Escherichia coli* urinary tract infection and normal renal ultrasound. *Arch Dis Child*. 2017;102(9):804–808

45. Craig JC, Knight JF, Sureshkumar P, Lam A, Onikul E, Roy LP. Vesicoureteric reflux and timing of micturating cystourethrography after urinary tract infection. *J Urol*. 1998;159(4):1410

46. Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Imaging strategy for infants with urinary tract infection: a new algorithm. *J Urol*. 2011;185(3):1046–1052

47. Hoberman A, Chao HP, Keller DM, Hickey R, Davis HW, Ellis D. Prevalence of urinary tract infection in febrile infants. *J Pediatr*. 1993;123(1):17–23

48. Hellström M, Jacobsson B, Jodal U, Winberg J, Odén A. Renal growth after neonatal urinary tract infection. *Pediatr Nephrol*. 1987;1 (3):269–275

49. Doganis D, Siafas K, Mavrikou M, et al. Does early treatment of urinary tract infection prevent renal damage? *Pediatrics*. 2007;120 (4):e922–e928

50. Shaikh N, Mattoo TK, Keren R, et al. Early antibiotic treatment for pediatric febrile urinary tract infection and renal scarring. *JAMA Pediatr*. 2016;170(9):848–854

NeoReviews Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via a handy blue CME link in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A 2-month old infant presents with fussiness, poor feeding, and fever. Diagnostic evaluation is suspicious for urinary tract infection. Which of the following statements regarding newborns and urinary tract infections is correct?
    A. Urinary tract infections represent the most common bacterial infection in febrile newborns.
    B. Most infants with urinary tract infections present with fever.
    C. Younger neonates with urinary tract infection (<1 week old) are more likely to have fever than older infants (>2–3 months) with urinary tract infection.
    D. Urinary tract infections in infants younger than 2 months are exceedingly rare, with prevalence of 1 per 1,000 live births.
    E. Urinary tract infection in a 2-month-old signifies a greater than 50% likelihood of renal anomaly.
2. A 3-week-old male infant is found to have urinary tract infection after presenting with poor feeding, emesis, and intermittent fever. A urine culture is noted to be growing bacteria. Which of the following is the most common causative organism for urinary tract infection in the neonatal period?
    A. *Enterobacter* species.
    B. *Klebsiella* pneumonia.
    C. *Escherichia coli.*
    D. *Pseudomonas aeruginosa.*
    E. *Staphylococcus aureus.*
3. A 1-month-old infant is being evaluated for fever and lethargy. The urinalysis findings are suspicious for urinary tract infection. Which of the following increases the risk for urinary tract infection by approximately 10-fold?
    A. Absence of circumcision.
    B. Being female compared with male.
    C. White race compared with any other race.
    D. Cesarean delivery.
    E. Placement of gastric suction catheter during delivery resuscitation.
4. An 8-day-old infant presents with jaundice and irritability. Serum direct bilirubin level is elevated. Which of the following statements regarding presentation of urinary tract infection in neonates is correct?
    A. Neonates with urinary tract infections almost always (>90% of the time) present with 1 of the following: temperature greater than 101.3°F (38.5°C) or hypothermia with temperature less than 95°F (35°C).
    B. The risk of bacteremia associated with urinary tract infection in infants is directly and linearly correlated with increasing age.
    C. The most common presenting sign of urinary tract infection is hyperglycemia.
    D. Prolonged jaundice can be a presenting symptom in both term and preterm neonates.
    E. Although jaundice can be a symptom of urinary tract infection, testing for urinary tract infection should only be performed for indirect hyperbilirubinemia that presents after 2 weeks of age.

NOTE: Learners can take *NeoReviews* quizzes and claim credit online only at: http://Neoreviews.org.

To successfully complete 2018 *NeoReviews* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2020, however, credit will be recorded in the year in which the learner completes the quiz.

2018 *NeoReviews* now is approved for a total of 10 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the ABP MOC Portfolio Program. Complete the first 5 issues or a total of 10 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as May 2018.

5. A 3-month-old infant presents to the emergency department with low-grade fever, feeding intolerance, and increasing lethargy. Which of the following statements regarding testing for urinary tract infection in this patient is correct?
    A. The initial urinalysis should be performed by using a capillary tube on a wet diaper.
    B. Suprapubic aspiration should be performed on each of the 4 quadrants of the bladder.
    C. A urine culture growing more than 50,000 colony-forming units per milliliter of a single organism would be considered as a confirmatory diagnosis of urinary tract infection.
    D. Bagged urine specimens are just as accurate as catheterized specimens in the neonatal period.
    E. Elevated C-reactive protein concentration is a highly sensitive and specific test for bacterial urinary tract infection in infants up to 6 months of age.

Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants

Angela Lai, Kyle O. Rove, Sachin Amin, Gino J. Vricella and Douglas E. Coplen

NeoReviews 2018;19;e337
DOI: 10.1542/neo.19-6-e337

Diagnosis and Management of Urinary Tract Infections in Premature and Term Infants

Angela Lai, Kyle O. Rove, Sachin Amin, Gino J. Vricella and Douglas E. Coplen

NeoReviews 2018;19;e337
DOI: 10.1542/neo.19-6-e337