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Urinary Tract Infections in the Infant

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Introduction

Urinary tract infections (UTIs) in infants are common. UTIs may be the sentinel event for underlying renal abnormality, although normal anatomy is most common. Prompt diagnosis and initiation of treatment is important in preventing long-term renal scarring. However, increasing antibiotic resistance may delay initiation of appropriate therapy. Antibiotic prophylaxis remains controversial.

Epidemiology and Risk Factors for Urinary Tract Infections in Infants

Occurrence of Urinary Tract Infections in the First 3 Days of Life Is Exceedingly Rare

The true incidence of UTI in the first days of life is difficult to assess, as most large studies have included such cases in the broader age categories (7%–9%).^{1–4} Small studies indicate the incidence in the febrile infant is between 10.7% and 15.4%.^{5,6} Occurrence of UTIs in the first 3 days of life is reportedly rare (0%–1%) in the United States^{7,8} and up to 1.8% in developing countries.^{9,10} Even in premature infants, virtually no cases are detected in the first 24 hours of life.⁸

Escherichia coli Is the Most Common Cause of Neonatal Urinary Tract Infection

The most common bacterial etiology for neonatal UTIs, similar to other age groups, is *Escherichia coli*.^{3,11–14} However, some studies found that the overall burden of disease by *E. coli* was lower in this age group (about 50% of all positive cultures) compared with older age groups in which *E. coli* is responsible for up to 80% of UTIs.^{10,15} In particular, male infants with vesicoureteral reflux (VUR) were more likely to present with UTIs caused by other pathogens.^{3,5,12,15} These pathogens include other gram-negative organisms: *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Proteus vulgaris*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Morganella morganii*.^{5,12} Neonatal UTI with gram-positive organisms is rare, but cases of *Enterococcus faecalis*, *Staphylococcus aureus*,

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Group B *streptococcus*, and *Streptococcus pneumonia* have been reported.^{6,16–18} Coagulase-negative staphylococci may be causative agents in premature infants, with isolation of the organism in 14% of catheterized urine culture samples from infants with suspected infection and 18% concordance with positive blood cultures.¹⁹ However, this finding remains controversial; one study, which included mostly premature infants, showed a less than 1% incidence of coagulase-negative staphylococci UTI.²⁰ *Candida* UTIs occur more commonly in extremely premature infants. One study reported that 42% of UTIs in a neonatal intensive care unit were caused by *Candidia* spp, with *Enterobacter cloacae* being the second most common.²¹ Table 1 lists the most common pathogens associated with neonatal UTI.

Uncircumcised Male Infants Have the Highest Risk of Urinary Tract Infection

A clear male predominance has been associated with neonatal UTI, with boys making up approximately 70% to 90% of all cases.^{5,11,12} This finding is also true in premature infants.^{22,23} To evaluate the effect of circumcision on male risk for infantile UTI, Zorc and colleagues³ conducted a prospective multicenter trial, which included approximately 1000 febrile infants less than 60 days of age whose evaluation for sepsis included a urine culture and urinalysis. Infants who had growth of a single organism in the urine culture were included in the subsequent evaluation. Uncircumcised boys had the highest incidence of UTIs (21%), whereas circumcised boys (2%) and girls (5%) has similar incidences. These results were similar to those in a meta-analysis,¹ in which 20% of the uncircumcised boys less than 90 days of age with fever had a UTI compared with 2% of circumcised boys and 8% of girls. Phimosis, limited retraction of the foreskin, is significantly associated with an increase in UTIs in male infants.²⁴ A recent study in older children that examined the periurethral flora in boys between the ages of 6 weeks and 96 months before and after circumcision found that the presence of the prepuce results in a significantly higher burden of uropathogens.²⁵

Underlying Renal Abnormalities Increase the Risk of Neonatal Urinary Tract Infection

VUR is associated with approximately 20% of neonatal cases of UTI,^{5,26} although the incidence of VUR is not significantly different between genders, birth weight, gestational age, or mode of delivery.^{26,27} A study of infants less than 2 months of age in a neonatal intensive care unit with a median gestation age of 28 weeks reported a less than 5% rate of anatomic abnormalities in patients with UTI. VUR was, however, associated with a younger age at UTI presentation and was 4-fold higher in infants with *Klebsiella* UTI compared with *E coli* UTI.^{5,26} A study of 45 male infants with a first UTI renal ultrasound scan (RUS) and voiding cystourethrogram (VCUG) found a renal abnormality in half of the infants, the most common being VUR and other abnormalities, including duplicated collecting system, posterior urethral valves, ureteropelvic junction stricture, and renal atrophy and scarring.²⁸ The dimercaptosuccinic acid (DMSA) scan was abnormal almost exclusively in those with grade 3 or higher VUR. These results are similar to those in a recent study, in which 47% of febrile infants less than 30 days of age with a UTI had renal abnormalities, most of them hydronephrosis (27%) and pelviectasis (20%).⁵ However, even in the absence of any abnormalities on the RUS or VCUG, infants with UTI can have an abnormal DMSA scan, indicating renal cortical damage, although that may be an effect rather than a cause of a UTI.²⁹ Representative images for RUS and VCUG in infants are shown in Figs. 1 and 2.

Maternal History of Urinary Tract Infection Is Associated with a Higher Risk of Urinary Tract Infection in the Infant

A history of maternal UTI during pregnancy has been associated with up to a 5.9-fold higher risk of UTI in infants.^{30,31} Milas and colleagues³¹ also observed a higher incidence of UTIs in febrile infants born after premature rupture of membranes. This incidence may be because these mothers are more likely to harbor uropathogens transmitted to the infant that then result in an ascending UTI.

Clinical Correlations

Full-term infants with UTIs often present with fever ($> 38^{\circ}\text{C}$), poor feeding, vomiting, diarrhea, and lethargy (Table 2).^{12,32} The clinical manifestations in premature infants are similar. In addition, greater than 50% of premature infants with UTI present with respiratory symptoms such as apnea, hypoxia, or tachypnea.³³ A fever greater than 39°C is more likely among infants with a serious bacterial illness such as a UTI compared with infants with a viral illness.^{3,12,34}

Neonatal UTIs have been associated with jaundice^{12,31}; 6% to 18% of full-term or preterm infants presenting with prolonged or worsening jaundice were found to have UTIs.^{35–38} Onset of jaundice after 8 days of life in particular has been associated with UTI.^{37,39} Twenty-eight of 30 infants with UTI-induced jaundice had indirect hyperbilirubinemia, and about half of them had renal cortical changes on DMSA scan.³⁹ In another cohort,³⁷ most of the infants presenting with a UTI after 8 days of life had direct hyperbilirubinemia. The American Academy of Pediatrics recommends that infants with elevated direct bilirubin levels be screened for UTIs.⁴⁰ However, those with elevated unconjugated bilirubin levels should not be excluded, especially if other concerning clinical features are present. A urinalysis may not be sufficient to exclude UTI in infants with jaundice, and a urine culture should be obtained.⁴¹ *E coli* is the most commonly isolated pathogen in UTIs associated with jaundice.^{37,38,41,42}

Infants with Urinary Tract Infection Are at Risk for Concomitant Bacteremia and Meningitis

Several studies have examined the concordance between UTI, bacteremia, and cerebrospinal fluid (CSF) pleocytosis/culture positivity. In a cohort of 163 infants less than 1 month of age with a UTI only 2 had meningitis.⁴³ Another study from the United States reported that 44 of 100 patients had concomitant positive blood and urine culture; *E coli* was isolated in all cases.⁵ A study from India reported a 6.3% concordance between blood and urine cultures.¹⁰ Concordance between urine, blood, and CSF cultures is higher in infants less than 26 weeks' gestation and those with candiduria.^{19,21}

Diagnosis

Blood Cell Indices and Inflammatory Markers Are not Specific Indicators of Urinary Tract Infections

Laboratory values such as white blood cell (WBC) count, erythrocyte sedimentation rate, and C-reactive protein are not significantly different among infants with and without UTIs.^{5,44}

Urethral Catheterization is the Preferred Method for Sample Collection

Urine culture is typically obtained through 3 different methods in infants: urinary catheterization, suprapubic aspiration, or sterile bag collection. The sterile bag collection method has a contamination rate as high as 46% compared with about 9% to 12% for the other methods and, when possible, should be avoided.^{45,46} Although contamination rates for suprapubic aspiration are slightly lower than those for urethral catheterization,⁴⁵ it does require a more advanced skill set and has lower parental acceptance rate, making the latter the preferred method by most providers. Although definitions vary, some investigators have defined a positive urine culture as growth of a known bacterial pathogen from a catheterized specimen at a level of (1) 50,000 colony-forming units (cfu)/mL or (2) 10,000 cfu/mL in association with a positive dipstick test or urinalysis.^{3,5,47}

Pyuria Is Defined as White Blood Cell Count of 10/mm³

The standard method of detecting pyuria, defined as at least 5 WBCs per high-powered field, is useful in predicting less than half of the UTIs in infants.⁴⁸ However, a method (often termed the *enhanced* method) initially described by Dukes,⁴⁹ in which WBCs are counted using a hemocytometer in uncentrifuged urine and reported as cells per cubic millimeter has been shown to be reproducible and more closely related to a positive urine culture. A pediatric study including young infants showed that a WBC count of 10/mm³ had a sensitivity of 91% and a specificity of 96% for predicting a positive culture of 50,000 cfu/mL.⁵⁰ A more recent study, also including young infants, compared the enhanced method with automated urinalysis and found similar sensitivity and specificity for detecting pyuria associated with a bacterial culture of 50,000 cfu/mL.⁵¹ For bacteriuria, the same study found that the enhanced method using a manual Gram stain for organisms was about 10% more sensitive and specific than the automated analysis.

Urine Nitrites and Leukocyte Esterase Are Unreliable Parameters in Infants

Other commonly examined urinalysis parameters include nitrites and leukocyte esterase. The nitrite test indicates the presence of nitrate reductase, produced by some but not all uropathogens, which converts endogenous nitrates to nitrites. Leukocyte esterase is released by WBCs and indicates the presence of pyuria. In a systematic review of several studies, nitrites and leukocyte esterase were shown to have good sensitivity and specificity for detection of UTI in older children but were less reliable in infants.⁵² This is likely related to frequent micturition in infants which does not allow for sufficient concentrations of these substrates to develop. However, a more recent study of infants between 1 and 90 days of age showed that when microscopy is added to the urine dipstick the negative predictive value is

99.2%, but would result on average in 8 false positives for every missed episode of true UTI.⁵³

Treatment

Local Patterns of Antibiotic Resistance Should Determine Choice of Empiric Therapy

Empiric therapy for neonatal UTI and sepsis are similar because of common etiology. Traditionally parental antibiotics such as ampicillin and gentamicin are started once appropriate cultures are obtained. Within the US, the incidence of ampicillin resistance in neonatal *E. coli* isolates has been reported to be as high as 75% and gentamicin resistance as high as 12%–17%.^{54,55} In spite of approximately 90% resistance against ampicillin among the *E. coli* isolates from a neonatal ward, Taheri and colleagues⁵⁶ reported that clinical response was obtained in 50% of the patients, suggesting that there is a discordance between *in vitro* and *in vivo* activity of these drugs. This may be because the urinary concentration of ampicillin is much higher than the plasma level since it is excreted through the kidneys which may allow it to overcome the minimum inhibitory concentration of certain pathogens.⁵⁷

Peripartum Use of Maternal Antibiotics Increases the Risk of Resistant Clones in Infants

Use of maternal peripartum exposure antibiotics increases the risk of neonatal UTI and bloodstream infections with β -lactamase producing *E coli*: 82% versus 36% in infants of treated and untreated mothers, respectively.¹³ Common scenarios for maternal antibiotic exposure include preterm premature rupture of membranes (PPROM)^{58,59} and intrapartum prophylaxis.^{13,60}

Treatment of Candiduria

The presence of candiduria in a neonate indicates hematogenous spread and systemic disease. Treatment of systemic candidiasis is reviewed elsewhere in this issue by Kelly and colleagues and Wade and colleagues.

Neonatal Urinary Tract Infection can be Treated with a Combination of Parental and Oral Therapy

Data regarding the length of duration of treatment and the transition from parenteral to oral therapy in the infant are lacking. In the extremely premature infant, bioavailability of most antibiotics is not known; therefore, intravenous therapy is typically preferred. Documentation of negative blood and CSF cultures in both extremely premature and older infants provides optimal care. In older infants, Benador and colleagues⁶¹ found that the risk of renal scarring was no different between infants that received 3 days of parental therapy followed by 7 days of oral therapy compared with 10 days of oral therapy. In older and more mature infants with negative blood and CSF cultures, 3 to 4 days of parental therapy followed by transition to oral medications to complete a 7- to 14-day course of treatment can be used.⁶²

Renal Imaging Usually Includes a Renal Ultrasound Scan During the Acute Infection and a Voiding Cystourethrogram to Identify Vesicoureteral Reflux Approximately 2 to 4 Weeks After Resolution of Infection

Most practitioners recommend a RUS after an episode of UTI in the neonatal period to rule out congenital abnormalities. A VCUG is usually delayed for 2 to 4 weeks after successful treatment to assess for vesicoureteral reflux. Grade III or higher VUR is significantly associated with a higher risk of renal cortical damage; a DMSA scan should be considered to assess for renal scarring.²⁸

In a study of 100 infants with UTI, 47% had an abnormal RUS.⁵ However, the incidence of abnormalities was much lower in premature infants (4%).⁶³ Siomou and colleagues⁶⁴ prospectively evaluated 72 infants with an RUS and DMSA scan within 72 hours of diagnosis. Approximately 71% of the kidneys with grade III or more VUR on RUS were found to have normal early DMSA scans, 7% had evidence of permanent renal damage at the 6-month follow-up, all of which had an abnormal early DMSA scan. Therefore, an acute DMSA scan may be helpful in identifying the risk of renal scarring, but it does not reliably diagnose VUR.

The Risk of Recurrence Is Highest in First 6 Months After an Episode of Urinary Tract Infection

A long-term follow-up of 71 infants with UTI showed a recurrence rate of 28%.⁶⁵ Recurrence in premature infants was slightly more common than in full-term infants, but the difference was not significant. Most of the episodes of recurrence (65%) occur in the first 6 months after the initial UTI, and 75% occur in patients without any renal abnormalities.

Prophylactic Antibiotics Are Not Effective in Reducing Renal Scarring, but Do Increase the Risk of Recurrence with a Resistant Strain

Evidence regarding the efficacy of prophylactic therapy to prevent recurrences after the first episode of UTI is lacking for the neonatal population. Even for older infants, several small trials have found that antimicrobial prophylaxis may not be effective in preventing renal scarring.^{66,67} Other more recent studies found that although the prophylaxis may decrease the risk of recurrence, its effect on renal scarring is not significant, and recurrent episodes are more likely to be caused by a more resistant strain.^{68,69}

Summary

UTI is common in infants. It may indicate an underlying renal disorder, but most cases occur in the absence of any abnormalities. UTIs are rare in the first 3 days of life. Uncircumcised boys are at the highest risk for neonatal UTI. Diagnosis is by a urine culture in association with a positive dipstick test or urinalysis. Ampicillin and gentamicin are the traditional empiric therapies; however, local antibiotic resistance patterns and maternal use of antibiotics before delivery should be considered. The risk of recurrence is highest in the first 6 months after an episode of UTI. Use of prophylaxis is controversial because, although it may reduce the risk of recurrence, it is unclear if there is any effect on renal scarring, and use of prophylaxis increases the risk of infection with a resistant strain if recurrence occurs.

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Key Points

- Uncircumcised boys have the highest risk of urinary tract infection.
- *Escherichia coli* is the most common pathogen.
- Premature infants are at increased risk for *Candida* urinary tract infections.
- Infants with urinary tract infection are at risk for concomitant bacteremia and meningitis.
- Prophylaxis may increase the risk of antibiotic resistance for recurrent urinary tract infection.

Best practices box

What is the current practice?

Urinary Tract Infections in Neonate

Best Practice/Guideline/Care Path Objective(s)

- Early recognition of UTIs in neonates
- Initiation of appropriate empiric therapy
- Reduction in long-term renal sequelae

What changes in current practice are likely to improve outcomes?

- Recognition of enhanced risk for bacteremia and meningitis in neonates with UTI
- Empiric treatment of UTI based on prior maternal use of antibiotics during pregnancy and local antibiotic susceptibility profiles among uropathogens
- Cautious use of prophylactic antibiotics to prevent recurrent UTI and knowledge of the risk for emergence of resistant organisms

Major Recommendations

- Obtain urine specimen for bacterial culture by urethral catheterization; other urine parameters can be misleading in infants (grade 1A).
- Empiric therapy should include coverage against common uropathogens such as *E coli* and *Klebsiella* spp
 - Ampicillin and gentamicin are the most commonly used empiric regimen (grade 1A).
- Infants with prolonged or late-onset jaundice should be evaluated for a UTI (grade 1B).
- Infants with UTI should be evaluated for concomitant bacteremia and meningitis (grade 1B).
- Renal ultrasound scan should be done immediately after an episode of neonatal UTI, followed by a VCUG 2 to 4 weeks later to rule out anatomic abnormalities (grade 1B).
- Prophylactic antibiotics do not reduce the risk of scarring and can increase the risk of recurrent UTI with resistant organisms (grade 1B).

Summary statement

UTI in infants may indicate an underlying renal disorder; therefore, appropriate diagnosis and prompt initiation of therapy are essential to reduce long-term renal scarring.

Data from Refs. 5,19,43,46,69,72

Fig. 1. Ultrasound appearance of neonatal hydronephrosis. (A) Right kidney in an infant showing normal structures. (B) Left kidney in the same infant with edematous swollen slightly hyperechoic right kidney. (*Courtesy of Dr T.S.A. Geertsma, Ziekenhuis Gelderse Vallei, Ede, The Netherlands.*)

Fig. 2.

Grade III vesicoureteric reflux during micturition: reflux into the ureter and the calices with mild dilatation. (*Courtesy of Dr Adriana Dubbeldam, Belgium. Available at: www.radiopedia.org.*)

Table 1
Common pathogens isolated in neonatal UTI

Organism	Incidence (%)	References
Gram-negative rods		
<i>E. coli</i>	40–72	5,12,42
<i>Klebsiella</i> spp	7–40	5,35
<i>Enterobacter cloacae</i>	3–8	5,42
<i>Proteus vulgaris</i>	3	5
<i>Serratia marcescens</i>	1–7	5,35
<i>Pseudomonas aeruginosa</i>	1	5
Gram-positive cocci		
<i>Enterococcus</i> spp	10–16	5,42
<i>Staphylococcus aureus</i>	1–5	5,42
Group B <i>streptococcus</i>	1–3	5,70
<i>Staphylococcus, coagulase negative</i>	1	5
<i>Viridans streptococcus</i>	1	5
Yeast		
<i>Candida</i> spp	25–42	21,71

Table 2
Common symptoms and signs associated with neonatal UTI

Signs and Symptoms	Percentage	References
Fever >38.5°C	77–85	12,32
Poor feeding	48–90	12,32
Tachypnea or grunting	36–45	12,33
Lethargy	26–30	12,33
Jaundice	6–18	12,36
Diarrhea	13	12
Vomiting	8–9	12,32
Failure to thrive	7	12