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ARCHIVES OF MEDICINE

2015
Vol. 7 No. 5:4

Therapeutics of Pediatric Urinary Tract Infections

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Abstract

Infection of the urinary tract occurs after bacteria from the gastrointestinal tract colonize the urethra and a misbalance between the host responses and bacterial virulence. Symptoms vary depending on the location of the infection (lower or upper tract) and the age of the child. The gold standard for diagnosis is the urine culture. The urinalysis has good sensitivity and specificity and inflammatory markers although usually elevated are not perfect markers of infection. Voided urine or "bagged" specimens are not recommended and catheterized samples are necessary in children who are not toilet trained. After the first episode of urinary tract infection (UTI) in a young child, a renal and bladder ultrasound is recommended. The goals of treatment are eliminate the infection and prevent renal scarring. Oral and intravenous (IV) routes are feasible depending on the clinical situation; starting IV therapy with transition to oral is acceptable. Antibiotics commonly used in the treatment of UTI in children include cephalosporins, amoxicillin-clavulanate acid, and trimethoprim-sulfamethoxazole, but fluoroquinolones, aminoglycosides, and nitrofurantoin may be used in some scenarios. Given growing resistance of common uropathogens to various antibiotics, it is important to review susceptibility testing results and alter the selected antibiotic regimen accordingly.

Keywords: Urinary Tract Infection (UTI), children, Vesicoureteral Reflux (VUR), fever, cystitis, pyelonephritis

Abbreviations: **UTI:** Urinary Tract Infection, **AAP:** American Academy of Pediatrics, **IDSA**: Infectious Disease Society of America, **WBC:** White blood cell counts, CRP: C-reactive Protein, **ESR:** Erythrocyte Sedimentation Rate, **VCUG:** Voiding Cystourethrogram, **VUR:** Vesicoureteral reflux, DMSA: Dimercaptosuccinic acid, **IV**: Intravenous, **TMP-SMX**: Trimethoprim: Sulfamethoxazole

Introduction

Infection of the urinary tract in children may present with or without clinical symptoms; therefore, establishing the exact incidence of urinary tract infections is challenging [1]. Despite this, the pooled prevalence of UTI in febrile children 2 to 24 months of age is about 5% [2]. **Table 1** shows the most common organisms involved in the pathogenesis of UTI in children.

Pathophysiology

UTI usually results from gastrointestinal bacteria colonizing and ascending through the urethra. In infants younger than 12 weeks of age, UTI may be secondary to hematogenous spread of bacteria [3]. Bacterial colonization of the urethra occurs on regular basis early in life. Yet, disease does not develop unless there is misbalance between the host responses and bacterial virulence [1,4,7]. Bacterial virulence factors include adhesion (facilitated by bacterial fimbriae), lipopolysaccharides (endotoxins), capsular polysaccharides, hemolysin (pore-forming protein), and metabolic competition (iron and other nutrients) [1,8]. Host factors that predispose a child to UTI, recurrent infections, and renal scarring are summarized in **Table 2**.

Clinical Presentation

Clinical manifestations depend on the location of the infection (upper or lower tract). For instance, symptoms confined to the lower urinary tract or "cystitis" include dysuria, urgency, and suprapubic pain. Symptoms such as fever, malaise, and back pain are suggestive of upper tract disease, specifically pyelonephritis or ureteritis [1]. Symptoms may not reliably distinguish the site of infection [3].

The clinical presentation of UTI differs between younger and older children, and young children may be unable to localize

Table 1. Organisms involved in pediatric UTI.

Pathogen			Characteristics
Bacteria	Gram -	*Escherichia coli*	The most common causative organism at all ages 70-90% [1,3,4]
		Other Enterobacteriaceae	*Klebsiella, Enterobacter, Citrobacter, Proteus, Providencia, Morganella, Serratia, Salmonella, Shigella, Campylobacter* [1,3,4]
		Pseudomonas aeruginosa	Low virulence unless host is immunocompromised [1]
	Gram +	*Enterococcus spp*	Most common gram positive in young children [3]
		Group B Streptococcus	Occasionally isolated in neonates and adolescents [4]
		Staphylococcus aureus (MRSA and MSSA[a])	Rarely causes infection unless there is an in-dwelling catheter, bacteremia, or occult infection [3,4]
		Staphylococcus epidermidis	Recent history of urinary tract instrumentation [5]
		Staphylococcus saprophyticus	15% of female adolescents UTI [4]
	AFB [b]	*Mycobacterium*	Suspect in sterile pyuria and endemic area or epidemiologic contact [4]
Fungi	*Candida spp*		Associated with in-dwelling catheter or recent history of urinary tract instrumentation [3]
Virus	BK		Hemorrhagic cystitis in immunosuppressed children [4]
	Adenovirus		Hemorrhagic cystitis [3,4]
Protozoa	*Enterobius vermicularis*		Cause dysuria and pyuria in school age females [4]
	Schistosoma		In endemic areas [6]

[a]MRSA methicillin resistant *Staphylococcus aureus* and MSSA methicillin susceptible *Staphylococcus aureus*
[b]AFB acid-fast bacilli

Table 2. Host risks factors for UTI and renal scarring in children.

Factors	Description
Age	< 1 year of age [1,3,4,9-11]
Genetic predisposition	Age at first UTI [1,4] History of UTI in the mother [1,8] [a] Blood group phenotypes [1] [b] Genetic polymorphisms [8]
Race and ethnicity	White and Hispanic [1,10]
Anatomic abnormalities	Hydronephrosis [1,9] [c] VUR [1,4, 8,12] Hydroureter [1,8] Renal hypodysplasia [1,8]
Other factors	Prematurity [8,13] Uncircumcised < 3-6 months boys [9,10] Lack of breast-feeding [13] Sexual activity [10] Urologic procedures [1] Bladder and bowel dysfunction [1]

[a] P1, ABO
[b] Adhesion molecules (ICAM-1), transforming growth factor-β, TLR, and vascular endothelial growth factor
[c] VUR vesicoureteral reflux

existing symptoms. Neonates may have concomitant infections (e.g. bacteremia, meningitis) and usually present with nonspecific signs and symptoms of infection, such as irritability, poor feeding, weight loss, jaundice, emesis, seizures, or cyanosis [12,14]. Fever may or may not be present in neonates [1,14]. In older children and adolescents, fever and cystitis symptoms are more prevalent [1,4,9,12]. Presence of a renal mass may indicate hydronephrosis or pyonephrosis and a renal abscess should be suspected if there is persistent fever despite adequate therapy [4].

Recurrent episodes of pyelonephritis have been associated with renal scarring which can lead to hypertension and ultimately to end-stage renal disease [1,3,8]. These complications are rare in healthy children after the first episode of UTI [2].

Diagnostic Tests

Urine culture is considered the gold standard for diagnosis. In young children, a culture is positive if there are ≥ 50,000 CFU/mL of a single pathogen from a reliable specimen. Fewer colonies may represent infection if urinalysis is consistent with the diagnosis, especially in children 2 months to 2 years of age [2,15].

The sensitivity and specificity of the urinalysis is 82% and 92% respectively, 16 and sensitivity has been reported up to 97% even in younger children. 17 The presence of positive leukocyte esterase and nitrites in urine strips are consistent with infection. However, the lack of nitrites in the urinalysis cannot rule out infection. Not all organisms capable of causing UTI reduce nitrate and this conversion requires a relatively long incubation period in the bladder (minimum 4 hours) that may not occur in children who void frequently [1,14]. While cultures from catheterized urine are almost as sensitive and specific and certainly less painful than those obtained through suprapubic aspiration, cultures from bag specimens have undesirable rates of false-positive results [2,15]. In older children who are toilet trained, a clean urine specimen is acceptable for analysis.

Elevated serum markers such as white blood cell counts (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are associated with bacterial infection in young children [8,18] but they are imperfect markers for diagnosing UTI [2, 18-20]. In a Cochrane review evaluating the usefulness of inflammatory markers for the diagnosis of pyelonephritis, the authors concluded

Table 3. Age-based UTI Treatment Guidelines.

Age	Recommended Regimen	Total Duration (days)	Notes
< 2 months	Ampicillin IV + Gentamicin IV	7-14	May transition to oral therapy after clinical improvement if tolerating oral intake Oral therapy: amoxicillin-clavulanate or other antibiotic based on sensitivity testing Ampicillin and gentamicin may be administered IM if no IV access
	Ceftriaxone IV ± Ampicillin IV	7-14	Use cefotaxime in place of ceftriaxone in patients < 1 month Consider addition of ampicillin if concern for *Enterococcus* Ceftriaxone and ampicillin may be administered IM if no IV access
2 months to 2 years Asymptomatic bacteriuria	None		
UTI	TMP-SMX	7-14	Follow sensitivity testing results
	Amoxicillin-clavulanate	7-14	Follow sensitivity testing results
	Cephalexin	7-14	
	Cefprozil, cefuroxime, cefdinir, cefixime, cefpodoxime, or ceftibuten	7-14	Reserve for organisms resistant to above 3 options or if used for first-line therapy, de-escalate as indicated by sensitivity testing results
	Ceftriaxone IV or IM	7-14	Transition to oral therapy when tolerating oral intake
	Aminoglycoside IV	7-14	Transition to oral therapy when tolerating oral intake
	Ciprofloxacin PO	7-14	Reserve for patients with organisms resistant or other contraindications to above options
Children > 2 years			
Asymptomatic bacteriuria	None		
Acute cystitis	Nitrofurantoin	5	
	TMP-SMX	3-5	Follow sensitivity testing results
	Cefprozil, cefuroxime, cefdinir, cefixime, cefpodoxime, or ceftibuten	5	Utilize in areas where local sensitivities indicate high-level resistance of uropathogens to above medications
Pyelonephritis	TMP-SMX	7-14	Follow sensitivity testing results
	Amoxicillin-clavulanate	7-14	Follow sensitivity testing results
	Cephalexin	7-14	Local susceptibility patterns may preclude first-line use
	Cefprozil, cefuroxime, cefdinir, cefixime, cefpodoxime, or ceftibuten	7-14	Reserve for organisms resistant to above 3 options or if used for first-line therapy, de-escalate as indicated by sensitivity testing results
	Ceftriaxone IV or IM	7-14	Transition to oral therapy when tolerating oral intake
	Aminoglycoside IV	7-14	Transition to oral therapy when tolerating oral intake
	Ciprofloxacin PO	7-14	Reserve for patients with organisms resistant or other contraindications to above options

that ESR is not helpful, low CRP value is modestly useful in ruling out pyelonephritis, and procalcitonin seems a more promissory marker. Unfortunately, the heterogeneity and the limited number of studies thwarted robust conclusions [21]. A growing body of literature indicates that in children with acute pyelonephritis, serum procalcitonin might be a better predictor for parenchymal involvement than other serum markers during early disease, as well as a good predictor for late scarring [19,22-28].

The American Academy of Pediatrics (AAP) and the National Institute for health and Care Excellence (NICE) in the United Kingdom have recommendations for imaging guidelines after a febrile UTI. The AAP recommended in 2011 ultrasound (US) of the kidneys and bladder after the first UTI in young children reserving the voiding cystourethrogram (VCUG) for cases of hydronephrosis or after a second episode of UTI [2,15]. The NICE recommends US only in children younger than six months or older children with "atypical" UTI while VCUG only for those infants less than six months of age if they have "atypical" UTI and in those with recurrences [29]. Literature remains controversial regarding imaging recommendations and it may be possible that US and VCUG are complementary [30,31].

Management

Regardless of patient age, the goals of treatment for a UTI are similar. First and foremost, acute infection should be eliminated in order to prevent spread of infection. Additionally, it is desirable to prevent any permanent renal damage. These goals can be accomplished by initiating an appropriate antimicrobial regimen once the diagnosis of a UTI is suspected [2,15].

Route of Administration

Route of administration should be chosen based upon the clinical situation. Those patients who are toxic-appearing, dehydrated, vomiting, unable to take or retain oral intake, or would be anticipated to have poor oral compliance may be candidates for parenteral therapy, at least initially, but should be transitioned to oral when feasible [4,15]. A 2014 Cochrane Review found no significant difference in time to fever resolution, rate of bacteriuria recurrence, or risk for persistent UTI at 72 hours when comparing courses of only oral antibiotics to courses initiated with intravenous antibiotics and then completed with oral options [32]. Neonates have a higher incidence of septicemia associated UTI and unpredictable enteral absorption, making parenteral antibiotic therapy the appropriate choice [33,34].

For those patients whom are initiated on parenteral antibiotic therapy, the exact duration of IV therapy before switching to oral remains debated, but IV antibiotics should continue at least until response if noted. 4, 15 One study compared the rate of treatment failure in infants under 6 months of age long duration (≥ 4 days) IV antibiotics to short duration (≤ 3 days). They found a failure rate of 2.2% in the long course group and 1.6% in the short course. No other differences in results were noted between the two groups and the authors conclude short course IV therapy is unlikely to affect re-admission rates in young infants [35]. Another study evaluated children 6 months to 16 years of age with pyelonephritis and acute lesions on dimercaptosuccinic acid (DMSA) scintigraphy to compare the efficacy of a 14-day course of oral ceftibuten to that of a 3-day course of IV ceftriaxone followed by an 11-day course of an oral cephalosporin. The authors found that the clinical courses of the two groups were similar. Additionally, 26% of patients in the oral group and 46% of patients in the IV/oral group developed renal scarring ($p = 0.2$). The authors concluded that oral antibiotics were equally as effective as intravenous therapy at preventing renal scarring [36]. Given the equivalent efficacy of oral and intravenous therapy, the AAP recommends the use of oral antibiotics when possible [15].

Antimicrobial Therapy

Frequently utilized antibiotics in the treatment of UTI in children include cephalosporins, amoxicillin-clavulanate acid, and trimethoprim-sulfamethoxazole (TMP/SMX); however fluoroquinolones, aminoglycosides, and nitrofurantoin may be used in some scenarios. **Table 3** provides age-based treatment guidelines for pediatric patients. The decision of which to choose should be primarily based upon local susceptibility patterns of the more common organisms [2,15]. A 2005 study by the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) pooled data from 30 medical centers in the USA and 11 in Canada to demonstrate significant variation in resistance among the various geographic regions [37]. Other studies have revealed that the overall rate of resistance for E.coli and other uropathogens to various antibiotics continues to rise in the outpatient and inpatient settings [38-40]. Given this growing rate of resistance, it is prudent to follow up susceptibility testing results and alter the selected antibiotic regimen accordingly.

Trimethoprim-Sulfamethoxazole

TMP-SMX is frequently used for the treatment of UTI secondary to growing rates of amoxicillin resistance in *E. coli* [41]. Rates of resistance vary among geographic regions, but in many regions are approaching the 20% threshold established by the Infectious Disease Society of America (IDSA), indicating that in the near future, TMP-SMX may no longer be a first-line drug for the treatment of UTI [42]. Studies in pediatric patients have reported 24%-30% resistance rate among urinary *E. coli* [39-40]. Patients begun empirically on this drug for treatment of UTI should have their therapy optimized based on culture. Because TMP-SMX can cause displacement of bilirubin, resulting in an increased risk of kernicterus, infants less than 2 months of age should not receive this antibiotic [43].

Amoxicillin-Clavulanate

Secondary to the development of resistance among *E. coli* isolates to aminopenicillin therapy, amoxicillin-clavulanate has become a commonly utilized therapy for the treatment of pediatric UTI [15]. This antimicrobial also has activity against enterococci. The most common adverse effect associated with amoxicillin-clavulanate therapy is diarrhea caused by the clavulanate. Therefore, utilizing formulations with higher ratios of amoxicillin to clavulanate (7:1 or 14:1) can allow for twice a day dosing without increasing the risk of associated diarrhea [43].

Cephalosporins

Cephalosporins may be useful in the treatment of UTI, depending on the clinical situation. They have activity against most Enterobacteriaceae; however they have no Enterococcus coverage and should be avoided in patients in whom initial Enterococcus coverage is deemed important [4]. Cephalexin is an oral first-generation cephalosporin, which may be used in place of TMP-SMX, especially in pediatric patients. It is well tolerated and resistance rates remain relatively low (< 10%) [39,44].

Ceftriaxone and cefotaxime are parenteral third-generation options that can be utilized in those patients who are not candidates for oral therapy [43]. Ceftriaxone is very effective when administered once daily, making it a convenient option for outpatient parenteral therapy or for patients in the emergency department [4,43]. Second generation cephalosporins, such as cefprozil and cefuroxime, and third generation cephalosporins like cefixime, cefpodoxime, ceftibuten, and cefdinir are options that are available for oral administration. All of these agents provide the advantage of only once or twice daily dosing, which may improve compliance rates. With the continuing development of resistance of *E. coli* to TMP-SMX and the aminopenicillins, second and third generation cephalosporins may play an increasing role in the treatment of pediatric UTI [39]. Cefdinir demonstrated excellent in vitro activity against the more common UTI pathogens [45]. Resistance of uropathogens to the third generation cephalosporins is uncommon at this time [45,46]. The balance between the use of these broader spectrum antibiotics and development of resistance, particularly extended spectrum beta-lactamases, must be closely monitored.

Aminoglycosides

Aminoglycosides are only available via the parenteral route. This class has broad activity against Gram-negative organisms, including *Pseudomonas aeruginosa*. Most of the dose is excreted unchanged in urine and a small amount accumulates in the renal tubular cells, making aminoglycosides ideal for the treatment of pyelonephritis [47]. A Cochrane Review compared once daily aminoglycoside administration to thrice daily and found no difference in outcomes between the two regimens [32]. Given the potential for improved tolerance and less toxicity, a once daily course should be chosen if aminoglycosides are used for UTI treatment. In any scenario, aminoglycoside levels should be monitored to confirm adequate levels for treatment of an infection and to avoid accumulation [43].

Fluoroquinolones

The safety of fluoroquinolones in pediatric patients has been debated for many years [4,48]. Fluoroquinolones are broad-spectrum antibiotics that have adequate coverage of common uropathogens but are also the only oral antibiotics with activity against *Pseudomonas aeruginosa*. Ciprofloxacin is the only fluoroquinolone that is FDA approved for the treatment of complicated UTI and pyelonephritis in children 1-17 years of age due to *E. coli* [43]. This class is not recommended for first-line for UTI due to concern for potential adverse effects, especially arthropathies. Irreversible cartilage damage has been noted in beagle puppies that received fluoroquinolones; however, such irreversible damage has not been noted in any human studies [48]. Overuse of fluoroquinolones may foster the development of antibiotic resistance. The use of fluoroquinolones for the treatment of UTI should be reserved for those patients with multidrug-resistant gram-negative organisms [4,48].

Nitrofurantoin

Nitrofurantoin is excreted in the urine and the resulting high urine concentrations of this drug make it effective for the treatment of UTI [4,43]. Nitrofurantoin does not achieve therapeutic concentrations in the bloodstream, and should therefore be avoided in febrile infants with or at risk for urosepsis or in those where concerns of pyelonephritis or systemic infection exist [18]. Nitrofurantoin should also not be used in patients with renal insufficiency.

Duration of Treatment

Optimal duration of therapy in pediatric patients has not been established. The use of a short course (single parenteral dose or a maximum of 3 day total course) has been the standard of care for adult women with uncomplicated lower UTI [42]. This type of data is lacking for pediatric patients. A meta-analysis of randomized controlled trials by Keren et al. compared short course (≤ 3 days) to long course (7-14 days) therapy in pediatric patients and found a relative risk (RR) of treatment failure with short-course of 1.94 (95% CI: 1.19-3.15) [49]. A Cochrane Review by Michael et al. sought to compare short (2-4 days) to long (7-14 days) courses of therapy for UTI in children. There were no differences between the two groups with respect to persistence of bacteriuria at completion of treatment or in the number of children with recurrence one to 15 months after therapy. However, none of the studies included in the review provided data on resolution of clinical symptoms and most studies excluded patients with febrile UTI and pyelonephritis, making it difficult to determine the true efficacy of the courses and to apply to a broad pediatric population [50]. Another review of randomized controlled trials in children with lower UTI, by Fitzgerald et al. found that conventional 10-day treatment significantly decreased persistent bacteriuria (RR 2.01, 95%CI 1.06 to 3.80) compared with short course, but short course was defined as a single dose treatment [51]. With the evidence of uncertain efficacy associated with short courses, the AAP continues to recommend duration of 7 to 14 days for treatment of a UTI in children [15].

Non-antimicrobial Therapy

The dysuria associated with a UTI can be quite painful. Phenazopyridine may be utilized to provide symptomatic relief. It is an AZO dye with analgesic and antiseptic properties. In the early 1900's, it was used as the primary treatment for a UTI until it was discovered that it did not in fact have bactericidal activity. Controversy continues to exist over the appropriate use of phenazopyridine [52]. Due to a significant side effect profile and risk for toxicity, this medication should be reserved for older patients, in whom there is more experience or most severe cases. Patients must be monitored for methemoglobinemia and hemolytic anemia and should be informed of a red-orange discoloration of all bodily fluids and the potential for staining clothing [53,54].

Prophylaxis

Non-pharmacologic therapy

Current evidence suggests that the preventive health benefits of elective circumcision such as significant reduction in the risk of UTI in the first year of life outweigh the risks of the procedure. This procedure is recommended for boys, if the parents so choose [55].

Pharmacologic therapy

One of the more significant changes over the past decade in the management of UTI is the recommendation that prophylactic antibiotics should no longer be routinely prescribed. A meta-analysis performed within the most recent AAP guidelines for the treatment of UTI in infants and children found no difference in the rate of recurrence of UTI in either infants without VUR or in those with grades I, II, III, or IV VUR. There were too few infants with grade V reflux to draw any conclusions about this group. 15 However, a recent randomized intervention for children with vesicoureteral reflux (RIVUR) showed that among children with VUR and UTI, antimicrobial prophylaxis was associated with decreased risk of recurrence by 50% but there was no difference on renal scarring (although scarring was not the primary outcome of the study) [56].

Several studies have found much higher rates of resistant organisms in those patients who have UTI recurrences and are receiving prophylactic antibiotics [56-62]. The groups receiving no prophylaxis had a resistance rate of 0 to 39% versus the prophylaxis group rate of 53 to 100%. 2 At this time, antibiotic prophylaxis does not appear to significantly reduce rates of UTI recurrence but may promote the development of resistant organisms.

Alternative nutrient supplementation

The utility of cranberry concentrate for the prevention of UTI continues to be debated. It is believed that the mechanism of action for cranberry is to prevent adherence of bacteria, particularly *E. coli*, within the urinary tract. Recent small clinical trials in pediatric patients have shown minor and statistically insignificant reductions in the incidence of recurrent UTI [63,64].

Other potential therapies for the prophylaxis of recurrent UTI include probiotics and vitamin A. The concept of probiotics is promotion appropriate colonization of the genitourinary tract. Vitamin A has anti-inflammatory properties and can potentially reduce renal scarring [63]. Both of these therapies need to be further studied to determine their impact on the incidence of recurring UTI.

Catheter-associated UTI

Catheter-associated bacteriuria is the most common healthcare-associated infection [5]. Its pathogenesis is most often related to extraluminal acquisition, as the catheter interrupts host defenses and provides easy access to the bladder for microorganisms [65]. It is important to distinguish between catheter-associated asymptomatic bacteriuria and catheter-associated UTI. Both entities are combined under the name catheter-associated bacteriuria. Per the IDSA guidelines, the diagnosis of catheter-associated UTI is made when the patient meets the following criteria-has a catheter in place or had a catheter removed within the past 48 hours, has signs and/or symptoms of UTI, has no other source of infection, and has bacteria at a concentration of greater than 1000 colony-forming units/milliliter from a catheter urine specimen or a midstream voided urine specimen. These diagnostic criteria are intended for use in adult patients [5]. Lack of data on any differences between the pathogenesis and diagnosis in pediatric patients, makes these criteria applicable to the younger population as well.

Because catheter-associated UTI can be polymicrobial and may result from multi-drug resistant organisms, it is recommended that a urine culture be performed prior to initiating treatment. Cultures must be monitored closely, so the regimen can be adjusted if indicated. If the catheter is no longer needed, it should be removed. In those patients who have had an indwelling catheter in place for at least two weeks and have continued need for catheterization, it is recommended that the catheter be replaced to promote faster resolution of the infection. 5 Catheter –associated UTI should be treated for 7 days in those patients who have prompt resolution of symptoms and for 10 to 14 days for slow responders. There is currently a limited amount of data on shorter courses, all of which is in the adult population. Data do not support the use of catheter irrigation with antimicrobials to eradicate bacteriuria or UTI [5].

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