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Antimicrobial Pharmacotherapy Management of Urinary Tract Infections in Pediatric Patients

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Abstract

Objective: To discuss the risk factors, microbial resistance rates, and pharmacotherapy, including antimicrobial choices and medication dosage regimens, for urinary tract infections (UTIs) in pediatric patients. **Data Sources:** A MEDLINE literature search (1985 to December 2017) was performed using the following keywords and associated medical subject headings: *urinary tract infection, antimicrobial, treatment*, and *children*. **Study Selection and Data Extraction:** Search was conducted to identify clinical trials, systematic reviews, and guidelines. Search was filtered to include studies with age range between birth and 18 years and published in English. Additional references were identified from selected review articles. **Data Synthesis:** In total, 27 studies investigating microbial resistance, 31 studies assessing antimicrobial efficacy, 34 studies describing prophylaxis, and 6 systematic reviews were included. The resistance patterns differed across age groups and affected the choice of empirical therapy. If pyelonephritis is suspected, empiric antimicrobials should have high urinary and sufficient parenchymal concentrations. Nitrofurantoin has low microbial resistance rates and can generally be used empirically for treating uncomplicated cystitis in children >1 month of age. Trimethoprim-sulfamethoxazole resistance has increased and should be avoided unless local susceptibility data are available. Certain patients with recurrent UTIs or renal abnormalities may require antimicrobial prophylaxis, which may be associated with adverse effects, such as intolerability or an increased risk of microbial resistance. **Conclusion:** The resistance pattern of uropathogens should be considered prior to initiating therapy. Controlled trials with large samples are needed to compare the treatment duration of various antimicrobial regimens and the specific role of prophylactic antimicrobials.

Keywords

urinary tract infections, pediatrics, disease management, prophylaxis, antibiotic resistance

Introduction

Urinary tract infections (UTIs) are among the most common infections in pediatric patients.[1] Approximately 1.5 million outpatient pediatric visits in the United States are due to UTIs.[1] The prevalence of UTIs varies according to age and gender. After 6 months of age, approximately 11% of girls and 4% of boys suffer from UTIs.[2] The early and proper management of UTIs is critical, particularly in young pediatric patients, to prevent complications, such as renal scarring.[3]

Several guidelines have been published to aid in the diagnosis and management of this disease.[4-7] While most guidelines provide extensive recommendations regarding diagnosis and imaging, specific guidance regarding the choice of antimicrobial agents for pediatric patients, particularly those who are at a risk of developing resistant organisms, is not provided. Knowledge of the local susceptibility patterns is important for choosing the appropriate agent. Many studies have evaluated the microbial resistance patterns in different countries, and several review articles have discussed these data. However, recent literature summarizing the resistance patterns in different geographical areas and a comprehensive evaluation of the choice of antimicrobial therapy and prophylaxis for UTIs in pediatric patients is lacking. Other factors also affect the choice of antimicrobial treatment. These factors include the type of UTI (ie, upper or lower UTI, complicated or uncomplicated UTI, first or recurrent UTI) as well as the patient care setting (inpatient or outpatient) and patient-specific characteristics (eg, age, history of hospitalization,

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etc). One should consider all these factors along with local susceptibility patterns before a proper empiric antimicrobial could be chosen, as complicated UTI and pyelonephritis, for instance, may lead to severe and permanent complications such as renal scarring if not appropriately managed early. Furthermore, neonates and young infants presented with fever should be evaluated for UTI.

The purpose of this article is to discuss the risk factors, microbial resistance rates, and pharmacotherapy, including antimicrobial choices, medication dosage regimens, and treatment durations, in various types of UTIs and settings and the roles of adjunctive treatments and prophylactic agents in certain specific patients for UTIs in pediatric patients from birth to 17 years of age.

Literature Review

The literature search was performed using MEDLINE (from 1985 to December 2017) to identify articles written in English involving pediatric patients with the following search terms: *urinary tract infection, antimicrobial, treatment*, and *children*. Additional references were identified from selected review articles and relevant publications. Research studies, systematic reviews, and guidelines describing microbial resistance, antimicrobial efficacy, and prophylactic agents for the treatment of UTIs in pediatric patients were included. Case reports were excluded. In total, 27 studies investigating microbial resistance, 31 studies assessing antimicrobial efficacy, 34 studies describing prophylaxis, and 6 systematic reviews were included.

Risk Factors

Several risk factors have been linked to the development of UTIs in pediatric patients. In infants younger than 2 months of age, uncircumcised males were at a higher risk of developing UTIs than females or circumcised males. However, after 6 months of age, girls are at a higher risk of developing UTIs.[8] Furthermore, abnormal congenital anomalies in the kidneys and urinary tract (such as the high-grade vesicoureteral reflux [VUR] grade IV-V) may increase the risk of recurrent UTIs.[9] White individuals are at a higher risk of developing UTIs than Hispanic or African American individuals.[8] Additionally, White infants and children have an increased risk of developing recurrent UTIs.[10] Immunocompromised status (such as cancer patients) may increase risk of UTIs.[11] As a child grows, certain behavioral aspects, such as incomplete voiding, the presence of severe constipation, and being sexually active, may be associated with an increased risk of developing UTIs.[12]

Microbial Resistance

The development of resistance to antimicrobials is a major consideration, particularly in selecting an appropriate empiric treatment for a specific patient. Resistance patterns may change over time or by the geographical location of the host. Several risk factors are linked to the emergence of resistant uropathogens in pediatric patients. Exposure to antibiotics within the previous 60 to 90 days is associated with the development of microbial resistance in children with UTI.[13,14] Specifically, amoxicillin exposure in the previous 30 days was associated with microbial resistance to both amoxicillin and amoxicillin-clavulanate. The magnitude of the resistance (minimum inhibitory concentration [MIC] values) may decrease over time following the antibiotic exposure. Exposure to amoxicillin more than 2 months prior to a UTI was not associated with amoxicillin resistance. Restricting the use of a specific antimicrobial can also reduce the resistance against that antimicrobial. The resistance of *Escherichia coli* to ciprofloxacin decreased from 12% to 9% by nationally restricting the use of fluoroquinolone in a study involving both adults and children.[15] Recent hospitalization (hospital-acquired UTI) also increases the possibility of developing resistant uropathogens.[13,14] Hospitalizations in the 30 to 60 days prior to the UTI was associated with trimethoprim-sulfamethoxazole resistance and increases in extended-spectrum β-lactamase (ESBL)-producing *E coli* infections.

Antimicrobial treatment of recurrent UTIs may also increase the risk of bacterial resistance. Certain patients with recurrent UTIs, particularly those with urological abnormalities, such as high-grade VUR and prenatal hydronephrosis, may be prescribed long-term prophylactic antibiotics. Three studies evaluated the risk of using prophylactic antibiotics in children with recurrent UTIs and found that antibiotic prophylaxis is associated with an increased risk of uropathogen resistance.[9,16,17] Additionally, the selected prophylactic antibiotic affected the extent of the resistance.[18] Using cephalosporin as a prophylactic agent in patients with VUR is associated with an increased risk of developing ESBL-producing organisms, suggesting that the use of this antibiotic in these patients should be limited. However, using trimethoprim-sulfamethoxazole as a prophylactic agent was not associated with an increased risk of developing ESBL-producing organisms, although the antimicrobial susceptibility to trimethoprim-sulfamethoxazole significantly decreased.

Several studies have been conducted in different countries to assess the resistance patterns of microorganisms in children with UTIs across different age groups, genders, and clinical settings.[14,19-38] Studies included in this review were conducted in the United States, Canada, Belgium, France, Switzerland, Serbia, Turkey, Iran, Israel, Jordan, and Taiwan.

Tables 1, 2, and 3 summarize these studies in outpatient, inpatient, and combined outpatient and inpatient settings, respectively. The tables include the uropathogen rate and resistance pattern reported in each study. The resistance rates of uropathogens exceeding 20% were combined for

Table 1. Studies Evaluating Uropathogen Rates and Resistance Patterns in the Outpatient Setting.

Study	Place and Time Frame	Design and Urine Source	Age Group and Number	Uropathogen Rate	Resistance Pattern	Comments
Gaspari, 2005[21]	United States; 2002-2004	Retrospective Database Urine source was not specified	269 neonates 2124 (1-24 months) 7593 (2-12 years) 2745 (13-17 years)	Among all age groups *E. coli* 70% *Enterococcus* 13% *Klebsiella* 8%	*E. coli* resistance: *Neonates*: ≥20% (AMP) <20% (AMP, Amox/clav, CFZ) *1-24 months* ≥20% (AMP, TM/SMX) <20% (Amox/clav, CFZ, Cip, NIT) *2-12 years* ≥20% (AMP, TMP/SMX) <20% (Amox/clav, CFZ, NIT) *13-17 years* ≥20% (AMP) <20% (Amox/clav, CFZ, Cip, NIT, TMP/SMX)	Individuals with indwelling catheters were excluded
Kizilca, 2012[30]	Turkey; 2008-2009	Retrospective Bladder catheterization	344 children 2 months to 18 years	*2-12 months*: ESBL 53% Non-ESBL 42% >12 months: ESBL 47% Non-ESBL 58%	Resistance patterns of ESBL vs non-ESBL: TMP/SMX 83% vs 62% CIP 47% vs 10% NIT 18% vs 5% Carbapenems 39% vs 21% Pip/Taz 40% vs 10%	Study included patients with UTI recurrence
Borsari, 2008[32]	Switzerland; 2004-2008	Prospective Bladder catheterization/ midstream urine	100 children (5 weeks to 17 years)	*E coli* 88.5%	*E. coli* resistance: ≥20% (AMP, TMP/SMX) <20% (Amox/clav, NIT)	
Yolbas, 2013[34]	Turkey; 2010-2011	Retrospective Sterile urine bags and midstream urine	150 children (1 month to 15 years)	*E coli* 75% In females 87% In males 47% *Klebsiella* 21% In females 13% In males 50% *Proteus* 2.7% *Pseudomonas* 1.3%	*E coli* resistance: ≥20% (AMP, TMP/SMX, amox/clav, CRO) <20% (AMK, NIT, carbapenem)	
Al-Mardeni, 2009[35]	Jordan; 2006-2007	Retrospective Included all types of urine sources	529 children <4 years Outpatients	Females vs males *E. coli*: 85% vs 15% Non–*E coli*: 68% vs 32%	Multidrug-resistant *E coli* 60% Resistance patterns of *E coli* vs non–*E coli*: AMP 82% vs 83% TMP/SMX 72% vs 80% LEX 37% vs 52% NIT 21% vs 71% CRO 20% vs 28%	Non–*E coli*: Females: *Proteus* was the highest rate, while in males *Klebsiella* was the highest rate
Edlin, 2013[36]	United States; 2009	Retrospective Database analysis Urine source was not specified	25 418 children (195 sites) <18 years Outpatients	Females vs males *E. coli*: 83% vs 50% *Enterococcus*: 5% vs 17% *Proteus*: 4% vs 11% *Klebsiella*: 4% vs 10%	*E coli* resistance: ≥20% (AMP, TMP/SMX) <20% (Amox/clav, CIP, CFZ, CRO, NIT)	

Abbreviations: AMK, amikacin; Amox/clav, amoxicillin-clavulanate; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CFZ, cefazolin; CIP, ciprofloxacin; CRO, ceftriaxone; CXM, cefuroxime; ESBL, extended-spectrum β-lactamase; GEN, gentamicin; GNB, gram-negative bacilli; LEX, cephalexin; NIT, nitrofurantoin; P, *Pseudomonas*; PIP, piperacillin; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VAN, vancomycin.

Table 2. Studies Evaluating Uropathogen Rates and Resistance Patterns in the Inpatient Setting.

Study	Place and Time Frame	Design and Urine Source	Age Group and Number	Uropathogen Rate	Resistance Pattern	Comments
Taheri, 2012[19]	Iran; 2001-2010	Retrospective case series SPA/bladder catheterization	97 neonates Inpatients	*E coli* 76% *Proteus* 10% *Enterococcus* 7%	*E coli* resistance ≥20% (AMK, AMP, GEN, TMP/SMX) <20% (CRO, CAZ)	81% responded to empirical therapy with AMP
Clarke, 2010[20]	Canada; 2004-2006	Retrospective Bladder catheterization	64 neonates NICU	*E coli* 23% CoNS 26% *Klebsiella* 10%	NA	66% prescribed prophylactic antibiotics
Ismaili, 2011[23]	Belgium; 2006-2008	Prospective observational SPA/bladder catheterization	209 infants (<3 months) Inpatients admitted via ED	*E coli* 88% *Klebsiella* 7% *S aureus, Enterobacter* 2%	*E coli* resistance ≥20% (AMP, TMP/SMX) <20% (AMK, NIT, 2nd- and 3rd-generation cephalosporins)	UTIs affected more boys (74%) than girls (26%)
Yüksel, 2006[24]	Turkey; 2003-2004	Prospective cross-sectional analysis All methods including urine bags	33 infants (<12 months) 53 children (13-60 months) 79 children (>60 months) Inpatients for upper UTI, outpatients for lower UTI	Among all age groups: *E coli* 87% *Klebsiella* 10% *Enterococcus* 1.5% *Enterobacter* and *Proteus* 1.5%	*E coli* resistance *Infants*: ≥20% (AMP, CRO GEN, TMP/SMX) <20% (AMK, NIT, Cip) *Children 13-60 months* ≥20% (AMP, TMP/SMX) <20% (AMK, Cip, CRO, GEN, NIT) *Children >60 months* ≥20% (AMP, TMP/SMX) <20% (AMK, Cip, CRO, GEN, NIT)	Among all age groups, most ESBL-producing bacteria were obtained from infants
Jakovljević, 2013[25]	Serbia; 2009-2010	Prospective Observational Sterile tubes of urine bags	173 children <24 months 130 children 2-18 years Inpatients	*Children <24 months* Multidrug-resistant E coli 72% 2-18 years E coli: Females: 66%; males: 56% (P = .03) Multidrug resistant E coli 37%	*E coli* resistance *Children <24 months* ≥20% (AMP, CRO, LEX, TMP/SMX) <20% (AMK, Cip) *2-18 years* ≥20 (AMP, CRO, TMP/SMX) <20% Cip	Overall higher levels of resistance in males than in females (*P* < .0001)
Marcus, 2005[26]	Israel; 2001-2002	Prospective[a] Observational Urine bags were not used	158 children (<18 years old) Inpatients with CA-UTIs	*E coli* vs non–*E coli* Neonates: 27% vs 31% 1 month to 1 year: 33% vs 34% 1-5 years: 27% vs 17% >5 years: 13% vs 17%	*E coli* resistance: ≥20% (AMP, TMP/SMX) <20% (Amox/Clav, LEX, CXM, CRO, NIT, AMK, Cip, ATM) Non–E coli resistance: ≥20% (AMP, Amox/Clav, CXM, CRO, LEX, NIT, TMP/SMX) <20% (AMK, ATM, Cip, GEN)	

(continued)

Table 2. (continued)

Study	Place and Time Frame	Design and Urine Source	Age Group and Number	Uropathogen Rate	Resistance Pattern	Comments
Marcus, 2008[27]	Israel; 2001-2005	Prospective[a] Observational Urine bags were not used	322 Children (<18 years old) Inpatients with CA-UTIs	*P* vs non-*P* Neonates: 11% vs 28% 1 month to 1 year: 39% vs 38% 1-5 years: 18% vs 23% >5 years: 32% vs 12%	*Pseudomonas* resistance: PIP 13% Cip 12% CAZ 0%	
Marcus, 2012[28]	Israel; 2001-2005	Prospective[a] Observational Urine bags were not used	326 Children (<18 years old) Inpatients with CA-UTIs	Enterococcal vs GNB Neonates: −27% vs 26% 1 month to 1 year: 36% vs 37% 1-5 years: 23% vs 23% >5 years: 14% vs 13%	Enterococcus resistance: AMP 10% Amox/Clav 10% NIT 5% VAN 0%	
Dayan, 2013[29]	Israel; 2008-2011	Retrospective Case-control Data verified by telephone calls Urine bags were not used	150 children (25 cases vs 125 control) <18 years old Inpatients with CA-UTIs	Study group (ESBL): *E coli* 76% *Klebsiella* 24% Control group (non-ESBL): *E coli* 94% *Klebsiella* 6%	ESBL: ≥20% (Cip, GEN, NIT, TMP/SMX) <20% AMK Non-ESBL: ≥20% (TMP/SMX) <20% (AMK, Cip, GEN, NIT)	
Fan, 2014[14]	Taiwan; 2002-2006	Retrospective Case-control All methods including urine bags	104 ESBL cases vs 208 controls <15 years Inpatients CA-UTIs	ESBL-producing *E coli* 33%	ESBL-producing *E coli* in 2006: ≥20% (TMP/SMX, cip) <20% AMK	
Sakran, 2014[31]	Israel; 2003-2010	Retrospective SPA till age of 3 years Midstream urine in older children	456 First episode vs 106 recurrent UTIs <18 years Inpatients	First vs recurrent *E coli* 81% vs 75% *Klebsiella* 6% vs 5% *Proteus* 4% vs 5% *P aeruginosa* 2% vs 8%[P] ESBL 1% vs 7%[P]	All uropathogen resistance (first vs recurrent) ≥20% (AMP, TMP/SMX) AMK 8% vs 0% GEN 3% vs 5% CXM 6% vs 17%[P] NIT 6% vs 19%[P]	

Abbreviations: AMK, amikacin; Amox/clav, amoxicillin-clavulanate; AMP, ampicillin; ATM, aztreonam; CA-UTI, community-acquired urinary tract infection; CAZ, ceftazidime; CIP, ciprofloxacin; CoNS, coagulase-negative *Staphylococcus*; CRO, ceftriaxone; CXM, cefuroxime; ED, emergency department; ESBL, extended-spectrum β-lactamase; GEN, gentamicin; GNB, gram-negative bacilli; LEX, cephalexin; NICU, neonatal intensive care unit; NIT, nitrofurantoin; *P, Pseudomonas*; PIP, piperacillin; SPA, suprapubic bladder aspiration; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VAN, vancomycin.

[a]The prospective design of the study is questionable since informed consents were exempt.

Table 3. Studies Evaluating Uropathogen Rates and Resistance Patterns in Inpatient and Outpatient Settings.

Study	Place and Time Frame	Design and Urine Source	Age Group and Number	Uropathogen Rate	Resistance Pattern	Comments
Doré-Bergeron, 2009[22]	Canada; 2005-2007	Retrospective ASP/bladder catheterization	103 (1-3 m) 58 ambulatory treatment vs 45 inpatients	*E coli* 85% *Klebsiella* 7%	All strain resistance: GEN 2% (other resistance patterns not discussed)	Ambulatory IV treatment was feasible in infants 1-3 months old
Catal, 2009[33]	Turkey; 2000-2006	Retrospective All sources including urine bags	698 children 2 months to 14 years Inpatients and outpatients	Frequency of isolates in 2006[a]: *E coli* 56% *Klebsiella* 18% *Enterococcus* 8% *Proteus* 6%	Resistance patterns of *E coli*[a]: ≥20% (AMP, TMP/SMX, PIP) <20% (NIT, CTX, CIP, NIT)	
Saperston, 2014[37]	United States; 2009	Retrospective Database analysis Urine source was not specified	25 418 outpatients vs 5560 inpatients <18 years (195 sites)	Outpatients vs inpatients: *E. coli* 79% vs 54% In females 83% vs 64%; in males 50% vs 37% *Enterococcus* In females 5% vs 13%; in males 17% vs 27% *Klebsiella* In females 4% vs 10%; in males 10% vs 12%	*E coli* resistance outpatients vs inpatients: AMP 45% vs 55% TMP/SMX 24% vs 30% Amox/clav 5% vs 6% CIP 5% vs 9% CFZ 4% vs 8% CRO <1% vs 2%	
Garraffo, 2014[38]	France; 2011	Prospective Multicenter Midstream urine/ urine bags	110 children <12 years Inpatients and outpatients	*E coli* 78% *Proteus* 9% *Enterococcus* 4%	*E coli* resistance: ≥20% (AMX, TMP/SMX) <20% (Amox/clav, CIP, GEN, NIT)	Previous exposure to antibiotics within 12 months was correlated with resistance

Abbreviations: AMK, amikacin; Amox/clav, amoxicillin-clavulanate; AMP, ampicillin; AMX, amoxicillin; CFZ, cefazolin; CIP, ciprofloxacin; CRO, ceftriaxone; CTX, cefotaxime; GEN, gentamicin; NIT, nitrofurantoin; *P, Pseudomonas*; PIP, piperacillin; TMP/SMX, trimethoprim-sulfamethoxazole.
[a]Resistance pattern was discussed for all organisms in 2000 and 2006, and only the *E coli* resistance pattern in 2006 was included in this table.

clarity. This cutoff was chosen based on the recommendation of the Infectious Diseases Society of America (IDSA) guidelines for the treatment of UTI in adults to avoid antibiotics (such as trimethoprim-sulfamethoxazole) for which prevalence of resistance exceeds 20%.[39] This recommendation may not be extrapolated to pediatric patients but there are no pediatric-specific guidelines to avoid use of antibiotics based on resistance rate. In 2009, a retrospective, nationwide study was conducted using data from 195 American hospitals to compare the prevalence and antibiotic resistance patterns of the most common uropathogens in children in both inpatient and outpatient settings.[37] Expectedly, the overall uropathogen resistance rate was higher in the inpatient setting than that in the outpatient setting, particularly for third-generation cephalosporins and ciprofloxacin, highlighting the importance of compiling a separate antibiogram for inpatients and outpatients. Three additional studies conducted in the United States focused on pediatric patients in outpatient settings based on national databases.[1,21,36] *Escherichia coli* was most resistant to trimethoprim-sulfamethoxazole (at least 20% rate) in all age groups and least resistant to first-generation cephalosporins, amoxicillin-clavulanate, and nitrofurantoin. However, broad spectrum antibiotics, such as third-generation cephalosporin, were prescribed 25% of the time, and trimethoprim-sulfamethoxazole was prescribed approximately 50% of the time, even though the organisms exhibited a high resistance to the latter.[1] These studies are limited due to their reliance on results from data collected retrospectively with no documentation of clinical data or urine collection methods.

By analyzing resistance patterns in different age groups, in neonates, *E coli, Klebsiella* species, and coagulase-negative *Staphylococcus* were found to be among the most predominant organisms causing UTIs, whereas approximately 31% of infections were non–*E coli*.[20,23,26,40] *E coli* was primarily resistant to ampicillin (up to 96%), followed by gentamicin (53%) and trimethoprim-sulfamethoxazole (46%), and was generally susceptible to third-generation cephalosporins.[19,38] Interestingly, 82% of the neonates responded to an empirical treatment regimen that was not active against the microorganism in the in vitro testing. In another study, 66% of the neonates were prescribed prophylactic antibiotics after the first episode.[20] Notably, the non–*E coli* species were primarily resistant to cefotaxime, amikacin, and cephalexin.[26] However, interpreting the positive urine

Table 4. Risk Factors for Resistant Uropathogens or Non–*Escherichia coli* Pathogens and Suggested Antimicrobials.

Uropathogen	Risk Factors	Antimicrobials
Pseudomonas aeruginosa	Age <5 years Past history of UTI Hospitalization with UTI Previous antibiotic use within the past month Underlying renal abnormalities (abnormal urinary ultrasonography, neurogenic bladder, VUR, etc)	Ceftazidime, cefepime, Pip/Taz, carbapenems, aminoglycosides, fluoroquinolones
Enterococcus spp.	Male Newborn Underlying renal abnormalities	Ampicillin, Amox/clav, Pip/Taz, carbapenems
ESBLs	Age <1 year Long duration of prophylaxis use of 1-2 years Use of cephalosporin for prophylaxis Hospitalization within 3 months High UTI recurrence rate Preexisting conditions (neurological diseases, implanted devices, CIC, and nasogastric tubes)	Cystitis: Nitrofurantoin Pyelonephritis: carbapenems, Pip/Taz

Abbreviations: Amox/clav, amoxicillin-clavulanate; CIC, clean intermittent catheterization; ESBL, extended spectrum β-lactamase-producing organism; Pip/Taz, piperacillin-tazobactam; UTI, urinary tract infection; VUR, vesicoureteral reflux.

cultures from neonates in most studies is difficult due to potential contamination.[20] Certain isolated microorganisms may not cause pathogenic UTIs especially those with coagulase-negative *Staphylococcus* organisms.

Empirical antimicrobial therapy may not cover non–*E coli* pathogens. A study conducted in the United States demonstrated that approximately 10% of pediatric UTI patients received an inappropriate empirical therapy, which was associated with a longer hospitalization by 1.8 days (95% confidence interval = 1.5, 2.1).[41] One approach for reducing prescriptions of inappropriate empirical therapy is to evaluate the risk factors for acquiring uropathogens, such as *Pseudomonas aeruginosa, Enterococcus* species, and ESBL-producing organisms, which are resistant to standard empirical therapy. Table 4 summarizes the risk factors for infections with these organisms and the suggested antimicrobials. As previously mentioned, prior use of antibiotics and the general presence of urological abnormalities (eg, VUR and prenatal hydronephrosis) may lead to the emergence of resistant strains. In addition, according to a prospective observational study conducted in Serbia, multidrug-resistant *E coli* was significantly higher in children under 2 years of age and male patients.[25] The male gender has been associated with community-acquired Enterococcal and non–*E coli* infections.[26,28]

Infants and toddlers up to 24 months of age had significantly higher *E coli* resistance than older children, and the mean resistance rate was significantly higher in boys than that in girls (37% vs 25%) both in the inpatient and outpatient settings.[21,25] An age <1 year was also a risk factor for ESBL-producing infections.[30] Studies conducted in Israel and Turkey evaluated the 1 to 5 years age group in their age stratification.[24,26-28] *E coli* was most resistant to ampicillin and trimethoprim-sulfamethoxazole and least resistant to amikacin and ceftriaxone. *Pseudomonas* infection was significantly more common in older children (age >5 years) and adolescents than in the other age groups.[27] However, age was not found to be an independent risk factor for *Pseudomonas* in the same study. History of antibiotic use during the previous month and underlying renal abnormality, specifically abnormal renal ultrasound, were predictors of *Pseudomonas* UTI. *E coli* was less resistant to ampicillin and trimethoprim-sulfamethoxazole in older than in younger children in another study.[21]

Infections with ESBL-producing organisms are increasing as both hospital-acquired infections and community-acquired infections. According to a study conducted in Taiwan, ESBL-producing *E coli* have increased from 2% to 11% between 2003 and 2012 in inpatients with community-acquired UTIs.[14] In Turkey, 43% of children with UTIs among outpatients had ESBL-producing organisms.[30] Three case-control studies evaluated the risk factors for community-acquired UTIs caused by ESBL-producing organisms, and one study evaluated the clinical outcomes.[14,29,30,42] The main risk factors were as follows: preexisting conditions (particularly neurological diseases, implanted devices, clean intermittent catheterization, and nasogastric tubes), hospitalization within the previous 3 months, using antibiotics in the previous 3 months (statistically significant differences were observed among first-generation cephalosporins, ceftazidime, cefotaxime, ampicillin, aminoglycosides, and vancomycin), using cephalosporin prophylaxis, an age of less than 1 year, and *Klebsiella* species in the UTI. High recurrence rate of UTI and age <1 year were found to be independent risk factors, increasing the risk to 2.25-fold and 1.74-fold, respectively, in the study by

Kizilca et al.[30] However, these younger patients had other risk factors such as previous hospitalization, use of a cephalosporin for prophylaxis, and history of recurrent UTI. Another study showed that clean intermittent catheterization, recent hospitalization within 3 months, and history of infection in the past 3 months were independent risk factors, increasing the risk to almost twice for ESBL-positive UTI.[43] Notably, 92% of ESBL cases initially received an inappropriate empirical intravenous therapy; however, no differences were observed in the clinical and microbiological characteristics or the formation of renal scars between the case group and the control group.[42] Whether this favorable outcome could be achieved with oral antimicrobials rather than IV antimicrobials is unclear. However, another study showed that only 44% of ESBL-positive patients versus 95% of ESBL-negative patients had laboratory and clinical response to the empirical therapy ($P < .001$).[43] Notably, cephalosporins were used empirically in the majority of these patients. Recognizing the risk factors for UTIs that are caused by difficult to treat organisms may aid in the identification of high-risk subjects and the appropriate management of these cases.

Cephalosporins, specifically first-generation cephalosporins, are strong inducers to *AmpC* β-lactamases.[44] Treatment with cephalosporins may induce *AmpC*-producing organisms. No data in pediatric patients with UTI reported the prevalence of *AmpC*-producing organisms or the risk factors. This could be due to the low prevalence of *AmpC* β-lactamases in contrast to ESBLs. Studies evaluating the prevalence and risk factors of *AmpC* β-lactamases in pediatric patients with UTI are needed.

Managing Urinary Tract Infections in Children

The goals of pediatric UTI treatments include a rapid recovery from signs and symptoms and the prevention of subsequent complications, such as urosepsis, renal scars, and urolithiasis.[45] An early diagnosis and the rapid initiation of proper antibiotics are key elements for achieving these objectives. Several recent guidelines have been published to assist clinicians in the diagnosis and management of UTIs. The National Institute for Health and Care Excellence (NICE) issued the NICE clinical guidelines for the diagnosis and management of UTIs in children in 2007.[46] New literature is periodically reviewed to determine the need to update the guidelines, and the most recent evidence-based review was published in October 2013.[6] The American Academy of Pediatrics (AAP) published UTI guidelines in 2011 (reaffirmed in 2016) that were focused on febrile UTI in infants between the ages of 2 and 24 months.[4,5] The guidelines from the European Association of Urology (EAU) were published in 2015.[7]

Prior to initiating antimicrobial therapy, a urine sample should be obtained for culture and urinalysis. The AAP recommends using suprapubic bladder aspiration (SPA) or bladder catheterization to obtain urine samples for infants and non–toilet-trained children. If the likelihood of a UTI is low, clinicians may select less invasive methods, such as a urine bag collection to perform urinalysis; however, the SPA or catheterization methods should be used to obtain specimens for culture if the urinalysis is positive.[4] Positive urinalysis includes positive leukocyte esterase and nitrite results, and pyuria or bacteriuria.[4] The EAU recommends using SPA due to its high reliability for obtaining uncontaminated urine samples.[7] A sample of a proper clean catch of midstream urine is appropriate for urine culture in toilet-trained children.[7] To establish UTI diagnosis, positive urinalysis results along with the presence of at least 50 000 colony-forming units (CFUs) per mL are required if the specimen is obtained through SPA or bladder catheterization.[4] If the sample is obtained through midstream urine catch, presence of at least 10 000 CFUs/mL in patients with UTI symptoms and at least 100 000 CFUs/mL in patients without symptoms along with positive urinalysis are required.[7]

In preterm neonates and young infants, risk of urosepsis increased to 20%.[45] Thus, blood culture should also be obtained when febrile UTI is suspected in early infancy as well as in older children if they appear critically ill.

UTIs can be classified according to the site (lower UTI, i.e., cystitis, and upper UTI, i.e., pyelonephritis), episode (first or recurrent), symptoms (asymptomatic bacteriuria and symptomatic UTI), and complicating factors (uncomplicated and complicated UTIs). The EAU defined each classification in detail.[7] Determining the site and presence of complicating factors is important for selecting empiric antimicrobial therapy in children (Figure 1). After culture and sensitivity results are obtained, specific antimicrobial(s) should be chosen for the definitive treatment.

Choice of Antibiotics

The selection of empiric antibiotic(s) and the administration route should be determined based on the local antimicrobial sensitivity patterns, specific patient characteristics, and the UTI classification type.[4,7] Generally, antibiotics should provide a high in vivo urinary concentration. If systemic symptoms (eg, fever, poor appetite, and lethargy) or pyelonephritis are suspected, the antibiotics should also lead to adequate serum and parenchymal concentrations. Patient care setting is also an important factor. As mentioned earlier, inpatients or hospital-acquired UTI may be associated with higher antimicrobial resistance, requiring broader-spectrum antibiotics during empirical management.

The typical oral empiric antibiotics used for the treatment of UTIs include cephalosporins, amoxicillin-clavulanate,

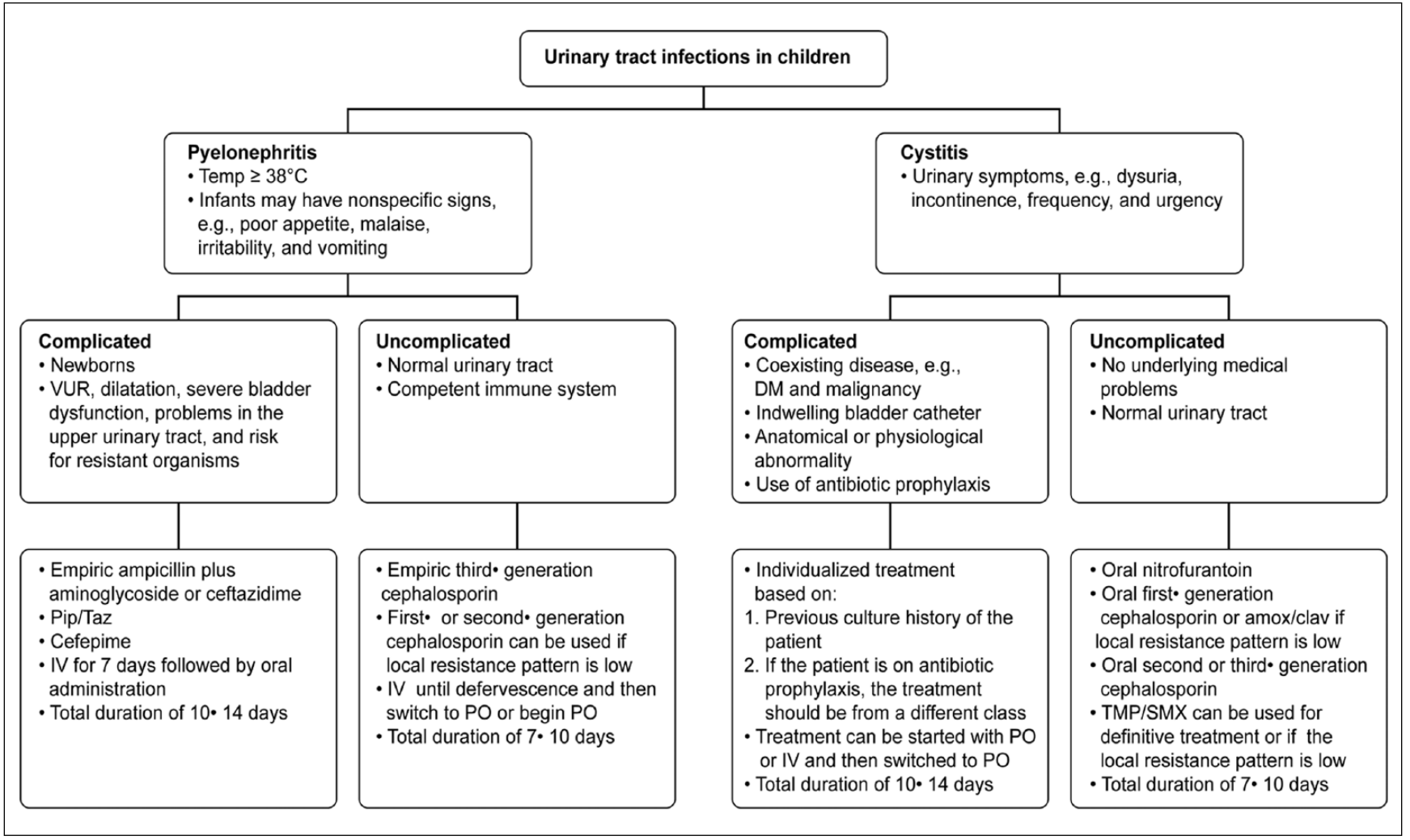

Figure 1. Urinary tract infection classifications and suggested pharmacotherapy management.

Abbreviations: Amox/clav, amoxicillin-clavulanate; DM, diabetes mellitus; IV, intravenous; PO, orally; Pip/Taz, piperacillin-tazobactam; TMP/SMX, trimethoprim-sulfamethoxazole; VUR, vesicoureteral reflux.

Antibiotics should later be adjusted according to the sensitivity result of the microorganism.

nitrofurantoin, and trimethoprim-sulfamethoxazole.[4] Table 5 lists frequently used antimicrobial agents and describes the spectrum of activity and daily dosage regimens. Trimethoprim-sulfamethoxazole is contraindicated in premature infants and newborns <8 weeks of age due to an increased risk of bilirubin displacement and kernicterus.[47] Nitrofurantoin has a potential risk of hemolytic anemia in early infancy; thus, it is contraindicated in newborns <1 month old.[48] Nitrofurantoin is also contraindicated in cases of reduced renal function with a creatinine clearance <60 mL/min. Certain studies have questioned the evidence for this contraindication.[49-51] The authors of these trials suggested that nitrofurantoin was safe and effective for short-term treatment in patients with reduced renal function.[50,51] However, it should be noted that these trials were conducted in older adults and thus extrapolation of these results to pediatric patients may not be possible. The AAP does not recommend using nitrofurantoin in febrile infants because the serum and parenchymal concentrations may be insufficient for treating urosepsis or pyelonephritis.[4]

Fluoroquinolones used to be contraindicated for use in pediatric patients due to their potential to cause arthrotoxicity in animal models and reversible musculoskeletal adverse effects in adults and children. In 2004, the US Food and Drug Administration (FDA) released a statement regarding ciprofloxacin usage in children.[52] It was approved for use in children from 1 to 17 years of age for complicated UTI and pyelonephritis due to *E coli* but not as first choice due to its adverse effects. In 2006, the AAP Committee on Infectious Diseases released additional recommendations for the use of systemic fluoroquinolones in pediatric patients.[53] The committee recommended its use in UTIs caused by *P aeruginosa* or other multidrug-resistant GNB (gram-negative bacilli) when there was no safe and effective alternative or if there was no other effective oral agent is available.

Fosfomycin is an old antibiotic that has gained attention due to the increased microbial resistance to other antibiotics.[54] Fosfomycin acts against gram-negative organisms, including ESBLs, and gram-positive organisms (eg, *Enterococcus* species). Fosfomycin is available in oral and parenteral forms in certain countries. The oral formulation (the only formulation available in the United States) is currently indicated for adult patients with uncomplicated cystitis. Fosfomycin leads to a high urinary concentration that persists for several days after the administration of a single dose and is administered once as a 3-g sachet in adults.[55] Fosfomycin is not yet approved by the FDA for use in pediatric patients. However, the use of a lower dose of (2 g) of fosfomycin to treat uncomplicated cystitis in patients <18 years of age has been reported.[54] Notably, fosfomycin might not be appropriate for all age groups due to limited literature. Oral fosfomycin may be an option for children with ESBLs, carbapenemase-producing Enterobacteriaceae, or multidrug-resistant *P. aeruginosa* in the absence of other established therapies.

Empiric antibiotics should be individualized for patients with certain risk factors for non–*E coli* or resistant uropathogens (Table 4). Patients with suspected *Enterococcus* infection (eg, neonates and patients with indwelling catheters) should also receive an anti-enterococcal antibiotic, such as ampicillin. Patients with risk factors for ESBL-producing organisms should receive an antibiotic that is active against ESBLs (eg, nitrofurantoin for cystitis, and carbapenems for pyelonephritis). Effectiveness of non-carbapenems has been evaluated for UTI empiric treatment in pediatric patients with ESBLs.[43,56] Both studies suggested that aminoglycosides may be an alternative to carbapenems in these cases. Aksu and colleagues suggested the combination of ampicillin plus amikacin as an empiric treatment in patients with acute pyelonephritis who had risk factors for ESBLs.[43] Another study retrospectively evaluated the use of amikacin monotherapy as first-line empiric treatment in febrile UTI among pediatric patients.[57] Fever was resolved within 48 hours in 95% of patients and within 72 hours for all patients. However, only 2 patients had ESBL strain; both strains were susceptible to amikacin. The regimen for one of these patients had to be changed to ertapenem but the reasons were not discussed. This suggests the effectiveness of aminoglycosides empiric treatment for uncomplicated pyelonephritis, but large randomized controlled trials are needed before drawing a definite conclusion. Aminoglycoside monotherapy was also suggested for uncomplicated ESBL UTI in the review by Hsu and colleagues.[58]

Due to the continued increase in drug-resistant GNB, in 2013, the IDSA issued a progress report regarding the development of novel drugs that are active against GNB.[59] Seven parenteral antimicrobials were in clinical development for the treatment of infections caused by resistant GNB. Subsequently, the FDA has approved 2 antimicrobials (ceftolozane-tazobactam and ceftazidime-avibactam) for the treatment of complicated UTI, including pyelonephritis, in adults.[60,61] The safety and efficacy of these agents are being investigated for use in pediatric patients.

Ceftolozane is a novel cephalosporin with potent activity against *P aeruginosa*, and tazobactam broadens the ceftolozane spectrum of activity by including ESBL-producing Enterobacteriaceae.[60] A phase 1 trial assessing the pharmacokinetics and safety of this drug in children <17 years of age with complicated UTIs is ongoing.[62]

The addition of avibactam to ceftazidime extends its spectrum of activity by including resistant organisms, such as *AmpC* β-lactamase, and ESBL-producing organisms, carbapenemase-producing Enterobacteriaceae, and multidrug-resistant *P aeruginosa.*[61] A phase 2 randomized, multicenter trial evaluating the safety, pharmacokinetics, and

Table 5. Frequently Used Antibiotics for Treating UTIs[a].

Antibiotic Agent	Dosage	Spectrum of Activity	Comments
Amox/clav	Amoxicillin component <3 months: 30 mg/kg/day divided q12h >3 months: 20-40 mg/kg/day divided q8h; Max 500 mg/dose	*S saprophyticus, Enterococci, E coli, K pneumoniae, P mirabilis*	Dose adjustment for renal insufficiency Not an empiric treatment of pyelonephritis
TMP/SMX	Trimethoprim component 8-10 mg/kg/day divided q12h; Max 160 mg/dose	*S saprophyticus, E coli, K pneumoniae, P mirabilis*	Not recommended in geographical areas with high resistance to TMP/SMX Dose adjustment for renal insufficiency Contraindicated in infants <8 weeks old Not an empiric treatment of pyelonephritis
Nitrofurantoin	5-7 mg/kg/day divided q6h; Max 50 mg/dose	*S saprophyticus, Enterococci, E coli, K pneumoniae*, AmpC β-lactamase, ESBL-producing gram-negative organisms	Not recommended for febrile UTIs Contraindicated for pyelonephritis Contraindicated in neonates <1 month Contraindicated with CrCl <60 mL/min
Ciprofloxacin	10-20 mg/kg/day divided q12h; Max 750 mg/dose	*S saprophyticus, Enterobacteriaceae, P aeruginosa*	Restricted use for resistant organisms or *Pseudomonas* in children >1 year old Dose adjustment for renal insufficiency
Cephalexin	25-50 mg/kg/day divided q6-12h; Max 250-500 mg/dose	*S saprophyticus, E coli, K pneumoniae, P mirabilis*	Recommended for uncomplicated cystitis Dose adjustment for renal insufficiency
Cefuroxime axetil	50-100 mg/kg/day divided q6-8h; Max 1.5 g/dose	*S saprophyticus, E coli, K pneumoniae, P mirabilis, Citrobacter, Enterobacteriaceae*	Not recommended for infants <3 months old Dose adjustment for renal insufficiency
Ceftriaxone[b]	50-75 mg/kg/day divided q12h; Max 2 g/day	*E coli, K pneumoniae, P mirabilis, Enterobacter, Serratia, Citrobacter, Morganella* spp.	Recommended for complicated and uncomplicated pyelonephritis Contraindicated in premature newborns and neonates <28 days due to the risk of hyperbilirubinemia Contraindicated in infants requiring calcium-containing IV solutions due to the risk of precipitation
Cefotaxime[b]	Neonates 50 mg/kg q6-12h (based on age and weight) Infants and children 75-200 mg/kg/day divided q6-8h; Max 8-10 g/day	*E coli, K pneumoniae, P mirabilis, Enterobacter, Serratia, Citrobacter, Morganella* spp.	Can be used in neonates when ceftriaxone is contraindicated In infants and children, higher dosage needed in severe infection
Ceftazidime[b]	Neonates 30 mg/kg q12h Infants and children 30-50 mg/kg q8h; Max 6 g/day	*E coli, K pneumoniae, Citrobacter, Enterobacter, Serratia, P aeruginosa*	Dose adjustment for renal insufficiency
Aminoglycosides[b]	Amikacin: 15 mg/kg/day divided q8h Gentamicin: neonates 5 mg/kg/day divided q12h; Infants and children: 7.5 mg/kg/day divided q8h	*E coli, K pneumoniae*, AmpC β-lactamase, MDR-*P aeruginosa*	Monitor serum concentration May be given safely in single dose daily Dose adjustment for renal insufficiency Combination therapy with ampicillin is recommended Recommended for complicated cystitis and pyelonephritis
Pip/Taz[b]	2-9 months: 80 mg/kg q6h >9 months: 100 mg/kg q8h Max 3.375 g q6h	*S saprophyticus, Enterococci, E coli, K pneumoniae*, AmpC β-lactamase, ESBL-producing *E coli*, MDR-*P aeruginosa*	Recommended for complicated cystitis and pyelonephritis Safety not established in <2 months Dose adjustment for renal insufficiency
Carbapenems[b]	Meropenem: 20 mg/kg q8h; Max 1 g/dose Imipenem-cilastatin: 25 mg/kg q6-12h; Max 4 g/day	*S saprophyticus, Enterococci, E coli, K pneumoniae*, AmpC β-lactamase, ESBL-producing organisms, *P aeruginosa*	Broad-spectrum antimicrobials Reserved for suspected or definitive treatment of complicated UTI and pyelonephritis with resistant organisms and/or ESBL-producing organisms Dose adjustment for renal insufficiency
Ertapenem[b]	3 months to 12 years: 15 mg/kg q12 h >12 years: 1 g once daily	*S saprophyticus, E coli, K pneumoniae*, AmpC β-lactamase, ESBL-producing organisms	No activity against *P aeruginosa and Enterococci* Dose adjustment for renal insufficiency

Abbreviations: Amox/clav, amoxicillin-clavulanate; CrCl, creatinine clearance; ESBL, extended spectrum β-lactamase; MDR, multidrug resistance; Pip/Taz, piperacillin-tazobactam; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

[a]Duration of treatment may range from 7 to 14 days as explained in the text.

[b]Parenteral antibiotics.

efficacy of ceftazidime-avibactam compared with cefepime in children with complicated UTIs is ongoing.[63]

Dosage Form of Antibiotics

Oral and parenteral antimicrobials may be equally efficacious in the treatment of UTIs. Several studies comparing the oral versus sequential parenteral followed by oral routes have shown no significant differences between the 2 routes.[64-66] Two prospective, randomized, multicenter studies compared the efficacy of oral cefixime versus intravenous (IV) ceftriaxone, followed by oral cefixime, in young children between 1 and 36 months of age.[64,65] Oral cefixime had comparable safety and efficacy in this age group, and certain patients were treated in the outpatient setting, which reduced the health care costs by more than 50%.[64] The choice of IV versus an oral route should be based on practical considerations, such as the suspicion of urosepsis, inability to tolerate oral medications, refusal of oral intake, nonadherence, and vomiting and diarrhea.[4,7] The EAU also recommended combining 2 parenteral antibiotics (ampicillin with either an aminoglycoside or a third-generation cephalosporin) in young infants <2 months of age due to the increased risk of urosepsis and severe pyelonephritis in this age group.[7] Generally, parenteral antibiotics may be used during the first 2 to 3 days if pyelonephritis is suspected or febrile UTIs are detected in infants <6 months of age. The antibiotics should later be adjusted according to the sensitivity result of the microorganism and may be switched to an oral route to complete a total course of 7 to 14 days.

Duration and Frequency of Treatment

The AAP recommended a total course of therapy between 7 and 14 days for febrile UTIs in patients 2 to 24 months of age.[4] The AAP did not define the optimal treatment duration for febrile UTIs because no data comparing 7 versus 10 versus 14 days of antibiotic therapies are available. The EAU recommendations for the duration of treatment were based on the age of the patient and the type of infection.[7] Newborns with pyelonephritis may get 7 to 14 days of parenteral therapy, followed by oral therapy, for a total treatment course of 14 to 21 days. Patients with complicated pyelonephritis and infants 6 months of age and younger were recommended a total treatment course of 10 to 14 days. Patients with uncomplicated pyelonephritis should complete 7 to 10 days of antibiotic therapy. Patients with febrile UTIs may require 7 to 14 days of treatment.

Most studies in children with lower UTIs found no significant differences between the 2 courses and concluded that short (≤3 days) courses were as effective as longer (≥10 days) courses of antibiotics.[67,68] However, these studies had small sample sizes in each group and failed to show significant differences between the short- and long-duration courses, which may have been caused by a type 2 error. A Cochrane systematic review of 10 studies (652 children) comparing short (2-4 days) and long (7-14 days) courses of the same antibiotic also concluded that there was no significant difference in the development of resistant organisms or the frequency of positive urine cultures in uncomplicated cystitis.[69] However, the studies included in this systematic review were of suboptimal quality. Another Cochrane systematic review of 16 studies (1116 children) assessing antimicrobial efficacy found that compared to single-dose treatments, a conventional 10-day antibiotic treatment significantly reduced bacteriuria.[70] However, the data were insufficient for a comparison of other treatment durations or the recommendation of a particular antibiotic regimen. Another meta-analysis of 17 studies (1126 children) found that long antibiotic treatments were correlated with fewer treatment failures and reinfections.[71] Notably, the short course in 11 studies involved a single-dose antibiotic, which may have affected the findings of this meta-analysis. Similarly, a fourth meta-analysis of 22 studies (1279 patients) showed that long courses achieved significantly higher cure rates than short courses for a variety of antibiotics used in children with uncomplicated cystitis.[72] Furthermore, this meta-analysis also found that a 3-day course of trimethoprim-sulfamethoxazole was as effective as a longer course, which suggested that certain antibiotics may be used effectively in short courses.[72] The antibiotic pharmacokinetics and renal parenchymal concentration may play a role in determination of dosage regimen for treatment. Notably, these studies excluded patients with urological abnormalities, and thus, these patients should not receive a short-course therapy.

Few studies have compared the efficacy of shorter (mostly 3 days) versus longer (≥7 days) durations of IV antibiotic therapy before switching to oral antibiotics in children with potential pyelonephritis.[66,73-75] Two studies found that long IV courses were more efficacious in preventing renal scarring but failed to show any statistically significant differences between the 2 groups, which may have been due to the small sample size.[66,74] A retrospective cohort study using a national database of infants <6 months of age showed that there was no association between the length of intravenous therapy (≤3 days vs ≥4 days) and treatment failure within 30 days.[73] Another retrospective study that included 3973 infants of age ≤60 days old showed that short duration of IV antibiotics (≤3 days) was not associated with readmission within 30 days.[75] These 2 studies, however, did not include patients with complicated UTIs.

Adjunctive Therapy

Effect of Additional Antibiotics. Studies have investigated the efficacy of additional drugs and certain vitamins for a synergistic effect with a standard antibiotic. In a prospective,

single-blinded randomized trial, patients with febrile UTIs were randomized to receive either a 10-day therapy with trimethoprim-sulfamethoxazole or a single dose of intramuscular ceftriaxone followed by the same 10-day course of trimethoprim-sulfamethoxazole to determine whether the addition of ceftriaxone facilitated the clearance of the UTI symptoms.[76] No difference was observed between the 2 groups in the resolution of fever or urine sterilization rate after 48 hours. Interestingly, a subanalysis demonstrated that patients with high-grade fever of more than 39°C were more likely to benefit from the addition of ceftriaxone therapy.[76]

Treatments with concurrent ampicillin and an aminoglycoside or third-generation cephalosporin may provide favorable therapeutic outcomes.[7] Several studies comparing 1 versus 3 daily dosages of aminoglycosides in children with UTI showed similar clinical and bacteriologic efficacy, with no significant difference in ototoxicity and nephrotoxicity.[77,78]

Effect of Vitamins. Two studies investigated the benefit of adding a vitamin to conventional antibiotic treatment. In a prospective, double-blinded study involving patients with uncomplicated recurrent UTI, 24 patients received either a single dose of 200 000 IU of vitamin A or a placebo in addition to the antimicrobial therapy.[79] The patients were followed for 1 year, and the frequency of lower UTIs was evaluated. The infection rate during the 0-, 6-, and 12-month follow-up periods was 3.58, 0.75, and 1.75 versus 2.75, 2.83, and 2.66 in the therapy versus placebo group, respectively, suggesting that the vitamin A supplementation may have a synergistic effect on the antibiotic treatment efficacy in recurrent UTIs.

Another study investigated the effect of adding vitamin A or vitamin E to IV antibiotics in patients with acute pyelonephritis to determine the efficacy of these vitamins on the prevention of renal scarring.[80] The patients were randomized to receive a 10-day treatment of vitamin A, vitamin E, or a placebo in addition to the conventional antibiotic. All patients underwent technetium-99m-dimercaptosuccinic acid (DMSA) scans prior to treatment and at the 6-month and 12-month follow-ups. Vitamin A and vitamin E were both effective in preventing renal scarring in the kidney, and the vitamin E supplementation was the most beneficial ($P < .001$).

Effect of Corticosteroids. A double-blind, placebo controlled study examined the effect of adding oral methylprednisolone for 3 days to conventional parenteral antibiotic therapy to prevent renal scarring in patients with acute pyelonephritis.[81] The patients were assessed with DMSA scanning before treatment and at the 6-month follow-up. The patients in the methylprednisolone group had a significantly lower renal scarring rate than the placebo group (33.3% vs 60%; $P < .05$), and the treatment group experienced faster defervescence after treatment, which could lead to a shorter hospital stay. An ongoing study (STARRS) is recruiting patients aged 2 months to 6 years to assess the effect of dexamethasone versus placebo in children with febrile UTI and determine the effect of corticosteroids in the prevention of renal scarring in the kidneys.[82] Additional studies are needed before corticosteroids can be recommended as an adjunctive treatment in patients with pyelonephritis.

Prophylaxis

Prophylaxis Antibiotic Versus Placebo or No Treatment. The evidence regarding the use of antibiotic prophylaxis for the prevention of recurrent UTIs in children is contradictory. Many initial studies were poorly designed, included subjects with heterogeneous characteristics, and/or did not assess the patient adherence to the prophylactic antibiotic. Two randomized, double-blind, placebo-controlled crossover trials assessed the efficacy of short-term (3-5 months) nitrofurantoin prophylaxis in patients with chronic neurogenic bladder on intermittent catheterization.[83,84] Both studies used the same nitrofurantoin dosage regimen (a daily dose of 25 mg for patients weighing 25 kg or less and 50 mg for patient weighing >25 kg) and found a significant decrease in symptomatic UTI infections. However, Schlager and colleagues found that nitrofurantoin was ineffective in eradicating bacteriuria in these patients.[84] In fact, the bacterial species changed from *E coli* to the more resistant *Klebsiella* and *Pseudomonas* species, and the carriage of the latter tripled during the nitrofurantoin phase, but the number of symptomatic infections was unaffected.

Table 6 lists 8 prospective randomized trials that assessed the effects of long-term (1-2 years) antibiotic prophylaxis versus a placebo or no treatment in patients with VUR. All studies used trimethoprim-sulfamethoxazole as a prophylactic antibiotic. However, the dosage regimen differed across studies. Two studies used amoxicillin-clavulanate or nitrofurantoin in the prophylactic group.[17,85] The frequency of UTIs with and without prophylaxis is shown in Table 6. Four studies did not support using prophylaxis.[17,85-87] In fact, the most recently published study found that long-term antibiotic prophylaxis with trimethoprim-sulfamethoxazole significantly increased the risk of UTIs by 15% compared with the placebo in children with grades I to IV VUR.[87] However, 67% of the children enrolled in this study were male. The other trials concluded that prophylaxis decreased the risk of UTI, particularly in certain patients with VUR (eg, bowel and bladder dysfunction, girls with dilating VUR, and boys with grade III VUR).[16,88-90] Because these studies used different types of antibiotics with different dosage regimens, no definitive conclusion can be reached. The rate of bacterial resistance to the prophylactic antibiotic used is also shown in Table 6. All studies found an increased

Table 6. Randomized Controlled Studies Assessing Prophylaxis Antimicrobials for the Prevention of UTIs in Children With VUR (2006-2017).

Study	Total No. of Patients (With VUR)	Age Range (Median)	Grade VUR	% Female	Antibiotic Dosage Regimen, mg/kg/day	Placebo Used	Follow-up Duration (Months)	Adherence %	Rate of UTI		Rate of Bacterial Resistance to Prophylactic Antibiotic		Study Supported Prophylaxis Use
									With Prophylaxis	Without Prophylaxis	With Prophylaxis	Without Prophylaxis	
Hari 2015[87]	93 (93)	1-12 years (4.6 years)	I-IV	33	TMP/SMX; 2/10	Yes	12	Monitored monthly, no difference	10/47 (21%)	3/46 (6%)	7/12 (58%)	1/5 (20%)	No, increased UTI
									$P = .03$		$P = .3$		
RIVUR 2014[90]	607 (607)	2 months to 6 years (1 year)	I-IV	92	TMP/SMX; 3/15	Yes	24	Not monitored	39/302 (13%)	72/305 (24%)	26/38 (68%)	17/69 (25%)	Yes, mostly in BBD
									$P < .001$		$P < .001$		
Brandström 2011[89]	203 (137)	12-24 months (21.3 months)	III-IV	63	TMP/SMX; 0.5 of TMP	No	24	Not monitored	10/68 (15%)	28/69 (41%)	8/10 (80%)	9/25 (36%)	Yes, in girls
									$P = .0002$		$P = .038$		
Craig 2009[16]	576 (243)	0-18 years (14 months)	I-V	64	TMP/SMX; 2/10	Yes	12	Monitored every 3 months, no difference	36/288 (13%)	55/288 (19%)	24/36 (67%)	13/52 (25%)	Yes
									$P = .02$		$P < .001$		
Pennesi 2008[86]	100 (100)	0–30 months (8.6 months)	II-IV	52	TMP/SMX; 1-2/5-10	No	24 (total 48)	Monitored by testing urine from patients with recurrences	42/50 (84%)	35/50 (70%)	42/42 (100%)	0/35 (0%)	No
									$P = .5$		Not reported		
Montini 2008[17]	338 (128)	2 months to 7 years (14.7 months)	I-III	69	TMP/SMX; 15 of SMX Amox/Clav; 15 of Amox	No	12	Questionnaire 86%, testing some samples of urine 71%	15/211 (7%)	12/127 (10%)	9/15 (60%)	1/12 (8%)	No
									95% CI = 2.34 (−3.8 to 8.4)		Not reported		
Roussey-Kesler 2008[88]	225 (225)	1-36 months (11.2 months)	I-III	69	TMP/SMX; 2/10	No	18	Not monitored	18/103 (17%)	32/122 (26%)	13/18 (73%)	13/32 (39%)	Yes, in boys
									$P = .15$		Not reported		
Garin 2006[85]	218 (113)	3 months to 12 years (24 months)	I-III	81	TMP/SMX; 1-2/5-10 NTF 1.5	No	12	Not monitored (high dropout rate due to poor compliance)	VUR 13/55 (24%)	No VUR 4/45 (9%)	VUR 13/58 (22%)	No VUR 14/60 (23%)	7/7[a] (100%) 0/1[a] (0%) No
									$P = .0633$		$P = .9999$		
											Not reported		

Abbreviations: Amox/clav, amoxicillin-clavulanate; BBD, bladder and bowel dysfunction; NTF, nitrofurantoin; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VUR, vesicoureteral reflex.
[a]In recurrent acute pyelonephritis.

resistance in the prophylactic group that ranged from approximately 60% to 100%. This increased resistance is a disadvantage of using long-term prophylactic antibiotics for the treatment of UTIs.

A Cochrane systematic review published in 2011 analyzed 5 studies (1069 children) comparing antibiotic prophylaxis with a placebo or no treatment.[91] The authors found that when all studies were included in the analysis, there was no significant reduction in recurring UTI infections using antibiotic prophylaxis. However, a significant effect of antibiotic prophylaxis was observed when evaluating only the 2 low-risk-of-bias studies.[16,17] The authors concluded that long-term antibiotic prophylaxis reduced the risk of recurrent UTI in children. Another meta-analysis pooled 8 randomized controlled studies for a total of 1594 children and found that there was a 37% decrease in the rate of UTIs with continuous antibiotic prophylaxis in children with VUR.[92] Notably, both meta-analyses reported that there was an increased risk of antibiotic-resistant bacteria.

Prophylaxis Antibiotic Versus Antibiotic. Few studies have compared the effectiveness of different antibiotics in preventing recurrent UTIs in children.[93-97] Nitrofurantoin was found to be more effective than trimethoprim-sulfamethoxazole in patients with urological abnormalities and young patients aged 1 to 5 years with normal urinary tract system.[93,94] Other studies that included patients without urinary tract abnormalities showed that nitrofurantoin was as efficacious as trimethoprim, cefixime, and pivmecillinam (an extended-spectrum penicillin, not available in the United States).[95,96] Nitrofurantoin was less tolerable than trimethoprim-sulfamethoxazole and pivmecillinam.[94,95] Belet et al compared the efficacy of trimethoprim-sulfamethoxazole, cefadroxil, and cefprozil in 80 children with normal urinary tract system.[97] No significant differences were observed among the 3 groups, but the number of recurrent UTIs was reduced in the cefadroxil group. The study had a small sample size in each group (21-35 children), which may have affected the conclusions.

Therefore, prophylaxis antibiotic agents may be used in certain patients with high VUR grades or those who suffer from recurrent UTIs but should be used with caution. If the frequency of the UTIs increases, other strategies, such as discontinuing the prophylactic antibiotic or using a different prophylactic agent, be applied. The type of preventive antibiotic may also affect this process. Additional controlled studies with large sample sizes comparing different regimens of preventive antibiotics are needed.

Prophylaxis Antibiotic Versus Probiotic. One prospective randomized controlled trial compared the preventive effect of a probiotic with that of an antibiotic.[98] In total, 120 children with persistent primary VUR were randomized to receive either *Lactobacillus acidophilus* or trimethoprim-sulfamethoxazole daily for 1 year. No significant difference in the recurrent UTI rates was observed between the *Lactobacillus acidophilus* group (18.3%) and the trimethoprim-sulfamethoxazole group (21.6%; $P = .926$). However, the sensitivity of *E coli* to trimethoprim-sulfamethoxazole in the probiotic group was significantly higher than that in the antibiotic group (57.1% vs 0%; $P < .019$). This was the first study comparing a probiotic with an antibiotic in the prevention of recurrent UTIs in children with VUR. However, this study was limited because it had low calculated power. Additional studies with larger sample sizes are needed to compare different antibiotic and probiotic regimens. A retrospective study described the effects of an antibiotic/probiotic combination therapy in 10 children with recurrent UTIs and normal urinary tract system.[99] All children received a 14-day course of ciprofloxacin, 10 mg/kg twice daily and *Saccharomyces boulardii* 250 mg daily for 1 year. The frequency of the UTIs was significantly lower after therapy than that before therapy ($P = .0001$). During the follow-up period, 70% of the patients had no UTIs. This study was limited due to its retrospective nature, and the results should be validated in larger prospective controlled trials.

Cranberry Products. The use of antibiotic prophylaxis increases the risk of developing bacterial resistance. However, cranberry products may not change the normal gastric flora and, thus, may not increase bacterial resistance. Cranberry has been studied as a prophylactic agent in children with recurrent UTIs. Cranberry, particularly A-type proanthocyanidins (PACs), may function by interfering with the binding of bacteria to uroepithelial cells.[100]

Several studies assessed the prophylactic effect of cranberry products on recurrent UTIs both in children with normal urinary tract systems and patients with anatomical abnormalities.[101-105] The 3 clinical trials that involved children without urological abnormalities had favorable results for cranberry products.[101,104,105] However, the characteristics of the included patients were not homogenous in the 3 studies; thus, the results cannot be generalized or applied to other patients. For example, the patients included in the study conducted by Ferrara et al[101] were only females with *E coli* UTIs, and the study by Afshar et al[104] only included one male subject. Thus, these results may not be extrapolated to male patients or patients with non–*E coli* UTIs.

Trials involving patients with urological abnormalities demonstrated mixed results with cranberry products. Two studies found that cranberry products were no different than placebo or water in patients with a neurogenic bladder.[106,107] However, those studies had limitations of high dropout rates or sample sizes that were too small to detect a difference. A third crossover trial demonstrated a favorable outcome with cranberry extract capsules administered to patients with neurogenic bladders on intermittent catheterization.[108]

Only one trial discussed the effects of the PAC concentration in preventing UTIs. In this study, 40 children with

recurrent UTIs were blindly randomized to receive cranberry juice with a 37% PAC concentration versus cranberry juice with no PAC for 1 year.[104] There was a 65% reduction in UTIs in the treatment group after the 1-year period. However, there was also a high dropout rate of 30% in each group for multiple reasons, including refusal to drink the juice.

Two studies directly compared cranberry products to the antibiotics cefaclor and trimethoprim.[103,109] Both studies concluded that cranberry juice was comparable or noninferior to the antibiotic.

All previous studies used different forms of cranberry products with varying concentrations. Randomized clinical trials with large sample sizes and standardized concentrations of cranberry products are needed to draw a definitive conclusion regarding the effectiveness of cranberry in preventing recurrent UTIs.

Many children, particularly those with urological abnormalities, suffer from recurrent UTIs. The ideal prophylaxis agent should decrease the risk of UTIs, have few adverse effects, be palatable, be cost effective, and have a low risk of resistance. Controlled trials comparing probiotics versus antibiotics versus cranberry products must be performed.

Limitations

Generalizing the antibiotic resistance patterns from different geographical areas based on the resistance rates reported in the literature is challenging.

Summary

UTIs are among the most common infections in children. Empiric antimicrobials are often targeted for susceptible *E coli*. However, in certain cases, resistant microorganisms or non–*E coli* pathogens may cause infection. To the best of our knowledge, this is the first review to comprehensively evaluate antibiotic pharmacotherapy management while considering geographical differences in microbial resistance and risk factors for the development of resistant microorganisms. Knowledge regarding the type and site of the UTI, the local susceptibility data, patient care setting, and specific patient characteristics (eg, age, gender, and urological anatomy) is important for choosing the appropriate antimicrobial agent. Empirical treatment should be individualized in patients with complicating factors, hospital-acquired UTI, or a known history of recurrent UTI or resistant organisms. Definitive treatment may require adjustment of antimicrobials chosen for treatment based on culture and sensitivity results. Oral and parenteral antimicrobials appear to be equally efficacious in treating UTIs in patients who can take oral medications. Nitrofurantoin generally has high antimicrobial activity against *E coli* and can be used in children with uncomplicated cystitis who are >1 month of age. Trimethoprim-sulfamethoxazole resistance is increasing, and this treatment should not be used as an empiric antibiotic unless there are favorable local sensitivity data. Parenteral antibiotics should only be administered when oral antibiotics cannot be given or in patients with severe infections. A total course of 7 to 14 days is needed to complete the therapy. However, some patients who are otherwise healthy and only have uncomplicated cystitis may be effectively treated with a shorter course of 3 days without the risk of developing resistance. Adjunctive therapies, such as vitamin A or E and corticosteroids, are currently under investigation and appear promising for preventing renal scarring in patients with pyelonephritis.

Some patients with renal abnormalities are more prone to recurrent UTIs and may benefit from receiving a prophylactic antibiotic to reduce the risk of recurrent UTIs. A lack of efficacy in certain patients and the development of resistant microorganisms are disadvantages of using antibiotic prophylaxis. Other agents, such as probiotics and cranberry products, have shown some efficacy in certain patients. Controlled trials with large sample sizes comparing different regimens of antibiotic prophylaxis with other prophylactic agents, for example, cranberry and probiotics, are needed.

Declaration of Conflicting Interests

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