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Review

Antimicrobial treatment of urinary tract infections in children

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ABSTRACT

Urinary tract infections are the most frequently proven bacterial infections in pediatrics. The treatment options proposed in this guide are based on recommendations published by the *Groupe de Pathologie Infectieuse de Pédiatrique* (GPIP-SFP). Except in rare situations (newborns, neutropenia, sepsis), a positive urine dipstick for leukocytes and/or nitrites should precede a urine culture examination and any antibiotic therapy. After rising steadily between 2000 and 2012, the proportion of *Escherichia coli* strains resistant to extended-spectrum ß-lactamases (E-ESBL) has remained stable over the last ten years (between 7% and 10% in pediatrics). However, in many cases no oral antibiotic is active on E-ESBL leading either to prolonged parenteral treatment, or to use of a non-orthodox combination such as cefixime + clavulanate. With the aim of avoiding penem antibiotics and encouraging outpatient management, this guide favors initial treatment of febrile urinary tract infections (suspected or actual E-ESBL infection), with amikacin. Amikacin remains active against the majority of E-ESBL strains. It could be prescribed as monotherapy for patients in pediatric emergency departments or otherwise hospitalized patients.

Urinary tract infections (UTIs) are the most frequent proven bacterial infections in children. The prevalence of UTIs is estimated at 7.0% in children under 2 years of age consulting for fever [1]. Usually, a distinction is made between pyelonephritis and cystitis. The former are febrile and/or occur in high-risk patients (neonates, underlying uropathies), expose the patient to complications such as renal scarring, have high biological inflammatory parameters and justify prescription of antibiotics reaching serum pharmacokinetic-pharmacodynamic (PK-PD) parameters enabling treatment of a systemic infection. However, significant proportion of febrile UTIs have normal scans at the time of infection. Nevertheless, all febrile UTIs should be considered "*a priori*" as pyelonephritis and managed as such.

As for cystitis, it typically occurs in girls over 3 years of age, is not accompanied by fever or significant changes in biological inflammatory parameters (if these tests are performed) and does not expose the kidneys to scarring. Even though rare, non-febrile UTIs, with no underlying uropathy and no increase in biological inflammatory parameters, can also occur in boys and girls under the age of 3 years. Unlike febrile UTIs, cystitis requires only antibiotics with urinary concentrations above minimum inhibitory concentrations (MICs). This explains why, for the same antibiotic, breakpoint between febrile and non-febrile UTIs can be different; a strain can be classified on an antibiogram as susceptible for cystitis and intermediate or resistant for pyelonephritis.

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In clinical practice, microscopic analysis with Gram staining and culture should not be performed routinely in febrile infants or children. On the other hand, it should be carried out in those with a underlying condition (newborns, history of underlying uropathy, sepsis neutropenia) and in those with urinary function signs or unexplained fever lasting at least 48 h. A UTI risk calculator from the University of Pittsburgh (Fig. 2), taking into account age, sex, circumcision, duration of fever, history of UTIs and urine dipstick results is available at https://uticalc.pitt.edu/ [2]. In our opinion, it is a very useful tool to select infants for whom a urine cytobacteriological examination is required, and it can even contribute to the choice of urine sampling method.

The diagnosis of UTI may be complex. Pre-test probability varies widely from one child to another [1,2] and the risk of contamination for the least invasive urinary collection methods is high (50–60% for the sterile collection bag and 25% for clean catch midstream versus 10% for urinary catheterization and 1% for suprapubic puncture) [3,4]. Even under optimal sampling conditions, a sterile collection bag may be contaminated by commensal bacteria from the perineum similar to those implicated in UTIs. Aside from special situations (newborns, neutropenia, sepsis. . .), a negative urine dipstick (UD) makes the diagnosis of UTI highly unlikely (negative predictive value >90%) and eliminates the need for UCBE [2,5–7]. A positive UD test (urine dipstick) for leucocytes and/or nitrate) requires confirmation by microscopic analysis with Gram staining and culture.

If the urine sample has been taken from a sterile collection bag, it may need to be checked with another sample, with a lower risk of contamination (clean catch or midstream urine sampling, urinary catheterization or suprapubic puncture), unless the pre-test probability is very high (high positive predictive value if leukocyturia ≥ ++ and nitrites ≥ +). [2,5]. Simple methods such as suprapubic stimulation increase the probability of having midstream urine within 5 min [8,9]. Although rarely used in France, suprapubic puncture is considered the reference method [3,7]. The diagnostic approach must be adapted according to the pre-test probability

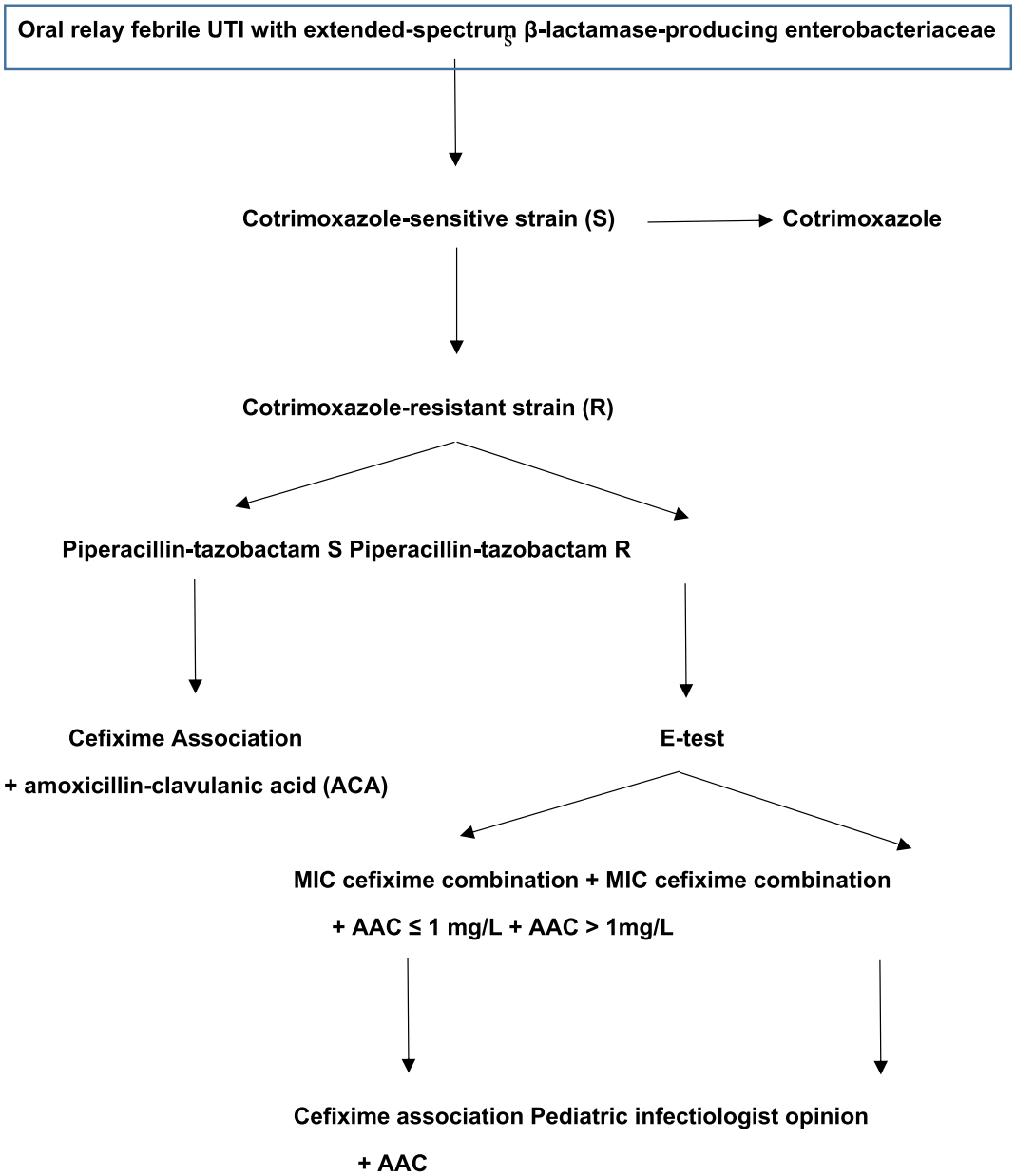

Fig. 1. Decision tree.

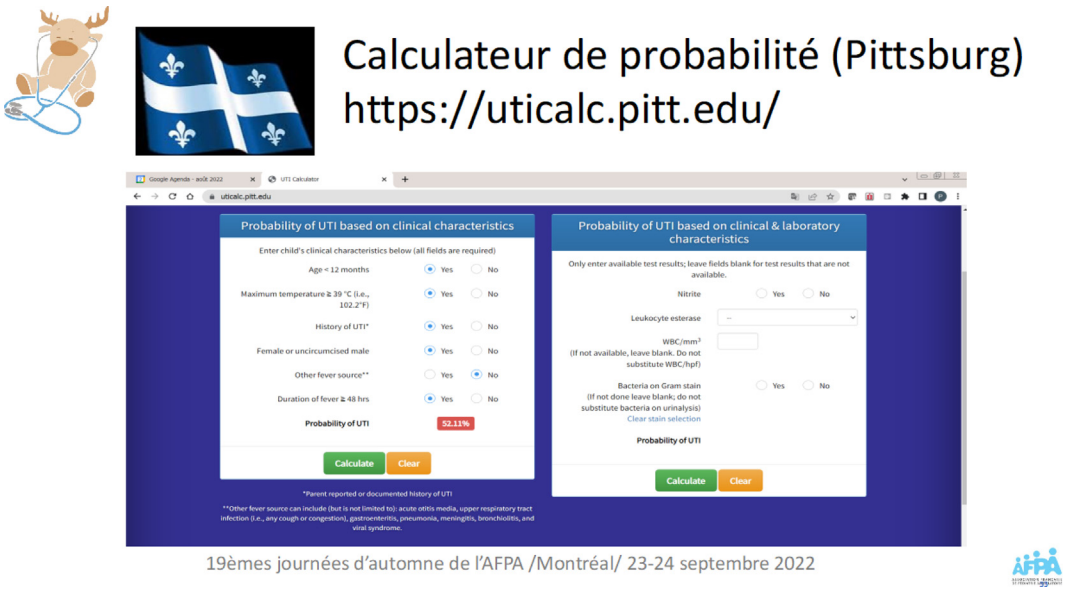

Fig. 2. Probability calculator.

estimate (sex, age, clinical picture, known uropathy, circumcision in boys, history of UTI, existence of a biological inflammatory syndrome…), degree of urgency and local customs [1,2,5]. Antibiotic therapy that is started too quickly can sterilize urine, making it impossible to diagnose UTI with certainty [5]; moreover, the urine sample must be transported rapidly to the laboratory at a suitable storage temperature to avoid the multiplication of contaminating bacteria.

By the oral route, neither amoxicillin nor the amoxicillin-clavulanate (ACA) combination have sufficient PK-PD parameters to consider using them as initial treatment, even on "in vitro" sensitive *E. coli*; the time above MIC does not exceed 20–30%, and an optimal time should be at least 40%. [10]. Some teams use these drugs as a relay treatment when the strain is sensitive.

The majority of febrile UTIs caused by extended-spectrum ß-lactamase (ESBL)-producing enterobacterales become apyretic even though patients are receiving inactive or weakly active antibiotics [11] despite inadequate serum PK-PD parameters. Nevertheless, even if patients are apyretic, there is a consensus to apply an "*in vitro*" active treatment to the strain responsible for the infection.

In France, the proportion of ESBL enterobacterales (E-ESBLs) in childhood urinary tract infections increased significantly from 2009 until 2011, when it stabilized, with prevalence currently below 5% [11–13]. Similarly, the proportion of E-ESBLs rose steadily between 2000 and 2012, and then stabilized between 7% and 10% in pediatrics (unpublished ACTIV data for rectal carriage of E-ESBL: 8.6% in 2020, 10.1% in 2021 and 9.9% in 2022) [14]. This proportion is higher in children who have recently received antibiotics, been treated for a UTI or been hospitalized [15,16]. Stabilization is probably linked to the significant reduction in cephalosporin prescriptions in France since 2011, following the guidelines (GPIP-SFP-SPILF) for treatment of ENT infections, the leading cause of antibiotic prescriptions. Quite often, no oral antibiotic is active on E-ESBL strains. For these reasons, the antibiotic choices proposed in this guide vary according to age, history and place of care (Table 1). In addition, antibiotic prescribing, particularly of "critical" antibiotics (those that are likely to generate bacterial resistance, or "last resort" antibiotics), must be carefully considered. For example, the use of quinolones, which generate resistance and sometimes severe and long-lasting side-effects, should be avoided whenever possible, particularly when the germ's sensitivity is known and there exists an alternative. [16]. For febrile *E. coli* ESBL UTIs, the aim should be to avoid first-line penems in the first instance. Amikacin monotherapy is the first-line treatment frequently recommended in this guide [8,17–20]. In point of fact, amikacin remains by far the most effective aminoglycoside against ESBL, and a single injection (slow IV) per day is sufficient, allowing outpatient treatment for the majority of patients [12]. The other penem-sparing alternatives (temocillin, cefoxitin, piperacillin-tazobactam) all require several injections a day and hospitalization. Finally, due to their low digestive concentrations, aminoglycosides appear to have a limited impact on the intestinal microbiota. Because of their efficacy and long half-life in renal parenchyma, some teams propose a 5-day treatment without oral relay, but there are no clinical studies confirming the efficacy of this treatment regimen.

E-ESBLs are generally resistant to all parenteral and oral third-generation cephalosporins. For over 10 years, following the first studies carried out in France, the addition of clavulanic acid to cefixime has been shown to restore the activity of this molecule "*in vitro*", at MIC levels comparable to non-ESBL-producing strains. [21]. In the case of UTIs caused by ESBL-producing *E. coli*, various clinical studies have confirmed the efficacy of the combination as a relay treatment [12,22]. Unfortunately, there is no marketed clavulanic acid without amoxicillin (the AAC combination should be prescribed), and there is as yet no randomized prospective study. Given the unconventional nature of the combination, before prescribing this treatment it is advisable to check the sensitivity of the strain using the double E-test technique. Recent data show an excellent correlation with susceptibility to piperacillin-tazobactam [22]. A study carried out at the associate *E. coli* National Reference Center at Robert Debré Hospital on 220 strains of E-EBSLs, showed in 99% of cases a correlation between piperacillin-tazobactam sensitivity and the cefixime + clavulanic acid combination (unpublished data). This study suggests that in cases of proven piperacillin-tazobactam resistance, an E-test should be systematically performed before cefixime + clavulanic acid can be prescribed (25% of strains remain sensitive to cefixime + clavulanic acid, even in cases of piperacillin-tazobactam resistance). Restrictions on the

Table 1
Treatment of urinary tract infections in children (excluding newborns).

Clinical situations	Preferred antibiotics (Initial probabilistic treatment)	Allergy alternatives	Comments
Febrile urinary tract infection (probable pyelonephritis) Target bacteria: *E. coli* Other bacteria - *Proteus* - *Klebsiella* - Enterococcus - *Staphylococcus saprophyticus*	**Hospitalized patients (1)** **Cefotaxime IV** 150 mg/kg/day In 3 divided doses Maximum 6 g/d or **Ceftriaxone** (IV or IM) 50 mg/kg/day in one injection Maximum 2 g/d + **Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d **Outpatients** **Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d or **Ceftriaxone** IV or IM 50 mg/kg/day in one injection Maximum 2 g/d or **Cefixime** oral **(3)** 8 mg/kg/day In 2 divided doses Maximum 400 mg/d **Caution if Gram-positive cocci on direct examination** **Amoxicillin IV** 100 mg/kg/day In 3 divided doses Maximum 3 g/d + **Gentamicin** IV 5 mg/kg/day in one IVL injection (30 minutes) Maximum 320 mg/d	**Amikacin** IV **(2)** 20 mg/kg/day In 1 injection (30 minutes)/d Maximum 1 g/d **Teicoplanin** IV or IM 10 mg/kg every 12 hours 3 times, then 10 mg/kg/d	(1) Hospitalization is recommended for children aged < 3 months or suspected of sepsis, or with known severe uropathy. (2) After verification of normal renal function. (3) Due to a higher percentage of resistance than injectable C3Gs and modest PK-PD performance, initial treatment with cefixime should be reserved for patients at low risk of renal scarring: - Age >3 months - No underlying uropathy - No sepsis - Low PCT level - Good compliance, no vomiting, possibility of reconsulting if necessary Initial treatment is prescribed for a period of 2 to 4 days, which generally corresponds to both apyrexia and antibiotic susceptibility test (AST) results. Total duration of treatment (IV + per os) is 10 days. Before one month of age, prefer cefotaxime. Oral relay should be adapted according to the antibiotic susceptibility with, in order of preference: 1) Cotrimoxazole (>1 month) 30 mg/kg/d sulfamethoxazole, in 2 doses 2) Cefixime 8 mg/kg/d in 2 doses 3) Amoxicillin if infection with sensitive Enterococcus or *Proteus sp.* For *E. coli*, amoxicillin is used by some teams. However, the serum PK-PD performance of amoxicillin on *E. coli*, even when sensitive, is modest (20 to 30% of the time above the MIC). 4) Cefixime + amoxicillin-clavulanic acid combination for cotrimoxazole-resistant E-ESBL (see Fig. 1: decision tree) Quinolones should be avoided whenever possible as initial or follow-up treatment. -If an E-test is not possible, or if the strain is resistant to piperacillin-tazobactam, several options are available (after consulting an infectiologist): ● Oral relay with quinolones if sensitive strain (+sensitive nalidixic acid) ● Amikacin 5 days total ● Temocillin if S strain ● Cefoxitin if S strain For ESBL enterobacterales, some teams use amikacin for 5 days if there is no alternative for an oral relay (due to its long half-life in renal parenchyma and urine).
Non-febrile urinary tract infections (Cystitis) Target bacteria *E. coli* Other bacterial etiologies - *Enterococcus* - *Proteus* - *Klebsiella* - *Staphylococcus saprophyticus*	Before antibiotic susceptibility test **Amox/clav** oral (4) 80 mg/kg/d In 2 divided doses Maximum 3 g/d **(5 j)** If pubescent girl **Fosfomycin (5)** 1 sachet of 3 g 1 single oral dose	**Cotrimoxazole oral** 30 mg/kg/day sulfamethoxazole In 2 divided doses Max 1.6 g/d or **Cefixime** oral 8 mg/kg/day In 2 divided doses Max 400 mg/d **(5 j)**	(4) For Amox/ac. clav, the daily dose should be halved (e.g. for a 15 kg child: 1 and ½ doses every 12 hours). (5) in the absence of underlying uropathy. Hygiene advice must be combined with antibiotic treatment. If the clinical course of Amox/ac.clav is favorable, there is no need to modify the treatment according to the antibiotic suceptibility. High and prolonged concentrations of clavulanic acid in urine, which inhibits the majority of ß-lactamases, explains why critical concentrations for high and low urinary tract infections are different. The same *E. coli* may be classified as sensitive to the amoxicillin-clavulanic acid combination for cystitis and resistant for pyelonephritis. If the disease progresses unfavorably on Amox/ac. clav, the treatment must be modified according to the antibiotic suceptibility test and the order of preference according to sensitivity: - Cotrimoxazole - Cefixime NB: *Staphylococcus saprophyticus is naturally resistant to fosfomycin.*
Urinary tract infections due to - *Pseudomonas sp* - Highly resistant bacteria - Carbapenemase-producing bacteria - Glycopeptide-resistant enterococci Complicated urinary tract infections: abscesses, lithiasis…		Pediatric infectious disease specialist advice required	
Prostatitis		Pediatric infectious diseases specialist advice required	
Urethritis		Refer to adult recommendations	

IV: Intravenous; IM: Intra-muscular; IVL: Intravenous slow; PO: Oral; Amox-ac. clav: Amoxicillin-clavulanic acid combination.

use of quinolones mean that this combination should be prescribed preferentially as a relay treatment in cases of cotrimoxazole-resistant *E. coli* ESBL infection.

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Author's contribution

RC and FM wrote the first draft of the article and all of the authors revised and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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