

EMLc
ATC codes: [J01CR02](#)

Indication	Infectious cystitis ICD11 code: GC80.1
INN	Amoxicillin + clavulanic acid
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	Parenteral > General injections > IV: 500 mg (as sodium salt) + 100 mg (as potassium salt) powder for injection ; 1000 mg (as sodium salt) + 200 mg (as potassium salt) powder for injection Oral > Liquid: 125 mg + 31.25 mg powder for oral liquid (EMLc) ; 250 mg + 62.5 mg powder for oral liquid (EMLc) Oral > Solid: 500 mg (as trihydrate) + 125 mg (as potassium salt)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents . 
Wikipedia	Amoxicillin + clavulanic acid 
DrugBank	Amoxicillin  , Clavulanic acid (Clavulanate) 

Expert Committee recommendation

The Expert Committee endorsed the inclusion of the following medicines as first-choice therapies on the EML and EMLc list: • lower UTI: amoxicillin or amoxicillin + clavulanic acid or sulfamethoxazole + trimethoprim or nitrofurantoin • pyelonephritis or prostatitis, mild to moderate: ciprofloxacin • pyelonephritis or prostatitis, severe: ceftriaxone or cefotaxime. The Expert Committee endorsed the inclusion of the following medicines as second-choice therapies on the EML and EMLc list: • pyelonephritis or prostatitis, mild to moderate: ceftriaxone or cefotaxime. The Committee recommended the addition of amikacin (in combination with ceftriaxone or cefotaxime) for severe pyelonephritis or prostatitis to the EML and EMLc for UTI therapy.

Background

Urinary tract infections (UTI) in the outpatient setting are a common reason for young women in particular to seek medical attention. Randomized controlled trials (RCTs) have addressed the type and duration of antibiotic treatments in this and other populations. Use of antibiotics for asymptomatic bacteriuria can drive antibiotic resistance and may also increase the risk for subsequent symptomatic UTI. While it is accepted practice that asymptomatic bacteriuria should be treated in pregnant women and in men about to undergo urological procedures, the benefits of therapy in other groups have been questioned and addressed in RCTs.

Summary of evidence

A 2010 Cochrane systematic review (21 RCTs; 6016 participants) of acute uncomplicated UTI, found that sulfamethoxazole + trimethoprim (SMX-TMP) was equivalent to fluoroquinolones in achieving short-term (risk ratio (RR) 1.00; 95% confidence interval (CI) 0.97–1.03) and long-term (RR 0.99; 95% CI 0.94–1.05) symptomatic cure. Beta-lactam drugs were similar to SMX-TMP for short-term (RR 0.95, 95% CI 0.81 to 1.12) and long-term (RR 1.06, 95% CI 0.93 to 1.21) symptomatic cure but criteria for equivalence were not met (1). Short-term cure with nitrofurantoin was similar to that with SMX-TMP (RR 0.99; 95% CI 0.95–1.04) as was long-term symptomatic cure (RR 1.01; 95% CI 0.94–1.09). For asymptomatic bacteriuria, a 2015 Cochrane review of nine RCTs (1614 participants) that compared antibiotics with placebo/no treatment showed that symptomatic UTI (RR 1.11; 95% CI 0.51–2.43), complications (RR 0.78; 95% CI 0.35–1.74) and death (RR 0.99; 95% CI 0.70–1.41) were similar in the two treatment arms (2). A 2014 Cochrane review of antibiotics for pyelonephritis in children (27 studies; 4452 children) reported no significant differences in duration of fever (2 studies; 808 children; mean difference (MD) 2.05 hours; 95% CI –0.84 to 4.94), persistent UTI at 72 hours after start of therapy (2 studies; 542 children; RR 1.10; 95% CI 0.07–17.41) or persistent kidney damage at 6–12 months (4 studies; 943 children; RR 0.82; 95% CI 0.59–1.12) between oral antibiotic therapy (10–14 days) and IV therapy (3 days) followed by oral therapy (10 days) (3). Similarly, there were no significant differences in persistent bacteriuria at the end of treatment (4 studies; 305 children; RR 0.78; 95% CI 0.24–2.55) or persistent kidney damage (4 studies; 726 children; RR 1.01; 95% CI 0.80–1.29) between IV therapy (3–4 days) followed by oral therapy and IV therapy (7–14 days) (3). No significant differences in efficacy were found between daily and three times daily administration of aminoglycosides (1 study; 179 children; persistent clinical symptoms at three days: RR 1.98; 95% CI 0.37–10.53).

Guidelines

The Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend nitrofurantoin and SMX-TMP for acute uncomplicated cystitis in women (4). Amoxicillin + clavulanic acid is an alternative choice. Oral fosfomicin is recommended where available because of its minimal propensity for resistance. Ceftriaxone is recommended for acute pyelonephritis in women, as is ciprofloxacin. However, the guideline recommends that resistance rates for empirically selected antibiotics should be below 10% for pyelonephritis and below 20% for treatment of lower UTI, a threshold no longer met for fluoroquinolones in many countries. Amoxicillin + clavulanic acid and SMX-TMP are also recommended for empirical treatment in children aged 2–24 months by the American Academy of Pediatrics (5). The European Association of Urology and European Society for Paediatric Urology state that antimicrobial choice is dictated by local resistance patterns (6). For young children, newborns and infants, parenteral therapy is advised, such as combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or a third-generation cephalosporin. For pyelonephritis during the first 6 months of life, ceftazidime plus ampicillin or an aminoglycoside plus ampicillin is recommended. A third-generation cephalosporin is recommended for children over 6 months of age for uncomplicated pyelonephritis while ceftazidime plus ampicillin or aminoglycoside plus ampicillin are suggested for complicated pyelonephritis. Although the guidelines list parenteral as well as oral cephalosporins, in addition to beta-lactams (including piperacillin, amoxicillin, amoxicillin + clavulanic acid, nitrofurantoin and aminoglycosides), fluoroquinolones are considered second- or third-line antibiotics for complicated urinary tract infection. The recommendations of the Italian Society for Pediatric Nephrology are similar (7).

Rationale for antibiotic selection

The systematic review evidence showed that SMX-TMP was equivalent to fluoroquinolones for uncomplicated UTI and that nitrofurantoin was equivalent to SMX-TMP. SMX-TMP and nitrofurantoin are therefore proposed as core antibiotics. Fluoroquinolones were not included because of the need to preserve this class of antibiotics. Oral fosfomicin is proposed because of minimal resistance and good safety profile. Amoxicillin + clavulanic acid is proposed for young children while ampicillin and gentamicin are for children with severe illness. Fosfomicin is included as a core antibiotic.

Committee considerations

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML and/or EMLc. Ampicillin, fosfomicin and gentamicin were excluded. Amikacin was preferred to gentamicin because it is generally more active on Enterobacteriaceae; ciprofloxacin was added as a recommended

first-line option for empirical treatment in mild-to-moderate pyelonephritis and prostatitis because of its good bioavailability and penetration (if local/national epidemiological data allow). Recommended first- and second-choice antibiotics are reported above. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML recommendations: Infectious cystitis

First choice

nitrofurantoin

amoxicillin + clavulanic acid

sulfamethoxazole + trimethoprim

trimethoprim

Second choice

1. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. *Cochrane Database Syst Rev.* 2010;(10):CD007182.
2. Zalmanovici Trestioreanu A, Lador A, Sauerbrun-Cutler MT, Leibovici L. Antibiotics for asymptomatic bacteriuria. *Cochrane Database Syst Rev.* 2015;(4):CD009534.
3. Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev.* 2014;(7):CD003772.
4. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011;52(5):e103–20.
5. Roberts KB, Subcommittee on Urinary Tract Infection Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics.* 2011;128(3):595–610.
6. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C et al. Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol.* 2015;67(3):546–58.
7. Ammenti A, Cataldi L, Chimenz R, Fanos V, La Manna A, Marra G et al. Febrile urinary tract infections in young children: recommendations for the diagnosis, treatment and follow-up. *Acta Paediatr.* 2012;101(5):451–7.

