# Piperacillin + tazobactam



EMLc | Codes ATC: J01CR05

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|---|---|
| **Indication** | Peritonitis Code ICD11: DC50.Z |
| **INN** | Piperacillin + tazobactam |
| **Type de médicament** | Chemical agent |
| **Groupes d'antibiotiques** | WATCH |
| **Type de liste** | Liste de base |
| **Formulations** | **Parenteral > General injections > IV:** 2 g (as sodium salt) + 250 mg (as sodium salt) powder for injection ; 4 g (as sodium salt) + 500 mg (as sodium salt) powder for injection |
| **Historique des statuts LME** | Ajouté pour la première fois en 2017 (TRS 1006) |
| **Sexe** | Tous |
| **Âge** | Aussi recommandé pour les enfants |
| **Équivalence thérapeutique** | La recommandation concerne ce médicament spécifique |
| **Renseignements sur le brevet** | Patents have expired in most jurisdictions<br>Lire la suite sur les brevets. |
| **Wikipédia** | Piperacillin + tazobactam |
| **DrugBank** | Piperacillin, Tazobactam |

## Recommandation du comité d'experts

The Expert Committee endorsed the inclusion of the following medicines on the EML and EMLc for complicated intra-abdominal infections (cIAI) • mild to moderate: amoxicillin + clavulanic acid, or ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy, and ciprofloxacin in combination with metronidazole as second-choice therapy • severe: ceftriaxone or cefotaxime in combination with metronidazole as first-choice therapy. The Expert Committee recommended the addition of piperacillin + tazobactam as first-choice therapy and meropenem as second-choice therapy for severe complicated intra-abdominal infections.

## Contexte

Complicated intra-abdominal infections (cIAI) extend beyond the organ of origin into the peritoneal space and are associated with either peritonitis or abscess formation. They represent a diverse group of infections for which there are a broad spectrum of causative agents, although streptococci, Enterobacteriaceae and anaerobes predominate. The application did not consider primary peritonitis from haematogenous dissemination (e.g. spontaneous bacterial peritonitis in the absence of an underlying infection of an organ), usually in the setting of an immunocompromised state, or dialysis-related infections.

## Résumé des preuves

A 2005 review (1) evaluated 40 studies (5094 patients) to compare the efficacy of various antibiotics for secondary peritonitis (infection of the visceral organ that extends beyond the organ), such as complicated appendicitis or cholecystitis. Of the 40 studies, 38 compared two regimens of antibiotics and two compared three regimens. The antibiotics evaluated included carbapenems (meropenem or imipenem), as single agents compared with each other or with cephalosporin and metronidazole combination or with piperacillin + tazobactam; regimens of clindamycin and an aminoglycoside (gentamicin or amikacin or tobramycin) were compared with piperacillin + tazobactam. The trials were non-inferiority and all showed similar efficacy and no differences in mortality. There were no differences in overall mortality or mortality due to infection when aminoglycoside and anaerobic regimens were compared with others, although confidence intervals were very large: odds ratio (OR) 2.03, 95% confidence interval (CI) 0.88–4.71 and OR 1.51, 95% CI 0.66–3.43, respectively. However, aminoglycoside-based regimens were shown to be inferior to all available comparators in terms of clinical success (OR 0.65; 95% CI 0.46–0.92). When broad-spectrum beta-lactams were compared with other regimens, there were no significant differences in infection-related mortality (OR 0.54; 95% CI 0.05–6.08) or in clinical cure (OR 1.22; 95% CI 0.56–2.66). When carbapenems were compared with other antibiotics, there was no significant difference in infection-related mortality (OR 0.78; 95% CI 0.30–2.03) or clinical cure (OR 0.71; 95% CI 0.47–1.07). For cephalosporins alone versus other agents, there was no difference in infection-related death (OR 0.63; 95% CI 0.10–3.84) or clinical success (OR 1.25; 95% CI 0.57–2.74). Similarly, for cephalosporin and anti-anaerobe regimens versus others, no difference was seen in infection-related death (OR 5.45; 95% CI 0.25–116.63) or clinical success (OR 0.71; 95% CI 0.29–1.75). However, the cephalosporins and beta-lactams were found to be superior in terms of clinical success to all other comparators (OR 3.21; 95% CI 1.49–6.92), as were fluoroquinolones combined with an anti-anaerobic agent (OR 1.74; 95% CI 1.11–2.73). As no specific antibiotic group was compared with any other specific antibiotic group, no firm conclusions could be drawn from this evidence. It is possible that an outlier antibiotic group (e.g. aminoglycoside-based antibiotics) was driving the inferiority of the comparator group, while other groups within the comparator group could have been non-inferior or even superior to beta-lactams. In a systematic review and meta-analysis comparing ertapenem with ceftriaxone (8 RCTs; 2883 patients), similar clinical success was reported (OR 1.13; 95% CI 0.75–1.71) (2). In a comparison of moxifloxacin with other antibiotics (4 RCTs; 2444 patients), results were similar for clinical cure (OR 0.80; 95% CI 0.61–1.04) and mortality (OR 0.91; 95% CI 0.45–1.83); there were more adverse events in the moxifloxacin group (OR 1.33; 95% CI 1.07–1.63), but the overall incidence of serious adverse events was similar (OR 1.23; 95% CI 0.59–2.60) (3). A review comparing ertapenem with piperacillin + tazobactam (6 RCTs; 3161 patients) found no difference in clinical success (OR 1.15; 95% CI 0.89–1.49) (4). In an older systematic review (5), ciprofloxacin + metronidazole was found to be superior in terms of clinical cure to beta-lactam antibiotics (OR 1.69; 95% CI 1.20–2.30), however, the studies on which these observations were based were conducted before the recent increase in fluoroquinolone resistance. Tigecycline, a tetracycline derivate and the first glycylcycline, received a boxed warning and the U.S. Food & Drug Administration (FDA) recommends against its use unless no better alternative agents are available. However, if the higher mortality were due to a lower efficacy of the drug, lower cure rates would be expected – which was not the case in the systematic review by Shen et al. 2015 (6), who found no difference in clinical and microbiological cure with tigecycline compared with imipenem or ceftriaxone in combination with metronidazole. For most comparisons, the precision in the summary estimates is very wide, and none met the applicant’s definition of non-inferiority; thus, a clinically significant difference cannot be ruled out. Moreover, the review of the clinical trial evidence does not point to superiority of any single agents or combination regimens. When statistically significant differences were found, these were obtained by aggregating several antibiotic groups at the expense of being able to identify the particular antibiotics responsible for better effects.

## Recommandations

The IDSA (Infectious Diseases Society of America) guideline (7) summarizes recommendations for empirical therapy. A very comprehensive approach is used, in terms of antibiotic choices, and the extensive list of recommended antibiotics includes several overlapping agents. This approach differs from the guiding principle of parsimony adopted for decisions on the EML. For community-acquired infection in children, the recommendations are aminoglycoside-based regimens (ampicillin and gentamicin or tobramycin in combination with metronidazole

or clindamycin), a carbapenem (ertapenem, meropenem, imipenem), a beta-lactam/beta-lactamase inhibitor combination (piperacillin + tazobactam, ticarcillin + clavulanic acid), or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) in combination with metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin in combination with metronidazole is recommended. Single-agent empirical therapy for adults with mild to moderately severe infections included cefoxitin, ertapenem, moxifloxacin, tigecycline and ticarcillin + clavulanic acid. For high-risk or severely ill adults, imipenem, meropenem, doripenem and piperacillin + tazobactam are recommended. Recommended combination regimens include a cephalosporin (cefazolin, cefuroxime, ceftriaxone, cefotaxime) or a fluoroquinolone (ciprofloxacin or levofloxacin), each in combination with metronidazole, for mild to moderately severe infections. For high-risk community-acquired cases or severely ill patients, a carbapenem, piperacillin + tazobactam, a fluoroquinolone (ciprofloxacin or levofloxacin) or a cephalosporin (cefepime, ceftazidime), in combination with metronidazole, is recommended. The guidelines also make recommendations for empirical therapy for health care-associated cIAI. If extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are among the pathogens most commonly involved in this type of infection locally, regimens including a carbapenem and aminoglycosides – but not cephalosporins – are recommended. Ceftazidime is not recommended where >20% Pseudomonas aeruginosa are resistant. Vancomycin is recommended in addition to other antibiotics when coverage for MRSA is needed, based on the local antibiogram. Cefazolin, cefuroxime or ceftriaxone is recommended for empirical treatment of acute, mild to moderate, community-acquired cholecystitis. A carbapenem (imipenem, meropenem, doripenem), piperacillin + tazobactam, a fluoroquinolone (levofloxacin or ciprofloxacin), or cefepime, in combination with metronidazole, is recommended for severe community-acquired cholecystitis. For acute cholangitis following bilioenteric anastomosis, or for health care-associated biliary infection of any severity, any of the aforementioned antibiotics in combination with metronidazole could be used. The guidelines recommend against the use of ampicillin + sulbactam because of high resistance rates in Escherichia coli, against the use of cefotetan and clindamycin because of resistance in the Bacteroides fragilis group, and against aminoglycosides in non-severe, non-hospital-acquired cases; caution is recommended in the use of fluoroquinolones because of increasing resistance rates. In contrast to the IDSA guidelines, the World Society of Emergency Surgery (WSES) guidelines (8) recommend either amoxicillin + clavulanic acid or ciprofloxacin in combination with metronidazole for extra-biliary or biliary acute intra-abdominal infection in patients who are not critically ill and have no risk factors for ESBLs. In those at increased risk for ESBLs and not critically ill, these guidelines recommend ertapenem or tigecycline for extra-biliary disease and tigecycline for intra-biliary disease. In critically ill patients with no risk for ESBLs, the guidelines recommend piperacillin-tazobactam for either extra- and intra-biliary disease. Where there is an increased risk of ESBLs, meropenem or imipenem with the option of adding fluconazole for extra-biliary disease and piperacillin and tigecycline with the option of fluconazole for intra-biliary disease are listed. For hospital-acquired intra-abdominal infection in the absence of critical illness where there is a risk for a multidrug-resistant organism, the guidelines recommend piperacillin, tigecycline and fluconazole. For hospital-acquired infection in a critically ill patient, piperacillin, tigecycline, and an echinocandin (caspofungin, anidulafungin or micafungin) or a carbapenem (meropenem, imipenem, doripenem), teicoplanin, and an echinocandin (caspofungin, anidulafungin or micafungin) are recommended.

## Justification de la sélection des antibiotiques

Since the overview of systematic reviews yielded inconclusive findings, the application’s proposals for the EML are based on clinical practice guidelines (CPGs). The proposed listings of antibiotics were based on the setting (community- versus hospital-acquired), as well as based on severity, applying the same approach as used in the IDSA guidelines. For community-acquired non-severe infections, amoxicillin–clavulanic acid or a cephalosporin (cefotaxime or ceftriaxone) with metronidazole fulfil the curative intent as well as guarding against resistance. For hospital-acquired or severe cases, the same cephalosporins, with metronidazole, can be used, or piperacillin–tazobactam can be used instead of amoxicillin + clavulanic acid. Fluoroquinolones should be considered as second-line therapy when beta-lactams/cephalosporins are contraindicated because of resistance concerns and there are concerns about potential harm. Of the fluoroquinolones, moxifloxacin has not been proposed, despite recommendations in one guideline, because of the availability of many other options and the possibility of higher

adverse event rates. Vancomycin should be used for patients with suspected MRSA infection. Teicoplanin was not proposed due to redundancy and several indications for vancomycin across all syndromes. Ceftazidime, meropenem and the aminoglycosides are proposed as targeted antibiotics, based on local resistance data, as alternatives to the core antibiotics. For additional enterococcal coverage, ampicillin can be considered if the regimen being used would not cover enterococci (e.g. ceftriaxone/metronidazole). Of the antibiotics listed in the guidelines, cefazolin, cefoxitin and cefuroxime were excluded for redundancy: ceftriaxone, which is listed, also offers broader Gram-negative coverage. Ticarcillin–clavulanate and piperacillin were also excluded: piperacillin–tazobactam is considered more appropriate and is listed for several syndromes. Tigecycline is a potential niche or last-resort antibiotic for multidrug-resistant pathogens or when no first- and second-line antibiotics can be used, but was not considered as a core or targeted antibiotic because of the boxed warning by the FDA relating to the presumed higher mortality rate. Cefepime was not proposed; it was felt to be redundant in view of the antibiotics already listed above, and there are concerns about inferiority in terms of mortality (see section on Febrile neutropenia). Ampicillin–sulbactam, cefotetan and clindamycin were not proposed: their use is discouraged in the IDSA guideline because of resistance concerns. Ertapenem was proposed for the preserved list as it is considered a niche antibiotic, particularly for patients with suspected ESBL when Pseudomonas aeruginosa coverage is not needed. Of the available carbapenems, the application proposed listing only meropenem as it is the most frequently recommended carbapenem across all syndromes; imipenem and doripenem were therefore excluded.

## Considérations du comité

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 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. Levofloxacin, ampicillin, ceftazidime, gentamicin, tobramycin and vancomycin were excluded. Ceftazidime, gentamicin, tobramycin and vancomycin have limited indications in community-acquired cIAI. Ampicillin provides only enterococcal coverage, which is usually not needed for mild to moderate cIAI. Ciprofloxacin was preferred to levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multidrug-resistant tuberculosis). Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

## Recommandations de la LME : Peritonitis

| Premier choix | Second choix |
|---|---|
| **MILD-MODERATE** | |
| ampicillin | ciprofloxacin |
| amoxicillin + clavulanic acid | |
| ceftriaxone | |
| cefotaxime | |
| **SEVERE** | |

piperacillin + tazobactam

meropenem

ampicillin

ceftriaxone

cefotaxime

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3. Mu YP, Liu RL, Wang LQ, Deng X, Zhu N, Wei MD et al. Moxifloxacin monotherapy for treatment of complicated intra-abdominal infections: a meta-analysis of randomised controlled trials. Int J Clin Pract. 2012;66(2):210–7.
4. An MM, Zou Z, Shen H, Zhang JD, Chen ML, Liu P et al. Ertapenem versus piperacillin/tazobactam for the treatment of complicated infections: a meta-analysis of randomized controlled trials. BMC Infect Dis. 2009;9:193.
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6. Shen F, Han Q, Xie D, Fang M, Zeng H, Deng Y. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. Int J Infect Dis. 2015;39:25–33.
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