Piperacillin + tazobactam

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.2. Watch group antibiotics

EMLc | ATC codes: J01CR05

Indication	Other specified pneumonia ICD11 code: CA40.Y
INN	Piperacillin + tazobactam
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core
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
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	Piperacillin + tazobactam
DrugBank	Piperacillin, Tazobactam

Expert Committee recommendation

The Expert Committee reviewed the evidence and limited its recommendation to hospital-acquired pneumonia. It did not include antibiotics for ventilator-associated pneumonia in this section because the condition is relatively rare and the choice of empirical antibiotic treatment in national guidelines is based on local epidemiology/microbiology. The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid, cefotaxime and ceftriaxone for first-choice therapy in hospital-acquired pneumonia. The Committee recommended the addition of piperacillin + tazobactam to the EML and EMLc for use in hospital-acquired pneumonia as one of the first-choice therapies.

Background

Hospital-acquired pneumonia (HAP) is defined as pneumonia with onset starting more than 48 hours after admission to hospital. Patients are often exposed to different regimens of antibiotics and thus have an increased potential to acquire resistant bacteria, making antibiotic treatment more challenging. Ventilator-associated pneumonia (VAP) is defined by the development of pneumonia while a patient is on a ventilator. Typically, the risk of infection with multidrug-resistant bacteria is high because of exposure to antimicrobials and the critical care setting. Various regimens have been assessed; a particular area of uncertainty is the need for double antipseudomonal coverage in severely ill patients. The two syndromes were combined in the application because of the relative lack of data on HAP and because the guidelines consider these together.

Summary of evidence

A 2015 Cochrane systematic review of 6 randomized controlled trials (RCTs; 1088 participants) comparing short-course with long-course antibiotics for HAP in critically ill patients, including patients with VAP (1). (There were few data from RCTs comparing duration of therapy in non-ventilated patients with HAP.) The authors found a short 7- or 8-day course of antibiotics, compared with a prolonged 10- to 15-day course, increased 28-day antibiotic-free days and reduced recurrence of VAP due to multi-resistant organisms (one study; n = 110; odds ratio (OR) 0.44; 95% confidence interval (CI) 0.21–0.95). For cases of VAP specifically due to non-fermenting Gram-negative bacilli, recurrence was greater after short-course therapy (two studies; n = 176; OR 2.18; 95% CI 1.14–4.16). A 2013 review compared use of linezolid and vancomycin for HAP (9 RCTs; 4026 participants) (2). The authors found an adjusted absolute mortality risk difference (RD) between linezolid and vancomycin of 0.01% (95% CI –2.1% to 2.1%; P = 0.992) and an adjusted absolute clinical response difference of 0.9% (95% CI –1.2% to 3.1%; P = 0.409). However, there were more gastrointestinal side-effects with linezolid than with vancomycin (RD 0.01; 95% CI 0.00–0.02; P = 0.05). In a 2013 systematic review (4 RCTs; 883 participants) comparing short-duration (7–8 days) and long-duration (10–15 days) antibiotic treatment of VAP there was no difference in mortality between the two groups (OR 1.20; 95% CI 0.84–1.72) (3). There was an increase in antibiotic-free days with the short-course treatment, with a mean difference of 3.40 days (95% CI 1.43–5.37), but no difference in relapses between the groups. A 2008 systematic review (41 RCTs; 7015 patients) compared various antimicrobial regimens for VAP and found no differences in mortality (4). The combination of ceftazidime and an aminoglycoside, however, was inferior to meropenem (risk ratio (RR) 0.70; 95% CI 0.53–0.93) for treatment failure. When monotherapy was compared with combined therapy, mortality rates were similar (RR 0.94; 95% CI 0.76–1.16) as were rates of treatment failure (RR 0.88; 95% CI 0.72–1.07).

Guidelines

The application reviewed three guidelines – from the Infectious Diseases Society of America (IDSA), the National Institute for Health and Care Excellence (NICE) and the British Society for Antimicrobial Chemotherapy (BSAC) (5–7). The NICE guidelines recommend that antibiotics for HAP be selected in accordance with local hospital policy (5). For early-onset infections (<5 days following admission to hospital) in patients with no recent exposure to antibiotics and no risk factors for multi-resistant pathogens, BSAC guidelines recommend the use of amoxicillin + clavulanic acid or of cefuroxime; for all other patients, cefotaxime or ceftriaxone, a fluoroquinolone, or piperacillin + tazobactam is recommended (6). For HAP patients with suspected Pseudomonas aeruginosa, ceftazidime, ciprofloxacin, meropenem, or piperacillin + tazobactam could be used. The IDSA guidelines suggest the following for HAP: for low-risk patients (in terms of mortality and MRSA carriage) piperacillin + tazobactam, cefepime, levofloxacin or a carbapenem (7). Vancomycin or linezolid should be added for low-risk patients with a higher MRSA risk, and aztreonam and ceftazidime can be considered for Gram-negative coverage instead of the antibiotics listed above. For high-risk patients or patients who have received IV antibiotics during the previous 90 days, empirical double coverage for Gram-negatives is recommended, and aminoglycosides are listed as an option in addition to the antibiotics listed above. The recommended duration of treatment is 5–7 days for both HAP and VAP.

Rationale for antibiotic selection

Amoxicillin + clavulanic acid is a core antibiotic that can be used within 5 days of hospital admission and if there is no prior antibiotic exposure or risk for resistance. Third-generation cephalosporins are another core choice, as is piperacillin + tazobactam. The systematic reviews suggest non-inferiority between vancomycin and linezolid. Linezolid, however, was not proposed as a core antibiotic since it is proposed for the preservation list of those antibiotics that are last-line for highly resistant pathogens. Use of empirical vancomycin should be restricted to cases where MRSA is suspected. Aminoglycosides are on the list for double antipseudomonal coverage if needed. The application proposed ceftazidime, cefepime and piperacillin + tazobactam for antipseudomonal coverage. It is recommended that the fluoroquinolones be used only when needed, for example, in the case of a serious allergy

to first-choice antibiotics. Given the concern about carbapenem resistance, these agents should be used only when there are no other alternatives.

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 Committee decided not to include VAP in this review because of the need to have local microbiology and epidemiological data to guide the choice of antibiotics and because it is a relatively rare condition. The Committee considered the various antibiotics proposed in the application under the guiding principle of parsimony and selected first-choice antibiotics for HAP for inclusion on the EML and/or EMLc. As a result, levofloxacin, moxifloxacin, ciprofloxacin, ceftazidime, aztreonam, meropenem, imipenem, amikacin, gentamicin, tobramycin and vancomycin were excluded. Recommended first-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended based on available evidence and are usually narrow-spectrum agents.

EML recommendations: Other specified pneumonia

First choice	Second choice
HOSPITAL-ACQUIRED PNEUMONIA	
piperacillin + tazobactam	
amoxicillin + clavulanic acid	
cefotaxime	
ceftriaxone	

1. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2015;(8):CD007577.
2. Kalil AC, Klompas M, Haynatzki G, Rupp ME. Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. BMJ Open. 2013;3(10):e003912.
3. Dimopoulos G, Poulakou G, Pneumatikos IA, Armaganidis A, Kollef MH, Matthaiou DK. Short- vs long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis. Chest. 2013;144(6):1759–67.
4. Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2008;36(1):108–17.
5. Eccles S, Pincus C, Higgins B, Woodhead M, Guideline Development Group. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. BMJ. 2014;349:g6722.
6. Masterton RG, Galloway A, French G, Street M, Armstrong J, Brown E et al. Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 2008;62(1):5–34.
7. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–111.