Amikacin

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.1. Access group antibiotics

EMLc | ATC codes: J01GB06

Indication	Neutropenia ICD11 code: 4B00.0Z
INN	Amikacin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	Parenteral > General injections > unspecified: 250 mg per mL in 2 mL vial (as sulfate)
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	Amikacin
DrugBank	Amikacin

Expert Committee recommendation

The Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid, with or without ciprofloxacin, as first-choice therapy in low-risk patients with febrile neutropenia. The Committee endorsed the inclusion of IV vancomycin and the addition of meropenem (indicated in specific situations in combination with first-line regimens) as second-choice therapy in high-risk patients with febrile neutropenia. The Committee recommended the addition of piperacillin + tazobactam and amikacin (indicated in specific situations in combination with a recommended beta-lactam agent) as first-choice therapy for high-risk patients with febrile neutropenia.

Background

Febrile neutropenia is a severe infectious syndrome needing empirical treatment in immunocompromised patients.

Summary of evidence

One systematic review compared various beta-lactam regimens for empirical treatment of febrile neutropenia (33 randomized controlled trials (RCTs); 4242 participants) and found that cefepime was associated with higher all-cause mortality than other beta-lactams at 30 days (relative risk (RR) 1.44; 95% confidence interval (CI) 1.06–1.94) (1). Carbapenems were associated with significantly more frequent adverse events, specifically pseudomembranous colitis (RR 1.94; 95% CI 1.24–3.04; 2025 participants) but with fewer treatment modifications, which is considered a negative outcome. Piperacillin + tazobactam gave rise to a lower rate of adverse events than comparators (RR 0.25; 95% CI 0.12–0.53). A more recent Cochrane review (44 RCTs; 3471 participants) also found a significantly higher mortality with cefepime compared with other beta-lactams (RR 1.39; 95% CI 1.04–1.86), and also concluded that piperacillin + tazobactam was superior to comparators in terms of mortality (RR 0.56; 95% CI 0.34–0.92) (2).

Importantly, the inferiority of cefepime was refuted by a meta-analysis conducted by the U.S. Food & Drug Administration (FDA) (88 trials; 9467 cefepime patients and 8288 comparator patients), which found no difference in mortality rates and confirmed these findings in a patient-level meta-analysis (3). However, this trial-level meta-analysis was not specific to febrile neutropenia. There were 24 studies in febrile neutropenia; most of the included studies were conducted in other populations: pneumonia (n = 26), intra-abdominal infections (n = 7), urinary tract infections (n = 7), and others (n = 24). Another Cochrane review, ranked highest in the application among the systematic reviews comparing different regimens, compared beta-lactam with beta-lactam plus aminoglycoside combination therapy in patients with febrile neutropenia (71 RCTs) (4). The authors found similar mortality results for trials comparing the same beta-lactam (alone or in combination with an aminoglycoside) (RR 0.74; 95% CI 0.53–1.06) and those comparing a broad-spectrum beta-lactam with a narrower-spectrum beta-lactam combined with an aminoglycoside (RR 0.91: 95% CI 0.77–1.09). Infection-related mortality was significantly lower with monotherapy (RR 0.80; 95% CI 0.64–0.99), and significantly more adverse events were associated with combination treatment, with a number needed to harm of 4 (95% CI 4–6). Similar findings were reported in a 2003 Cochrane review and a non-Cochrane review from 2002 (5, 6). A 2014 Cochrane review assessed empirical antibiotics for Gram-positive bacteria in febrile neutropenia (13 RCTs; 2392 patients) (7). There was no difference in mortality when a glycopeptide was used as part of the initial regimen (RR 0.82; 95% CI 0.56–1.20) and no difference in treatment failure was noted (RR 1.0; 95% CI 0.79–1.27). In contrast, an older and lower-ranked systematic review noted higher success rates were achieved by adding glycopeptides (odds ratio (OR) 1.63; 95% CI 1.17–2.28) (8). There were no differences for mortality outcomes but adverse events were more frequent when glycopeptides were added (OR 4.98; 95% CI 2.91–8.55). A systematic review of fluoroquinolones in low-risk children with febrile neutropenia (6 RCTs and 4 cohort studies) reported no difference in treatment failure as compared with non-fluoroquinolone antibiotics (RR 1.02; 95% CI 0.72–1.45) (9). Inferences were limited, however, given that the definition for treatment failure included antibiotic modification and that study quality was not assessed. Another review compared ciprofloxacin plus a beta-lactam with an aminoglycoside plus a beta-lactam for febrile neutropenia (8 RCTs) in a predominately adult population, and found no significant difference for mortality (OR 0.85; 95% CI 0.54–1.35) but marginally better clinical cure with a fluoroquinolone (OR 1.32; 95% CI 1.0–1.74) (10). Finally, a Cochrane review found no difference in outcomes with oral versus IV antibiotics in patients with febrile neutropenia (excluding leukaemia) who were haemodynamically stable and did not have organ failure, pneumonia, central-line or severe soft-tissue infections (treatment failure RR 0.96; 95% CI 0.86–1.06). However, neither this comparison nor the comparison of mortality rates (RR 0.95, 95% CI 0.54-1.68) met the applicant's definition for non-inferiorityy (11). In summary, there is no role for combining aminoglycosides with beta-lactams in empirical treatment of febrile neutropenia: there is no clinically relevant benefit but an increase in adverse events compared with beta-lactam monotherapy. The highest-ranked systematic review indicates that the same is true for routine use of glycopeptides (e.g. vancomycin) – no benefit in clinical cure but a higher rate of adverse events. Ciprofloxacin combined with a beta-lactam was found to be marginally superior to beta-lactam/aminoglycoside combinations. However, this is based on evidence published before 2005 when fluoroquinolone resistance had less significance than it has now. While this supports the notion that aminoglycosides should not be used routinely in this patient population, no conclusions can be drawn about the potential benefit of fluoroquinolones in the light of the current epidemiology of fluoroquinolone resistance. Overall, no single agent or regimen was found to be clearly superior to other standard regimens; clinical guidelines therefore guided proposals for inclusion on the EML. The exception was cefepime, which has been shown to be associated with a higher risk of death in several systematic reviews and is thus not considered a candidate for the core or targeted list.

Guidelines

The 2010 IDSA guidelines recommend that monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, ceftazidime, a carbapenem (meropenem or imipenem + cilastatin), or piperacillin + tazobactam be used (12). Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added to the initial regimen for management of complications, if antimicrobial resistance is suspected or as alternatives if patients are allergic to beta-lactam antibiotics. Alternatives in case of beta-lactam allergies also include aztreonam. Empirical treatment for fevers persisting after 4 days of broad-spectrum antibiotics includes empirical antifungals, e.g. echinocandins, voriconazole, amphotericin B (beyond the scope of this review). Ciprofloxacin combined with amoxicillin + clavulanic acid is recommended for oral empirical treatment in low-risk patients. The National Institute for Health and Care Excellence (NICE) guideline recommends monotherapy with piperacillin + tazobactam (13); use of empirical aminoglycosides is discouraged. Antibiotics can be switched to an oral regimen after 48 hours of treatment if the patient is at low risk for developing complications. The International Pediatric Fever and Neutropenia Guideline recommends monotherapy with an antipseudomonal beta-lactam or a carbapenem as empirical treatment in high-risk paediatric patients (14). A second Gram-

negative agent or glycopeptide should be added for patients who are clinically unstable, when a resistant infection is suspected, or in a centre with a high rate of resistant pathogens.

Rationale for antibiotic selection

Amoxicillin + clavulanic acid plus ciprofloxacin were proposed as core antibiotics for ambulatory low-risk patients presenting with febrile neutropenia. For all other patients, piperacillin + tazobactam, which is supported by all clinical guidelines for both adults and children, was proposed as a core antibiotic. Cefepime was not proposed for inclusion in the EML; it was felt to be redundant in view of the antibiotics already listed above, and there was concern about potential inferiority in terms of mortality. However, it has a potential role as a carbapenem-sparing agent for other indications and is therefore proposed for inclusion on the preserved list as a niche antibiotic. Colistin, aztreonam, daptomycin, linezolid and tigecycline are all proposed for the preserved list as alternative agents for febrile neutropenia and other indications if none of other antibiotics listed here is deemed appropriate because of resistance or other concerns. Ceftazidime was not proposed due to redundancy with the availability of piperacillin + tazobactam, and the fact that other alternatives, with indications for several more syndromes, have also been proposed for treatment of febrile neutropenia (e.g. meropenem, fluoroquinolones, aminoglycosides). In terms of carbapenems, only meropenem was proposed. Meropenem, aminoglycosides and vancomycin are to be used only if needed in addition to, or instead of, the first-line regimen, piperacillin + tazobactam. The choice of antibiotic should be based on local epidemiology and presentation of the patient as per the recommendations in the clinical guidelines, e.g. high suspicion for a central-line infection, or a patient presenting in septic shock.

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. Gentamicin was excluded. Amikacin was preferred to gentamicin because it is usually more active against Enterobacteriaceae. 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. The Expert Committee made recommendations in line with Talcott criteria for risk classification (15).

EML recommendations: Neutropenia

First choice	Second choice
LOW-RISK	
amoxicillin + clavulanic acid	
ciprofloxacin	
HIGH-RISK	
amikacin	vancomycin
piperacillin + tazobactam	meropenem

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