






|                         |  | EMLc             | ATC codes: J01CR02 |
|-------------------------|--|------------------|--------------------|
| Indication              | Bacterial cellulitis, erysipelas and lymphangitis  | ICD11 code: 1C00 |                    |
| INN                     | Amoxicillin + clavulanic acid  |                  |                    |
| Medicine type           | Chemical agent   |                  |                    |
| Antibiotic groups       |  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<br>Oral > Liquid: 125 mg + 31.25 mg powder for oral liquid (EMLc) ; 250 mg + 62.5 mg powder for oral liquid (EMLc)<br>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 equivalence | The recommendation is for this specific medicine   |                  |                    |
| Patent information      | Patents have expired in most jurisdictions<br>Read more <a href="#">about patents</a> .   |                  |                    |
| Wikipedia               | <a href="#">Amoxicillin + clavulanic acid</a>   |                  |                    |
| DrugBank                | <a href="#">Amoxicillin</a>  ,<br><a href="#">Clavulanic acid (Clavulanate)</a>    |                  |                    |

## Expert Committee recommendation

The Expert Committee endorsed the inclusion on the EML and EMLc of amoxicillin + clavulanic acid and cloxacillin (with a square box listing) as first-choice therapy and cefalexin as second-choice therapy for use in skin and soft-tissue infections.

## Background

Uncomplicated skin and soft-tissue infections refer to infections in which the host is healthy, including cellulitis, erysipelas, human and animal bites, and carbuncles. Complicated skin and soft-tissue infections occur when there may be vascular insufficiency, diabetes, pre-existing non-healing wounds. These infections are frequently polymicrobial and may have a greater chance for being caused by organisms that are multi-resistant to antibiotics. Surgical site infections are included here as a subgroup of skin and soft-tissue infections.

## Summary of evidence

Twelve systematic reviews were found to be relevant (1–12). Many of the reviews were focused on comparisons of vancomycin with antibiotics such as linezolid and daptomycin, for infections that would be caused by MRSA. In a 2014 systematic review and meta-analysis, six randomized controlled trials (RCTs; 1710 patients) compared daptomycin with other antibiotics (1). Clinical success was similar when daptomycin was compared with vancomycin (4 RCTs; odds ratio (OR) 1.19; 95% confidence interval (CI) 0.77–1.83) or with a penicillinase-resistant penicillin (2 RCTs; OR 1.05; 95% CI 0.84–1.31). Interpretation of this review was

hampered by the fact that RCTs of both complicated and uncomplicated skin and soft-tissue infection were included. Similarly, another systematic review (3 RCTs; 1557 patients) that looked at clinical success found no superiority for daptomycin compared with semi-synthetic penicillins (OR 0.89; 95% CI 0.63–1.25) (5). Several systematic reviews compared linezolid with vancomycin and other antibiotics (2, 4, 6, 10–12). One comparison that included 12 RCTs and 6093 patients showed linezolid to be superior in terms of clinical success (OR 1.67; 95% CI 1.31–2.12) (6). The authors concluded, however, that account should be taken of the use of less potent antistaphylococcal beta-lactams such as ceftriaxone in the comparator groups, the same all-cause mortality, and the higher probability of thrombocytopenia in the linezolid group, which may limit the use of linezolid to specific patient populations or to infections that are difficult to treat with other antibiotics. A 2013 Cochrane review that compared linezolid with vancomycin for skin and soft-tissue infections (9 RCTs; 3144 patients) again found linezolid to be associated with a significantly better clinical (risk ratio (RR) 1.09; 95% CI 1.03–1.16) and microbiological cure rate in adults (RR 1.08; 95% CI 1.01–1.16) than vancomycin (2). There were fewer incidents of red man syndrome (RR 0.04; 95% CI 0.01–0.29), pruritus (RR 0.36, 95% CI 0.17–0.75) and rash (RR 0.27; 95% CI 0.12–0.58) with linezolid than with vancomycin, but more people in the linezolid group reported thrombocytopenia (RR 13.06; 95% CI 1.72–99.22), and nausea (RR 2.45; 95% CI 1.52–3.94). Interpretation of these findings is complicated by a mix of complicated and uncomplicated infection and a high risk of bias reported by the authors. Another systematic review that also compared linezolid with vancomycin for the treatment of Gram-positive infections, including skin and soft-tissue infections (9 RCTs; 2489 patients), found linezolid to have apparently higher efficacy than vancomycin (OR 1.40; 95% CI 1.01–1.95) (10). For MRSA skin and soft-tissue infections, another systematic review (1 RCT; 59 patients) concluded that linezolid showed greater efficacy than vancomycin (RR 1.80; 95% CI 1.20–2.68) (11). A further review concluded that linezolid was superior to vancomycin for clinical and microbiological cure (OR 1.41; 95% CI 1.03–1.95 and OR 1.91; 95% CI 1.33–2.76, respectively) (4). Finally, in a review that compared linezolid with vancomycin for MRSA skin and soft-tissue infections in hospital inpatients (4 RCTs; 174 patients), no significant difference in clinical cure was found between the treatment groups although the point estimate was in favour of linezolid (RR 2.94; 95% CI 0.35–25) (12). For diabetic foot infections, a Cochrane systematic review (20 RCTs; 3791 patients) compared several antibiotic regimens including frequently-used antibiotics such as piperacillin + tazobactam, ampicillin + sulbactam, ceftazidime, vancomycin, ertapenem, imipenem, clindamycin and metronidazole (3). No antibiotic was found to be superior. However, the confidence intervals for most of the comparisons were very wide and so a potentially clinically significant difference could not be ruled out. The only comparisons that yielded significant differences were those of imipenem with piperacillin + tazobactam and piperacillin in combination with clindamycin: more adverse events were noted in the comparator groups (RR 3.5; 95% CI 1.56–7.86, and RR 3.70; 95% CI 1.19–11.11, respectively). A systematic review comparing beta-lactam antibiotics with macrolides or lincosamides in patients with cellulitis or erysipelas (15 RCTs; 462 patients for clinical cure and 3032 for adverse events) reported similar clinical cure in all groups (RR 1.24; 95% CI 0.72–2.41;  $P = 0.44$ ); however, the small sample size limits inferences (7). In a Cochrane review of interventions for non-surgically acquired cellulitis (25 RCTs; 2488 patients), macrolides and streptogramins were found to be more effective than penicillin (RR 0.84; 95% CI 0.73–0.98) (8). A Cochrane review of impetigo reported that, for oral therapy, penicillin was inferior to erythromycin (2 RCTs; 79 patients; RR 1.29; 95% CI 1.07–1.56) and to cloxacillin (2 RCTs; 166 participants; RR 1.15; 95% CI 1.01–1.32) for cure rates (9). In summary, several systematic reviews reported higher cure rates with linezolid compared with vancomycin and beta-lactam antibiotics in the absence of an effect on mortality but at the cost of a significant risk of thrombocytopenia. No data suggest that daptomycin should be preferred over vancomycin. The findings on other comparisons were also inconclusive. Penicillin was inferior to erythromycin and cloxacillin for treatment of impetigo.

## Guidelines

The 2014 IDSA (Infectious Diseases Society of America) guidelines on skin and soft-tissue infections (13), which covers both paediatric and adult patients, recommend the following oral options for treatment of impetigo: dicloxacillin, cefalexin, erythromycin, clindamycin and amoxicillin + clavulanic acid. For purulent skin and soft-tissue infections (most likely due to *Staphylococcus aureus*), recommendations include dicloxacillin, oxacillin, cefazolin, clindamycin, cefalexin, doxycycline and trimethoprim + sulfamethoxazole. For MRSA infections, or if MRSA is highly suspected, options include vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline and trimethoprim + sulfamethoxazole. For non-purulent skin and soft-tissue infections, penicillin G or V, clindamycin, nafcillin, cefazolin or cefalexin can be used, with the last two being specifically recommended for non-Type 1 penicillin allergy. For necrotizing infections of the skin, fascia and muscle, the IDSA guidelines recommend vancomycin or linezolid plus piperacillin + tazobactam or a carbapenem (meropenem, imipenem, ertapenem), or plus cefotaxime and metronidazole. Clindamycin in combination with penicillin is recommended for group A streptococcal necrotizing

fasciitis. Penicillin G, semisynthetic penicillins (nafcillin, oxacillin), cefazolin, vancomycin, clindamycin, doxycycline and ceftriaxone, as well as daptomycin, quinupristin + dalbavipristin and linezolid, are listed as options for specific pathogens such as *Streptococcus*, *S. aureus*, *Clostridium* sp., *Aeromonas hydrophila* and *Vibrio* infections. For animal bites, amoxicillin + clavulanic acid is recommended as oral therapy. For IV therapy, ampicillin + sulbactam, piperacillin + tazobactam, second- and third-generation cephalosporins (cefuroxime, cefoxitin, ceftriaxone, cefotaxime) can be used. Other listed options include carbapenems, doxycycline, trimethoprim + sulfamethoxazole, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and, for anaerobic coverage, metronidazole and clindamycin. For human bites, amoxicillin + clavulanic acid and ampicillin + sulbactam should be used; carbapenems and doxycycline are also listed as alternatives. Vancomycin, daptomycin, linezolid and colistin can be used in the presence of selective multidrug-resistant bacteria. For incisional surgical site infections of the intestinal or genitourinary tract, ticarcillin + clavulanic acid, piperacillin + tazobactam, carbapenems (imipenem, meropenem, ertapenem) are recommended single-drug regimens. Combinations regimens include ceftriaxone and metronidazole, a fluoroquinolone (ciprofloxacin or levofloxacin) and metronidazole, ampicillin + sulbactam plus gentamicin or tobramycin. After surgery of the trunk or extremity away from axilla or perineum, oxacillin or nafcillin, cefazolin, cefalexin, trimethoprim + sulfamethoxazole and vancomycin are suggested. For surgery of the axilla or perineum, either ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) is recommended in combination with metronidazole. Other than the usual advice to avoid certain antibiotics (fluoroquinolones, doxycycline) in young children if at all possible, the recommendations were independent of the age of the patients. For diabetic wounds, the 2012 IDSA guidelines recommend that clinically uninfected wounds are not treated with antibiotics; for infected wounds, antibiotic treatment should be supported by debridement as needed, as well as wound care (14). The following antibiotics are listed as potential options for mild infections: dicloxacillin, clindamycin, cefalexin, levofloxacin, amoxicillin + clavulanic acid; and doxycycline or trimethoprim + sulfamethoxazole for potential or confirmed MRSA infections. For moderate to severe infections, the list includes levofloxacin, cefoxitin, ceftriaxone, ampicillin + sulbactam, moxifloxacin, ertapenem, tigecycline, ciprofloxacin in combination with clindamycin, and imipenem + cilastatin; and linezolid, daptomycin or vancomycin for (potential) MRSA. For (potential) *P. aeruginosa* infections, piperacillin + tazobactam is recommended; other options are ceftazidime, cefepime, aztreonam and carbapenems.

### Rationale for antibiotic selection

Amoxicillin + clavulanic acid, dicloxacillin, cefuroxime and cefalexin are recommended in the IDSA guidelines and all provide appropriate Gram-positive coverage for treatment for mild skin and soft-tissue infections and bites. For moderate to severe infections, IV antibiotics are proposed as core antibiotics and also provide appropriate Gram-positive and – if needed, depending on the choice within this group – Gram-negative and anaerobic coverage). If anaerobes are a consideration (e.g. abscesses), metronidazole, also proposed as a core antibiotic, can be combined with another antibiotic that lacks anaerobic coverage. Clindamycin is proposed as a targeted antibiotic for mild infections, as an alternative agent if MRSA coverage is considered necessary, but as a core antibiotic for necrotizing fasciitis for moderate to severe infections. Other options if MRSA coverage is needed are doxycycline and sulfamethoxazole + trimethoprim, as well as vancomycin when IV treatment is needed; all are proposed as targeted antibiotics. Piperacillin + tazobactam is proposed as a targeted option in moderate to severe infections if broad Gram-negative coverage is needed (e.g. suspected polymicrobial necrotizing fasciitis, or diabetic foot infections that have already been extensively treated); meropenem is another alternative that provides even broader Gram-negative coverage. Fluoroquinolones should be used only if no other option is available because of the potential for harm and resistance associated with this group of antibiotics; they are therefore proposed as targeted antibiotics. Although data from RCTs have shown it to be superior to vancomycin and/or beta-lactams, linezolid was not included in the core or targeted antibiotic list because of several concerns. First, the beta-lactam comparators in many RCTs were not optimal antistaphylococcal beta-lactams (6). There was no significant effect on mortality, and the safety profile of linezolid is inferior because of the much higher risk of thrombocytopenia, which requires monitoring and has the potential to be a severe adverse event associated with prolonged hospitalization, platelet transfusion and admission to intensive care. Linezolid is therefore considered a niche antibiotic for patients in whom other options have failed or cannot be used; as such, it is proposed as a preserved list antibiotic. Despite being listed in clinical practice guidelines as potential options for treatment, daptomycin and quinupristin + dalbavipristin were not proposed because of a lack of data showing any benefit over well-established treatment options. Daptomycin can be considered as an alternative for IV MRSA coverage if vancomycin cannot be used and has several other niche indications in other syndromes; it was proposed as a preserved list antibiotic. Penicillin is not recommended for treatment of impetigo (based on guidelines and systematic review data). Nafcillin was not proposed: the IDSA guideline state that it is less convenient than cefazolin, and there is a risk of bone marrow suppression. Despite being listed in the IDSA guidelines, erythromycin is not included because of the concerns raised in the guidelines about resistance in *S. aureus* and

*S. pyogenes*. Colistin is proposed on the preserved list – it should only be used when no other options are available. Cefepime was not proposed: it was considered to be redundant in view of the antibiotics already listed, and there is concern about potential inferiority in terms of mortality (see section on Febrile neutropenia). Aminoglycosides, tigecycline, ceftaroline, aminoglycosides, ceftazidime and aztreonam are not considered for listing for skin and soft-tissue infections because of redundancy; other options are listed for several indications (e.g. vancomycin for MRSA, meropenem and piperacillin + tazobactam with broad spectrum activity against Gram-negatives including *P. aeruginosa*), however, cefepime, aztreonam and tigecycline are proposed on the preserved list for other syndromes. The application did not propose ampicillin + sulbactam or ticarcillin + clavulanic acid due to redundancy because of the other beta-lactams proposed (amoxicillin + clavulanic acid and piperacillin + tazobactam). Ertapenem is proposed as a preserved antibiotic as a niche product for use if, for example, empirical ESBL coverage is needed, and imipenem + cilastatin was not considered due to redundancy because meropenem is proposed for many more syndromes. Both meropenem and piperacillin + tazobactam should be used only if there is a concern for infection by Gram-negatives resistant to other beta-lactams/cephalosporins listed.

### 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. For mild skin and soft-tissue infections, the following antibiotics were excluded: dicloxacillin (as cloxacillin was listed), cefuroxime, clindamycin, doxycycline, levofloxacin, ciprofloxacin, moxifloxacin and trimethoprim + sulfamethoxazole. The antibiotics proposed in the application for severe skin and soft-tissue infections were excluded, since the Committee focused on the empirical treatment of common mild to moderate community-acquired infections. The Committee listed amoxicillin + clavulanic acid and cloxacillin for reasons of parsimony, particularly because both antibiotics provide good coverage for staphylococcal (non-MRSA) and streptococcal infections, which are the leading causes of mild to moderate community-acquired skin and soft-tissue infections worldwide. Amoxicillin + clavulanic acid also provides good coverage for bites. The Committee listed cloxacillin, but noted that any IV antistaphylococcal penicillin is appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred because of their better bioavailability. Recommended first- and second-choice antibiotics are reported above.

### EML recommendations: Bacterial cellulitis, erysipelas and lymphangitis

#### First choice

amoxicillin + clavulanic acid

cloxacillin

#### Second choice

cefalexin

- 1: Wang SZ, Hu JT, Zhang C, Zhou W, Chen XF, Jiang LY et al. The safety and efficacy of daptomycin versus other antibiotics for skin and soft tissue infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 2: Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ. Linezolid versus vancomycin for skin and soft tissue infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 3: Selva Olid A, Sola I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 4: Bounthavong M, Hsu DI. Efficacy and safety of linezolid in methicillin-resistant *Staphylococcus aureus* (MRSA) complicated skin and soft tissue infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 5: Bliziotis IA, Plessa E, Peppas G, Falagas ME. Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 6: Falagas ME, Siempos II, Vardakas KZ. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 7: Ferreira A, Bolland MJ, Thomas MG. Meta-analysis of randomised trials comparing a penicillin or cephalosporin with a macrolide or tetracycline for the treatment of skin and soft tissue infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 8: Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 9: Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC et al. Interventions for impetigo. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 10: Beibei L, Yun C, Mengli C, Nan B, Xuhong Y, Rui W. Linezolid versus vancomycin for the treatment of gram-positive bacterial infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 11: Gurusamy KS, Koti R, Toon CD, Wilson P, Davidson BR. Antibiotic therapy for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 12: Dodds TJ, Hawke CI. Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). *Cochrane Database Syst Rev.* 2010;(6): CD008001.
- 13: Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. *Clinical Infect Dis.* 2006;42:590-610.
- 14: Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG et al. 2012 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of diabetic foot infections. *Clin Infect Dis.* 2012;54:161-197.

