

Proposal for the inclusion of ceftriaxone, clindamycin, metronidazole, piperacillin + tazobactam and vancomycin on the EML and EMLc for the new indication of necrotizing fasciitis

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1. Summary statement of the proposal for inclusion, change or deletion.

This application concerns the updating of the forthcoming WHO Model Lists of Essential Medicines to add the indication 'necrotizing fasciitis' to currently listed antibiotics for children and adults:

- **Piperacillin-tazobactam in combination with clindamycin (for empiric treatment)**
- **Ceftriaxone in combination with metronidazole (this combination should be used only after *Streptococcus pyogenes* necrotizing fasciitis has been ruled out)**
- **Vancomycin (in combination with one of the above-mentioned options if methicillin-resistant *Staphylococcus aureus* is suspected)**

This application proposes an amendment to the core list in section 6.2.1 *Access group antibiotics* and 6.2.2 *Watch group antibiotics* as per the latest edition of the main EML (21st list, 2019) and EMLc (7th list, 2019).

Currently no antibiotic options are recommended in the EML and EMLc for severe community-acquired skin and soft tissue infections.

The reason is that in the 2017 update of the EML, the Committee focused only on empiric therapy of mild to moderate community-acquired infections. Even though a review of the evidence had been presented to the Committee, severe infections were not considered because it was decided to focus on the treatment of pathogens commonly encountered in the most common skin and soft tissue infections (usually *Streptococcus* spp., and methicillin-susceptible *Staphylococcus aureus*) and not to extend the recommendations to severe infections (which are rarer) because they would require treatment with broader-spectrum antibiotics (mostly against Gram-negative bacteria) and their choice would be largely influenced by the local epidemiology (e.g. risk of multidrug-resistant Gram-negative bacteria).

However, necrotizing fasciitis (the most severe among the spectrum of skin and soft tissue infections) requires further evaluation for consistency since for other types of infections the EML/EMLc specifically also considers severe infections. This application therefore asks the Committee to reconsider the evidence that was presented to the previous expert committee for this indication for the 2017 EML update. Since no major new evidence regarding antibiotic therapeutic options for this infection has become available since then, the evidence presented in 2017 still reflects the current evidence-base.

2. Relevant WHO technical department and focal point (if applicable).

WHO AMR Departments of Global Coordination and Partnership (GCP) and Surveillance, Prevention and Control (SPC).

3. Name of organization(s) consulted and/or supporting the application.

McMaster University in Hamilton, Canada has collaborated in the preparation of this application.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN	ATC
Ceftriaxone	J01DD04
Clindamycin	J01FF01
Metronidazole	J01XD01
Piperacillin-tazobactam	J01CR05
Vancomycin	J01XA01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Dose forms and strengths as currently listed on the EML and EMLc.

In addition, it is proposed that additional strength IV formulations of ceftriaxone (2 g powder for injection), clindamycin (600 mg and 900 mg) and vancomycin (500 mg and 1 g) be added to the EML to better meet the dosing needs of adults for this indication.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The application is to add an indication to ceftriaxone, clindamycin, metronidazole, piperacillin-tazobactam and vancomycin as individual medicines.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

The requirements for the identification of people eligible for the treatment of necrotizing fasciitis, include clinical evaluation, surgical exploration (for the direct visualization of necrotic tissue in the muscular fascia) and whenever possible obtaining a microbiology sample of the affected tissue to guide antibiotic treatment (e.g. samples can be collected at the time of surgical exploration). This allows the causative pathogen(s) to be determined so that adequate antibiotic treatment can be given. The reason is that necrotizing fasciitis can be both caused by a single pathogen (usually *Streptococcus pyogenes*) or by multiple pathogens (e.g. a mix of Gram-positive, Gram-negative and anaerobic bacteria).

Because of the severity of necrotizing fasciitis and the speed at which it can progress, empiric antibiotic treatment should be given immediately when necrotizing fasciitis is suspected, the antibiotics should cover both Gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*) and anaerobic pathogens. In patients at higher risk of a Gram-negative bacterial infection (e.g. patients with severe immunosuppression), additional empiric medicines should be considered that have activity against these pathogens.

The proposed therapeutic dosage regimens overlap those indicated in the 2017 application. The only exceptions concern the dose of ceftriaxone and piperacillin-tazobactam in adults and the dose of clindamycin, ceftriaxone, metronidazole and vancomycin in children (Table 1). Compared to the 2017 application, a higher dose is suggested for ceftriaxone and piperacillin-tazobactam in adults due to the severity of this condition.

In children the 2017 application suggested a higher daily dose of clindamycin and metronidazole while for ceftriaxone and vancomycin the daily dose suggested in 2017 was lower than the dose suggested in this application (Table 1).

Doses suggested in this application are based on the WHO report on consensus guidance on paediatric dosing regimens for Access antibiotics on the EMLc (1).

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Table 1 Pediatric doses

	Dose suggested in the 2017 application	Dose suggested in this application	Dose suggested in the WHO guidance document ^a
Clindamycin	40 mg/kg/day	Children: 30 mg/kg/day Neonates: 15 mg/kg/day in	Children: 20-40 mg/kg/day Neonates: 10-20 mg/kg/day
Ceftriaxone	50-75 mg/kg/day	80 mg/kg/day	Children: 50-100 mg/kg/day Neonates: 50 mg/kg/day
Metronidazole	30-40 mg/kg/day	Children: 22.5 mg/kg/day Neonates: 15 mg/kg/day	20-40 mg/kg/day
Vancomycin	40 mg/kg/day	Children: 45 mg/kg/day Neonates: 30 mg/kg/day	40-60 m/kg/day

^a WHO report on consensus guidance on paediatric dosing regimens for Access antibiotics on the EMLc.

To summarize, adequate doses for the treatment of necrotizing fasciitis are as follows:

Adults:

Piperacillin–tazobactam (IV): 4 g + 500 mg every 6 hours AND Clindamycin (IV): 900 mg every 8 hours.

If *Streptococcus pyogenes* has been ruled out Ceftriaxone (IV): 2 g once a day AND Metronidazole (IV): 500 mg every 8 hours can also be used.

if MRSA is suspected Vancomycin (IV) 15-20 mg/kg every 12 hours should be added to both of the above-mentioned options.

Children:

Piperacillin–tazobactam (IV): 100 mg/kg per dose of piperacillin component, given every 8 hours
AND clindamycin (IV):

- Neonates: 5 mg/kg per dose, given every 8 hours
- Children: 10 mg/kg per dose, given every 8 hours

If *Streptococcus pyogenes* has been ruled out Ceftriaxone (IV): 80 mg/kg per dose, once a day AND metronidazole (IV) can also be used:

- Neonates: 7.5 mg/kg per dose, given every 12 hours
- Children: 7.5 mg/kg per dose, given every 8 hours

if MRSA is suspected Vancomycin (IV) should be added to both of the above-mentioned options as follows:

- Neonates: 15 mg/kg per dose, given every 12 hours
- Children: 15 mg/kg per dose, given every 8 hours

Knowledge on the most appropriate duration of treatment is limited. Therefore, duration is often individualized based on clinical response, on the success of surgical source control and, if available, changes in laboratory markers of infection. Usually total treatment duration is about 2–3 weeks.

8. Information supporting the public health relevance.

Epidemiological information on disease burden

Necrotizing fasciitis is rare but associated with significant morbidity and mortality especially in case of delayed diagnosis and treatment. The disease is caused mostly by bacteria and is characterized by acute and fulminant necrosis with tissue destruction and signs of systemic toxicity. Risk factors include traumatic and surgical wounds especially in patients with diabetes, peripheral vascular disease or immunosuppression. However, necrotizing

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fasciitis can also occur in otherwise healthy patients irrespective of their age. Necrotizing fasciitis is very rare in children but may occur as a complication of varicella (chickenpox) or can be associated with a compromised immune system.

There are little data available regarding time trends in the epidemiology of necrotizing fasciitis, but some evidence exists about the mortality burden of this disease. For example, in the United States, over a 10-year period (2003-2013) the overall mortality rate for necrotizing fasciitis was 4.8 per 1 000 000 person-years (total deaths: 9 871) (2). For example, in Taiwan an overall annual incidence of 3.2 hospitalization per 100 000 person-years was reported between 2002 and 2011 (3).

Other studies report an incidence that ranges from 0.3 to 15 cases per 100 000 population (4-6). Among all invasive *Streptococcus pyogenes* infections, necrotizing fasciitis represents only a minority of cases (approximately 7% considering all ages combined in one study (7)).

Target population

Monomicrobial forms of necrotizing fasciitis can occur at any age, including in otherwise healthy individuals, and they are the most common form in children (8). On the other hand, polymicrobial forms occur most frequently in older adults and/or individuals with underlying comorbidities (mostly diabetes (9), peripheral vascular disease, immunosuppression) or traumatic or surgical wounds.

Likely impact of treatment on the disease

Prompt diagnosis and treatment is key in case of necrotizing fasciitis and delays in providing adequate treatment are associated with worse outcomes including an increased risk of death (10). In case of necrotizing fasciitis, antibiotic treatment is a complementary measure to adequate surgical source control of the infection. Prompt and aggressive surgical debridement is the cornerstone of treatment, however, antibiotics also play a major role in the successful management of this condition.

9. Review of benefits: summary of evidence of comparative effectiveness

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) and summary of available data

The review of benefits for the antibiotic options proposed in this application consists of the evidence that was presented for the 2017 EML update (see Appendix). The reason is that no major changes in antibiotic therapeutic options have since been made.

In particular the evidence concerning treatment of necrotizing fasciitis came from one guideline that covers both paediatric as well as adult patients ("Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America") and 12 systematic reviews addressing treatment of skin and soft tissue infections (including but not limited to necrotizing fasciitis).

10. Review of harms and toxicity: summary of evidence of safety.

This application is not for the inclusion of a new medicine in the EML. Ceftriaxone, clindamycin, metronidazole, piperacillin-tazobactam and vancomycin are widely used and potential side effects do not differ from those encountered when these antibiotics are used for a different indication. Therefore, no new data are added for this application that are specific to the treatment of necrotizing fasciitis. Additionally, considering the severity of this condition and the high mortality associated with delays in treatment, the benefits of adequate antibiotic treatment outweigh the potential side effects of each individual antibiotic.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

As the proposed medicines are already included on the Model Lists and in many national essential medicine lists, a review of the comparative costs and cost-effectiveness has not been undertaken.

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Regulatory information

12. Summary of regulatory status and market availability of the medicine.

Ceftriaxone, clindamycin, metronidazole, piperacillin-tazobactam and vancomycin have regulatory approval globally and are available as generics.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia).

Ceftriaxone, clindamycin, metronidazole, piperacillin-tazobactam and vancomycin are listed in multiple pharmacopoeias including the United States Pharmacopoeia and European Pharmacopoeia.

14. References

1. WHO report on consensus guidance on paediatric dosing regimens for Access antibiotics on the essential medicine list for children. Geneva: World Health Organization; [(https://www.who.int/selection_medicines/committees/expert/22/applications/ABWG_paediatric_dosing_AB.pdf), accessed 2021, April 21].
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Appendix

Relevant extract from the Review of Antibacterial Medicines for the WHO Model List of Essential Medicines 2017 Update by the Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Canada

Skin and soft tissue infections.

The full Review is available at:

https://www.who.int/selection_medicines/committees/expert/21/applications/comprehensive_antibiotics_rev/en/

Skin and Soft Tissue Infections (including cellulitis and surgical site infections)

Uncomplicated skin and soft tissue infections refer to infections where the host is healthy, including cellulitis, erysipelas, human and animal bites, or 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. In this section we also include surgical site infections as a subgroup of skin and soft tissue infections.

Synopsis of published evidence

We retrieved 23 completed systematic reviews and one protocol. The quality scores ranged from 55-75, with eight having high scores for recency. Twelve of the 23 systematic reviews were found to be relevant.[165-176] Other reviews were focused on topical agents, mechanisms for wound healing, or prophylaxis, which are not within the scope of this document. Many of the reviews that met our criteria were focused on comparisons to vancomycin, such as linezolid and daptomycin, for infections that would be caused by MRSA.

In a 2014 systematic review and meta-analysis, six RCTs (1,710 patients) compared daptomycin to other antibiotics.[165] Clinical success was similar when daptomycin was compared to vancomycin (4 RCTs) (OR 1.19, 95%CI 0.77-1.83) or to a penicillase-resistant penicillin (2 RCTs), OR 1.05, 95%CI 0.84 to 1.31. A difficulty in the interpretation of this review is that RCTs of both complicated and uncomplicated skin and soft tissue infection were included. Similarly, no superiority was found for daptomycin in a lower ranked systematic review that included 3 RCTs, 1557 patients with an OR of 0.89 (95% CI 0.63, 1.25) for clinical success as compared to semi-synthetic penicillins.[169]

Several SRs compared linezolid to vancomycin and other antibiotics.[166, 168, 170, 174-176] The best ranked SR on this comparison by Falagas et al. including 12 RCTs and 6,093 patients showed superiority of linezolid in terms of clinical success with an OR of 1.67 (95% CI 1.31-2.12).[170] They concluded, however, that the use of less potent anti-staphylococcal beta-lactams in the comparator groups such as ceftriaxone, the same all-cause mortality, and the higher probability of thrombocytopenia in the linezolid group, should be taken into account and may limit the use of linezolid to specific patient populations or infections that are difficult to treat with other antibiotics. Another lower ranked, but more recent 2013 Cochrane review compared linezolid to vancomycin for skin and soft tissue infection (9 RCTs, 3,144 patients).[166] Again, linezolid was associated with a significantly better clinical (RR 1.09, 95% CI 1.03 to 1.16) and microbiological cure rate in adults

(RR 1.08, 95% CI 1.01 to 1.16) than vancomycin. There were fewer incidents of red man syndrome (RR 0.04, 95% CI 0.01 to 0.29), pruritus (RR 0.36, 95% CI 0.17 to 0.75) and rash (RR 0.27, 95% CI 0.12 to 0.58) in the linezolid group compared with vancomycin, however, more people reported thrombocytopenia (RR 13.06, 95% CI 1.72 to 99.22), and nausea (RR 2.45, 95% CI 1.52 to 3.94) when treated with linezolid. The 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 also compared linezolid to vancomycin (9 RCTs, 2489 patients) for the treatment of gram positive infections, including skin and soft tissue infections.[174] Linezolid appeared to have higher efficacy than vancomycin in patients with skin and soft-tissue infections (OR 1.40, 95% CI 1.01-1.95). One systematic review to compare linezolid to vancomycin for MRSA skin and soft tissue infections included only 1 RCT of 59 patients and concluded better efficacy with linezolid than vancomycin (RR 1.80, 95%CI 1.20 to 2.68).[175] Another review also found superiority of linezolid in clinical and microbiological cure (OR 1.41, 95% CI 1.03-1.95 and OR 1.91, 95% CI 1.33-2.76, respectively).[168] Finally, another review compared linezolid to vancomycin for MRSA skin and soft tissue infections in hospital inpatients (4 RCTs, 174 patients) and found no significant difference in clinical cure between the groups although the point estimate was in favour of linezolid (RR 2.94; 95% CI 0.35-25).[176]

A Cochrane SR focussing on diabetic foot infections including 20 RCTs with 3,791 patients compared several antibiotic regimens including frequently used antibiotics such as piperacillin-tazobactam, ampicillin-sulbactam, ceftazidime, vancomycin, ertapenem, imipenem, clindamycin, and metronidazole.[167] No antibiotic was found to be superior, however, the confidence intervals for the vast majority of comparisons were very wide and could as such not rule out a potentially clinically significant difference. The only comparisons that yielded significant differences were comparisons of imipenem versus piperacillin-tazobactam and piperacillin plus clindamycin, where more adverse events were noted in the comparator groups (RR 3.5, 95% CI 1.56-7.86, and RR 3.70, 1.19-11.11, respectively).

A systematic review comparing beta-lactam antibiotics to macrolides or lincosamide in patients with cellulitis or erysipelas (15 RCTs, 462 patients for clinical cure, and 3,032 for adverse event outcomes), reported similar clinical cure between the groups (RR 1.24, 95 % CI 0.72-2.41, $p = 0.44$), however the small sample size limits inferences.[171] In a Cochrane review of interventions for non-surgically acquired cellulitis, 25 RCTs, 2,488 patients, macrolides and streptogramins were found to be more effective than penicillin, RR 0.84, 95%CI 0.73 to 0.98.[172] A Cochrane review of impetigo reported that, for oral therapy in 2 RCTs of a total of 79 patients, penicillin was inferior to erythromycin for cure rates, RR 1.29, 95%CI 1.07 to 1.56 and inferior to cloxacillin in 2 RCTs of 166 participants (RR 1.15, 95%CI 1.01 to 1.32).[173]

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In summary, several SRs reported higher cure rates with linezolid as compared to 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 undetermined, thus, no conclusions could be drawn. Penicillin was shown to be inferior to erythromycin and cloxacillin for treatment of impetigo, which may be related to cases related to *S. aureus* rather than Streptococci that are universally susceptible to penicillins.

Synopsis of guidelines

We reviewed 6 guidelines where the score ranged from 58% to 81%.[177-182] Only two of these, however, met the criteria of being relevant CPGs.[177, 178]

The broader guidelines on skin and soft tissue infections (IDSA 2014)[177] that covers paediatric as well as adult patients recommend the following oral options for treatment of impetigo: dicloxacillin, cephalexin, erythromycin, clindamycin, and amoxicillin-clavulanate. For purulent skin and soft tissue infections (most likely due to *S. aureus*), recommendations include (dicl)oxacillin, cefazolin, clindamycin, cephalexin, 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, either penicillin G or V, clindamycin, nafcillin, cefazolin, or cephalexin can be used with the latter two specifically recommended for non-Type 1 penicillin-allergy. For necrotizing infections of the skin, fascia, and muscle, the IDSA guideline recommend piperacillin-tazobactam and vancomycin, a carbapenem (meropenem, imipenem, ertapenem), or cefotaxime and metronidazole or clindamycin. Antibiotics including penicillin G, semi-synthetic penicillins (nafcillin, oxacillin), cefazolin, vancomycin, clindamycin, doxycycline, ceftriaxone, as well as daptomycin, quinupristin/dalfopristin, and linezolid, are listed as options for specific pathogens such as Streptococcus, *S.aureus*, Clostridium species, *Aeromonas hydrophila*, and Vibrio infections. For animal bites, amoxicillin-clavulanate is recommended as oral therapy. For intravenous 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-clavulanate and ampicillin-sulbactam should be used. Carbapenems and doxycycline are also listed as alternatives. Vancomycin, daptomycin, linezolid, and colistin are agents that can be used in the presence of selective multi-resistant bacteria.

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For incisional surgical site infections of the intestinal or genitourinary tract, ticarcillin-clavulanate, piperacillin-tazobactam, carbapenems (imipenem, meropenem, and 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, cephalexin, trimethoprim-sulfamethoxazole, and vancomycin are suggested. For surgery of the axilla or perineum, either ceftriaxone or a fluoroquinolone (ciprofloxacin or levofloxacin) in combination with metronidazole are recommended. Other than the usual recommendation not to use certain antibiotics in young children if it can be avoided (fluoroquinolones, doxycycline), the recommendations did not vary depending on age of the patients.

The guidelines specific for diabetic wound infections (IDSA 2012)[178] recommend that clinically uninfected wounds do not get treated with antibiotics, and that, if infected, antibiotic treatment should be supported by debridement as needed as well as wound care. For mild infections, the following antibiotics are listed as potential options: dicloxacillin, clindamycin, cephalexin, levofloxacin, amoxicillin-clavulanate, 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 with clindamycin, imipenem-cilastatin. For (potential) MRSA infections, linezolid, daptomycin, or vancomycin. For (potential) *P. aeruginosa* infections, piperacillin/tazobactam is recommended. Other options listed for *P. aeruginosa* are: ceftazidime, cefepime, aztreonam, and carbapenems.

Antibiotic selected as essential:

Amoxicillin/clavulanate, dicloxacillin, cefuroxime and cephalexin are recommended in the guidelines and all provide appropriate gram-positive coverage as needed for treatment for mild skin- and soft-tissue infections and bites. For moderate to severe infections, intravenous antibiotics are listed as core antibiotics that also provide appropriate gram-positive coverage, and if needed depending on the choice within this group, gram-negative and anaerobic coverage (see table). Metronidazole is also listed as a core antibiotic if combined with another antibiotic with no anaerobic coverage when anaerobs are a consideration (e.g. abscesses).

Clindamycin is listed as a targeted antibiotic for mild infections as an alternative agent if MRSA coverage is deemed to be needed, but as a core antibiotic for necrotizing fasciitis in the table for moderate to severe infections. Other options if MRSA coverage is needed is doxycycline and

TMP/SMX, as well as vancomycin when intravenous treatment is needed, which are all listed as targeted antibiotics. Piperacillin/tazobactam is listed as 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), as is meropenem as another alternative if even broader gram-negative coverage is needed.

The fluoroquinolones should only be used if no other option is available due to the potential harm and resistance associated with this group of antibiotics, and are therefore listed as targeted antibiotics.

Linezolid, although shown based on data from RCTs to be superior to vancomycin and/or beta-lactams, was not included in the core or targeted antibiotic list due to several concerns. First, as outlined by Falagas et al., the beta-lactam comparators in many RCTs were not optional anti-staphylococcal beta-lactams. Furthermore, there was no significant effect on mortality, and the safety profile of linezolid is inferior due to the much higher risk of thrombocytopenia, which requires monitoring and has the potential of severe adverse event associated with prolonged hospitalization, platelet transfusion and intensive care unit admission,. Therefore, linezolid is considered a niche antibiotic for patient population in which the other options cannot be used or failed, and is as such listed as a conserved antibiotic. Although being listed in CPGs as potential options for treatment, daptomycin and quinupristin/dalfopristin were not included due to the lack of data showing any benefit over well-established treatment options listed below. Daptomycin can be considered as an alternative for intravenous MRSA coverage if vancomycin cannot be used and has several other niche indications in other syndromes, and was as such added to the list of conserved antibiotics.

Penicillin is not recommended for treatment of impetigo based on guidelines and SR data. Nafcillin was not added as the IDSA guideline state that it is less convenient than cefazolin, and due to the risk of bone marrow suppression. Despite being listed in the IDSA guidelines, erythromycin is not included due to the concerns raised in the guidelines around resistance in *S. aureus* and *S. pyogenes*. Colistin is listed on the conserved list as it should only be used when no other options are available. Cefepime was not added as it was considered to be redundant with the antibiotics already listed below, and the potential concern about inferiority in terms of mortality (see chapter febrile neutropenia). Aminoglycosides, tigecyclin, ceftaroline, aminoglycosides, ceftazidime, and aztreonam are not considered for listing for skin and soft tissue infections due to redundancy as there are other options that are listed for several other indications (e.g. vancomycin for MRSA, meropenem and piperacillin/tazobactam with broad spectrum against gram-negatives including *P. aeruginosa*), however, cefepime, aztreonam and tigecyclin are listed on the conserved list for other syndromes.

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We further did not list ampicillin-sulbactam and ticarcillin-clavulanate due to redundancy with other beta-lactams listed (amoxicillin-clavulanate and piperacillin-tazobactam). Ertapenem is listed as a conserved antibiotic as a niche product e.g. if empiric ESBL coverage is needed, and imipenem-cilastatin was not considered due to redundancy with meropenem with the latter being listed for many more syndromes. Meropenem as well as piperacillin/tazobactam should only be used if there is a concern for infection by gram negatives resistant to other betalactam/cephalosporins listed.

List for mild skin and soft tissue infections (impetigo, uncomplicated cellulitis, mild diabetic foot infection, bites):

Antibiotic	Adults (per dose)	Paediatrics (per day)	SR	CPG	EML (A/P)	List
Amoxicillin/clavulanate	875mg/125mg	25mg/kg		√	+/+	c
Dicloxacillin	500mg PO	25-50mg/kg PO		√	-/-	c
Cefuroxime	500mg PO			√	-/-	c
Or cephalexin	250-500mg PO	25-50mg/kg PO		√	-/-	c
Clindamycin	300 PO	20mg/kg PO/IV		√	(+)/(+)	t
Doxycycline	100mg PO/IV			√	+/+	t
Levofloxacin	750mg PO			√	-/-	t
Or ciprofloxacin	500-750mg PO			√	+/+	t
Or moxifloxacin	400mg PO			√	-/-	t
Trimethoprim/sulfamethoxazole	160-800mg PO/IV	8-12mg/kg PO/IV		√	+/+	t

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List for moderate to severe skin and soft tissues infections including diabetic foot infections and necrotizing fasciitis

Antibiotic	Adults (per dose)	Paediatrics (per day)	SR	CPG	EML (A/P)	List
Penicillin G	2-4 Mio units	60-100000 units/kg IV		√	+/+	c
Amoxicillin/clavulanate	1g/200mg IV	25mg/kg		√	+/+	c
Oxacillin	1-2g IV	150-200/kg IV		√	-/-	c
Or cloxacillin	1-2g IV			√	+/+	c
Or cefazolin	1g IV	50mg/kg IV		√	+/+	c
Piperacillin-tazobactam	3.375g IV	200-300mg/kg IV		√	-/-	t
Cefoxitin	1g IV	160mg/kg IV		√	-/-	c
Or ceftriaxone	1g IV	50-75mg/kg IV		√	+/+	c
Or cefotaxime	1-2g IV			√	(+)/(+)	c
Clindamycin	600-900mg IV	40mg/kg IV		√	(+)/(+)	c
Levofloxacin	750mg PO/IV			√	-/-	t
Or ciprofloxacin	500-750mg PO/400mg IV	20-30mg/kg IV		√	+/+	t
Or moxifloxacin	400mg PO/IV			√	-/-	t
Meropenem	1g IV	60mg/kg IV		√	-/-	t
Metronidazole	250-500mg IV/PO	30-40mg/kg IV		√	+/+	c
Vancomycin	15-30mg/kg IV	40mg/kg IV		√	(+)/(+)	t

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The recommended treatment durations for erysipelas and cellulitis are 5 days if improved significantly within this time period. Seven days are recommended for impetigo. Pre-emptive treatment of 3-5 days is recommended after dog or cat bites in high-risk patients and based on the severity and location of the bite.

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