Proposal to upgrade cefalexin to first choice for skin and soft tissue infections on the WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children

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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 (EML and EMLc) to upgrade cefalexin from "second choice" to "first choice" for the treatment of skin and soft tissue infections in adults and children.

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

This application is not proposing to add a new medicine or indication to the EML/EMLc but only to upgrade an already listed medicine from second to first choice for the same indication. Cefalexin has been on the core list of the EML for more than a decade, having been listed since 2009 and was listed specifically for the treatment of skin and soft tissue infections in 2017.

The main reason for this proposal is that cefalexin offers good coverage for staphylococcal (non-MRSA) and streptococcal infections with a spectrum of activity and tolerability that is comparable with the other two first choice options currently recommended in the EML/EMLc for the empiric treatment of skin and soft tissue infections (cloxacillin and amoxicillin-clavulanic acid).

As indicated in the Committee considerations for antibiotics for skin and soft tissue infections in 2017, "the Committee listed amoxicillin-clavulanic acid and cloxacillin for reasons of parsimony 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" (1). Cefalexin was chosen as a second choice based on the principle of parsimony and not because of efficacy or safety concerns compared with the other two options. Cefalexin as second choice was intended to be considered when first choice options are not available or in penicillin-allergic patients who can tolerate cephalosporins. By upgrading cefalexin to first choice, it will be clearer to prescribers that these three antibiotic options represent equally adequate alternatives for the treatment of mild community-acquired skin and soft tissue infections (except for skin infections associated with bite wounds for which amoxicillin-clavulanic acid remains the best option among these three).

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.

Department of Health Research Methods, Evidence and Impact, McMaster University, Canada.

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

INN	ATC
Cefalexin	J01DB01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).
The proposed changes applies to all dose forms and strengths of cefalexin on the EML and EMLc.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
The application refers to cefalexin as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis
7. Treatment details (requirements for diagnosis, treatment and monitoring).
Most mild cases of skin and soft tissue infections are diagnosed based on the clinical presentation and do not require routine laboratory tests or imaging. In most cases oral antibiotic treatment is adequate and empiric antibiotic options need to have good activity against the most likely pathogens (*Staphylococcus* aureus and *Streptococcus* spp.) while routine empiric treatment against community-acquired methicillin-resistant *Staphylococcus* aureus (CA-MRSA) is not needed (but may be considered in certain cases based on individual risk factors and local prevalence of CA-MRSA).

The proposed therapeutic dosage regimens are:

- Adults: 500 mg every 8 hours
- Children: 25 mg/kg per dose, every 12 hours

Treatment duration: 5 days (the optimal duration is not known and it is often individualized based on the clinical response).

8. Information supporting the public health relevance.
Epidemiological information on disease burden
Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial infections) were the fourth leading cause of non-fatal diseases (2). Cellulitis, the most common skin infection, accounted for 0.04% (4 in 10.000) of the overall burden of all diseases combined in 2013. It was the only skin condition that showed a significant decrease (–13.2%) between 2005 and 2013 in disability-adjusted life years (DALYs), a proxy for morbidity and mortality; this decrease was attributed to reduced mortality (2). In 2017, the Global Burden of Disease study reported 43 million new cases of cellulitis worldwide (3). Diabetes, peripheral arterial disease, HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

Assessment of current use
Table 1 reports **the antibiotics currently recommended** in the EML/EMLc for the empiric treatment of community-acquired skin and soft tissue infections. The proposal of this application is to upgrade cefalexin to first choice so to have three alternative first choice options.

Table 1 Empiric antibiotic treatment for mild skin and soft tissue infections

	ADULTS	CHILDREN
First choice	Amoxicillin-clavulanic acid (oral): 500 mg + 125 mg every 8 hours Cloxacillin (oral): 500 mg every 8 hours	Amoxicillin-clavulanic acid (oral): 3-6 kg: 250 mg per dose, every 12 hours 6-10 kg: 375 mg per dose, every 12 hours 10-15 kg: 500 mg, every 12 hours 15-20 kg: 875 mg, every 12 hours 20-30 kg: 1000 mg, every 12 hours Cloxacillin (oral): 15-25 mg/kg per dose, four times a day

Second choice The proposed change would move cefalexin up to first choice.	Cefalexin (oral): 500 mg every 8 hours	Cefalexin (oral): 25 mg/kg per dose, every 12 hours

Target population
Children and adults diagnosed with mild skin and soft tissue infections.

Likely impact on the burden of disease
It is unlikely that the proposed change has an impact on the burden of disease per se.

9. Review of benefits: summary of evidence of comparative effectiveness.
The review of benefits for the empiric use of cefalexin for skin and soft tissue infections consists of the evidence that was presented for the 2017 EML update. No major changes or additional evidence discouraging its use for this indication have occurred since.

10. Review of harms and toxicity: summary of evidence of safety.
The same considerations made in the above section also apply to the review of harms and toxicity of cefalexin.

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

Regulatory information
12. Summary of regulatory status and market availability of the medicine.
Cefalexin has regulatory approval globally and is available as generic.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).
Cefalexin is listed in multiple pharmacopoeia including the United States Pharmacopeia and European Pharmacopoeia.

14. References

1. WHO. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization. (WHO Technical Report Series, No. 1006), 2017.
2. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA Dermatol. 2017;153(5):406-12.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789-858.