Amoxicillin + clavulanic acid

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

EMLc | ATC codes: J01CR02

Indication	Other specified prophylactic measures ICD11 code: QC05.Y
INN	Amoxicillin + clavulanic acid
Medicine type	Chemical agent
Antibiotic groups	A 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 **Oral > Liquid:** 125 mg (as trihydrate) + 31.25 mg (as potassium salt) / 5 mL powder for oral liquid (EMLc) ; 250 mg (as trihydrate) + 62.5 mg (as potassium salt) / 5 mL powder for oral liquid (EMLc) **Oral > Solid > dispersible tablet:** 200 mg (as trihydrate) + 28.5 mg (as potassium salt) (EMLc) ; 250 mg (as trihydrate) + 62.5 mg (as potassium salt) (EMLc) **Oral > Solid > tablet:** 500 mg (as trihydrate) + 125 mg (as potassium salt)
EML status history	First added in 2019 (TRS 1021) Changed in 2023 (TRS 1049)
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	Amoxicillin + clavulanic acid
DrugBank	Amoxicillin, Clavulanic acid (Clavulanate)

Expert Committee recommendation

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. In line with previous decisions for infectious syndromes, alternatives for use in case of allergy were not recommended. The Expert Committee endorsed listing of cefazolin, alone or in combination with metronidazole as first-choice options, and of amoxicillin + clavulanic acid and gentamicin as second-choice options for surgical prophylaxis on the core list of the EML and EMLc, as Access group antibiotics (Section 6.2.1). The Committee also recommended the addition of cefuroxime to the core list of the EML and EMLc as a second-choice option for surgical prophylaxis, as a Watch group antibiotic (Section 6.2.2), as an alternative to cefazolin. The expert Committee recommended the addition of cefuroxime in the EML and EMLc as a second choice treatment of surgical prophylaxis and classified under AWaRe as a Watch group antibiotic.

Background

Surgical site infections (SSIs) are the most frequent health care-associated infection (HAI) in low- and middle-income countries (LMICs) and the second most frequent HAI in Europe and the United States of America (1-4). In low- and middle-income countries (LMICs), 11% of patients who undergo surgery are infected in the process. In Africa, infection is the most frequent complication in surgery and up to 20% of women who have a caesarean section develop a postoperative wound infection, compromising both their health and the ability to care for their infants (WHO, unpublished data, 2017; (5)). SSIs are mainly caused by bacteria that enter through incisions made during surgery. Some involve only skin and subcutaneous tissue, but others are more serious and involve muscle, fascia, organ spaces or implanted material (6). SSIs are associated with longer postoperative hospital stays and may require additional surgical procedures and even intensive care, thus resulting in a higher attributable morbidity and mortality (7). They also add a financial burden to the health care system and patient out- of-pocket costs. In the USA, they contribute to patients spending more than 400 000 extra-days in hospital at a cost of an additional US$ 10 billion per year (8). Surgical antibiotic prophylaxis (SAP) is one of the pillars of SSI prevention and is defined as the prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery (9). It has also been defined as “the rational, safe and effective use of antimicrobial agents for the prevention of (initial) SSIs” (10) or as “the use of antibiotics to prevent postoperative infection” (11). WHO provides strong recommendations on the administration of SAP prior to surgical incision when indicated, depending on the type of operation and its timing and duration. However, SAP is often used inappropriately in many settings around the world and this misuse diminishes patient safety and increases acquisition and transmission of antimicrobial resistance (AMR) in surgical services. Inappropriate SAP mainly consists of incorrect antibiotic choice, dose, timing and/or means of administration, and/or duration. Results of a WHO global survey conducted in 2014 (https://www.who.int/gpsc/5may/global-surveys/en/) showed that inappropriate SAP duration is a major problem worldwide, with prolongation of antibiotic use beyond international standards (that is, one pre-operative dose and repetition during the intervention if necessary according to specific criteria) in 43.5% of procedures on average. The frequency of prolongation was higher than 60% in African, Eastern Mediterranean and Western Pacific countries. Inappropriate SAP is particularly frequent in LMICs (12-16). Based on these and other findings and considering the central role of SAP in SSI prevention, there is need for standardized, evidence-based global guidance on appropriate SAP, which involves several key aspects based on high-quality evidence: correct antibiotic choice, dose, timing, route of administration and duration.

Summary of evidence

The application presented the results of a rapid systematic literature review of systematic reviews on SAP. Inclusion criteria were that the systematic review addressed the effect of intravenous SAP on SSIs and either (1) recommended SAP; (2) recommended a specific agent; and/or (3) provided a head-to-head comparison of antibiotics used for SAP. In addition, systematic reviews based on insufficient evidence (for example, one or two randomized controlled trials [RCTs] with small sample sizes) were excluded. (Refer to the application for full details of the search strategy and study selection). Seventeen systematic reviews were included: 13 compared SAP regimens for specific procedure types including: neurosurgery (17, 18); neck surgery (19, 20); cardiac surgery (21, 22); upper gastrointestinal surgery (23); colorectal surgery (24, 25); caesarean section (26); gynaecological surgery (27); hernia surgery (28); and plastic surgery (29). Three compared specific SAP regimens for several procedure types combined (cardiac-, vascular-, orthopaedic-, and neurosurgery; cardiac-, vascular- and orthopaedic surgery; and cardiac- and orthopaedic surgery) (30-32). One specifically addressed SAP for MRSA SSI prevention (33). The included systematic reviews provided evidence that was generally in line with the recommendations for SAP from the evidence-based guideline issued jointly in 2013 by the American Society of Health System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA) (10) (see Guidelines section, below).

Guidelines

The application presented the results of systematic review and inventory of available relevant evidence-based SAP guidelines and protocols. Inclusion criteria were that the guideline was: (1) issued by a country, region or

organization/society (that is, not adopted locally or by a single centre); (2) issued within the last 5 years; and (3) based on a systematic, evidence-based approach. (Refer to the application for full details of the search strategy and guideline selection). Thirty records were included: 19 records met all three inclusion criteria (9-11, 34-49). Ten met the first two criteria, but did not rely on a systematic evidence-based approach (50-59) and one, which included recommendations on all relevant types of surgery, was systematically updated, but not issued in a national context or by a scientific society (60). The 11 records that did not meet all three inclusion criteria were deemed relevant as they were of high quality and/or addressed unique situations, such as LMICs or paediatric settings. All identified guidelines covered at least one of the most common surgical procedures. The most frequently recommended first-line antibiotics (first-choice antibiotics and second-choice agents as alternatives to first-choice) for SAP across all procedures were cefazolin, by far, followed by cefuroxime, then metronidazole (in combination with another agent), gentamicin and ampicillin-sulbactam. The most frequently recommended second-line antibiotics to be used for SAP in cases of known immediate severe or delayed severe penicillin hypersensitivity were vancomycin, clindamycin, gentamicin and metronidazole across all procedures. When considering wound classification (61-63), the most frequently recommended first-line antibiotics in clean surgical procedures with potential severe consequences of infection and/or procedures involving implantation of foreign material (for example, cardiac, breast and hernia surgery, central and peripheral vascular surgery, orthopaedic [excluding arthroscopy or neurosurgery] and non-cardiac thoracic surgery) were a first-generation cephalosporin (cefazolin), by far, followed by a second-generation cephalosporin (cefuroxime). The most frequently recommended second-line antibiotics to be used in cases of known immediate severe or delayed severe penicillin hypersensitivity were vancomycin and clindamycin, both as a single agent. For some procedures, some guidelines also mentioned a combination of vancomycin and gentamicin (cardiac and central vascular surgery) or a combination of clindamycin and gentamicin (breast surgery, hernia repair) or gentamicin and metronidazole (hernia repair) as possible second-line alternatives. In clean-contaminated surgical procedures (for example, head and neck, abdominal, gynaecological, obstetric, urologic and vascular surgery), the most frequently recommended first-line antibiotic was cefazolin (usually combined with metronidazole), by far, followed by metronidazole (in combination with another agent), then cefuroxime, cefoxitin, ampicillin-sulbactam and gentamicin. The most frequently recommended second-line antibiotic to be used in cases of known immediate severe or delayed severe penicillin hypersensitivity was gentamicin, followed by clindamycin, then metronidazole and vancomycin. For most procedures, guidelines recommended a combination of gentamicin with either clindamycin or vancomycin or metronidazole as possible second-line alternatives. Many guidelines recommended to consider the use of vancomycin across procedures in addition to the recommended agent(s) as a single pre-operative dose for patients known to be colonized with methicillin-resistant Staphylococcus aureus (MRSA) or at high risk for MRSA colonization (for example, recently-hospitalized patients, nursing home residents, hemodialysis patients) or in the absence of screening data (10, 11, 53, 56, 59, 60).

Rationale for antibiotic selection

The application proposed the antibiotics of choice for SAP for inclusion on the EML by type of surgical procedures and provided alternative options when the first-line choices are unavailable or contraindicated due to severe allergy. The proposed antibiotics were selected by consensus at a meeting of technical experts after consideration of the abovementitoned review findings. Among first-line antibiotics, the first choice recommended for most procedures was cefazolin or its second-generation equivalent, cefuroxime. It was noted that ceftriaxone and other antibiotics are often inappropriately used as first-line SAP options in many LMICs. Experts stressed the importance of ensuring that cefazolin and/or cefuroxime are broadly available worldwide at a reasonable price and as good quality products with good manufacturing practice labelling. For patients with confirmed immediate severe or delayed severe penicillin hypersensitivity, a non–beta-lactam antibiotic must be used instead. It was emphasized that the second-line antibiotics listed are suboptimal and should only be used in cases of known or highly suspected allergies. However, appropriate documentation of allergies prior to surgery is not common practice in all settings, particularly in LMICs. It was agreed that there is no good reason to use ceftriaxone for SAP as it belongs to the EML Watch group (64). In addition, it is included in the WHO highest-priority, critically important antimicrobials (CIA) list (65) as it is a third-generation cephalosporin and thus has a high risk of selection of

bacterial resistance (in particular, extended spectrum beta-lactamase-[ESBL] producing enterobacteriacae). Therefore, ceftriaxone should be reserved for the limited number of infectious conditions where it is indicated for therapeutic purposes. Conversely, it is widely overused, including for SAP for which ceftriaxone has no indication and does not add any value as it does not offer additional coverage for ESBL. It is also inferior to other antibiotics (for example, cefazolin) for methicillin-sensitive S. aureus and creates an unnecessary risk of collateral damage to the gut flora given its high biliary penetration. Considering the high resistance rates to quinolones in LMICs and the fact that they feature in the EML Watch category (64) and are among the highest-priority antimicrobials in the CIA list (65), participants agreed that the combination of an aminoglycoside (gentamicin or tobramycin) plus metronidazole is generally preferable as second-line antibiotics. However, for patients with renal insufficiency, quinolones may be more appropriate. Quinolones should be reserved for special circumstances where no other options are available. When they are used, ciprofloxacin should generally be favoured over levofloxacin. It was noted that many hospitals in the US have begun administering azithromycin in addition to cefazolin for pregnant women undergoing caesarean sections, based on the results of a RCT published in 2016 showing a 50% reduction in SSIs compared to a control group (66). Experts agreed that this study represents valuable evidence, but it would be premature to consider this option in the EML based on the results of a single study conducted in a high-income country. additional evidence emerges, it might be appropriate to add adjunctive azithromycin as a first-line option for caesarean section in future editions of the EML.

Committee considerations

The Expert Committee agreed with the views of the technical expert group that key factors for appropriate SAP include selecting the right antibiotic, taking into account the surgical procedure (as well as probable causative microorganisms and their resistance patterns based on SSI surveillance), route of administration, dosing, patient allergies and cost/availability; administering the antibiotic at the right time; and avoiding prolongation of the antibiotic after completion of the operation. For SAP to be effective, the tissue concentration of the antibiotic must be above the minimal inhibitory concentration at the time of incision and throughout the procedure. This depends on the half-life of the antibiotic chosen and may require re-dosing accordingly during the procedure. The Expert Committee agreed that administering SAP close to the time of incision is important for antibiotics with a short half-life and, in general, this could avoid the need for re-dosing during the procedure (depending again on the half-life of the particular antibiotic used). For example, administration closer to the incision time (<60 minutes) can be considered for antibiotics with a short half-life such as cefazolin. The Expert Committee noted the key considerations for dosing and re-dosing identified by the technical expert group: • observational data suggest that higher serum and tissue levels throughout the surgical procedure reduce the risk of SSIs; • higher doses should be favoured, as long as there are no concerns about toxicity; • re-dosing should generally be provided after twice the half-life of the antibiotic has passed since the initial preoperative dose; • there is little evidence to support weight-based dosing, but higher doses of cephalosporins may be advisable in morbidly obese patients.

EML recommendations: Other specified prophylactic measures

First choice	Second choice
SURGICAL PROPHYLAXIS	
cefazolin	cefuroxime
cefazolin	gentamicin
	amoxicillin + clavulanic acid

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