Application for the 21st Model List of Essential Medicines

Antibiotics of choice for surgical antibiotic prophylaxis

Applicant

WHO Department of Service Delivery and Safety (SDS)

Introduction

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 (USA) (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develop a postoperative wound infection, compromising both their health and the ability to care for their infants (WHO, unpublished data, 2017; (5)).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).

SSI prevention is therefore a high priority worldwide, but it is particularly complex as it needs to address multiple risks factors. 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 was also 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. For example, in a multicentre study on SSI prevention conducted in four sub-Saharan African countries, SAP was appropriately administered in only 12.8% of surgical patients at baseline (12). Furthermore, Aiken and colleagues observed that over 99% of surgical patients were prescribed postoperative antibiotic regimes instead of pre-operative SAP in a typical government hospital in Kenya (13). Another Kenyan study reported that the prescription of antibiotic prophylaxis was inappropriate in 45% of cases (14). In an Ethiopian tertiary care teaching hospital, ceftriaxone which is an antibiotic to be reserved for specific infection treatment and not for prophylaxis, was the most prescribed agent for SAP (84.5% of cases) (15). In Mexico, this habit of using restricted antibiotics applied to 17% of SAP regimens; furthermore, 96% of antibiotic regimens began with inappropriate timing, 83% were inappropriate regimens, 78% had inappropriate dosage and 86% inadequate length (16).

Based on these and other findings and considering the central role of SAP in SSI prevention, there is an urgent 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.

The objective of the current application is to propose the list of antibiotics of choice for SAP to be included in the WHO Model List of Essential Medicines (EML). The list should also specify antibiotic choices by type of surgical procedures and provide alternatives options when the first choice is unavailable or contraindicated due to severe allergy.

1. Methodology

The following methodology was used to develop the proposed list of antibiotics of choice for SAP:

- conduct of a systematic review and a grey literature search of existing guidelines and systematic reviews on SAP;
- a technical expert meeting was then convened to review the retrieved evidence and identify the antibiotics of choice for SAP.

Summary of evidence

As background evidence for expert discussion, the Infection Prevention and Control (IPC) Global Unit of the WHO SDS Department conducted a rapid systematic literature review and inventory of available relevant evidence-based SAP guidelines and protocols, including already existing systematic reviews on SAP. The methods and results of these two reviews are presented here.

A comprehensive evidence-based guideline issued jointly in 2013 (10) 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) was used as a reference point for the search. Existing evidence-based guidelines were identified by: (1) a systematic search in PubMed/Medline (see Appendix 1 for the search strategy) with a publication date ranging from 1 June 2010 (last search date of the reference guideline) to 23 October 2018; (2) a grey literature search using Google,

followed by a screening of the reference lists included in the identified documents; and (3) a request for information within the IPC Global Unit networks to approximately 100 experts in the field of IPC, infectious diseases, clinical microbiology, clinical pharmacology, surgery and anaesthesiology. 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. Guidelines in English, Dutch, French, German, Italian and Spanish were considered.

Systematic reviews were identified through the same process used to identify guidelines published after the reference guideline, except that no grey literature searches were performed. 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.

Results of the review of SAP guidelines

The systematic search yielded 20 full-text documents for assessment. The grey literature search produced an additional 36 articles and recommendations from experts yielded another 50 documents. After eliminating duplicates and off-topic documents, 50 records were retained for further consideration. Among these, 30 were included as the evidence base (9-11, 17-43) (see Appendix 2a for the study selection flow chart). Nineteen records met all three inclusion criteria (9-11, 17-22, 24, 26-29, 35, 36, 41-43). Ten met the first two criteria, but did not rely on a systematic evidence-based approach (23, 25, 30-34, 37, 38, 40) 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 (39). 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 (Appendix 3) (44-46), 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, 31, 34, 39, 40).

Results of the review of systematic reviews on SAP

The systematic search yielded 768 potentially relevant records published since June 2010. After screening titles and abstracts, 101 full-text articles were assessed for eligibility and 17 relevant systematic reviews were finally included (47-63) (see Appendix 2b for study selection flow chart). Thirteen systematic reviews compared SAP regimens for specific procedure types including: neurosurgery (47, 48); neck surgery (49, 50); cardiac surgery (51, 52); upper gastrointestinal surgery (53); colorectal surgery (54, 55); caesarean section (56); gynaecological surgery (61); hernia surgery (57); and plastic surgery (62). Three systematic reviews compared specific SAP regimens for several procedure types combined (cardiac-, vascular-, orthopaedic-, and neurosurgery; cardiac-, vascular- and orthopaedic surgery; and cardiac- and orthopaedic surgery) (58, 60, 63). One systematic review specifically addressed SAP for MRSA SSI prevention (59).

In brief, the identified systematic reviews provided evidence that was generally in line with the SAP recommendations of the reference guideline (10). The included reviews covered the following topics:

Neurosurgery – A 2014 systematic review identified five RCTs comparing third-generation cephalosporins to other regimens and found no difference in the SSI risk between the two regimens (odds ratio [OR] 0.94 [95% confidence interval (CI) 0.59–1.52])(47). A 2017 systematic review specifically on cranial surgery identified one RCT included in the 2014 systematic review and also found no difference in the SSI risk between third-generation cephalosporins and the other two regimens (OR 0.96 [95% CI 0.06-15.36]) (48).

Neck surgery – A 2013 systematic review on SAP regimens for ear, nose and throat cancer surgery provided a narrative description of the evidence concluding that ampicillin-sulbactam or clindamycin with gentamicin should be the preferred regimens (49). A 2015

systematic review on laryngeal surgery provided a narrative description of the evidence concluding that the first-choice regimen should be cefazolin with metronidazole in the case of expected anaerobe contamination (50).

Cardiac surgery – A 2012 systematic review on SAP in cardiac surgery identified 36 RCTs comparing the addition of Gram-negative to Gram-positive coverage *vs*. mainly Gram-positive coverage and found no difference in the SSI risk (relative risk [RR] 0.98 [95% CI 0.85-1.13]). Another 10 RCTs compared glycopeptides *vs*. beta-lactams and also found no difference in the SSI risk (RR 1.05 [0.90-1.22]). Finally, eight RCTs compared cephalosporins *vs.* penicillin-based prophylaxis and found no difference in the SSI risk (RR 0.86 [95% CI 0.70-1.06] (51). A 2018 broad systematic review on the prevention of sternal wound infection identified one RCT that compared cefazolin with a combination of cefazolin and gentamicin and observed no difference in the SSI risk. No quantitative data were provided (52).

Upper gastrointestinal surgery – A 2014 systematic review on the prevention of SSI in bariatric surgery found one RCT comparing cefazolin to placebo that was stopped early due to a high risk of infection in the placebo group (1/27=4% [cefazolin] *vs* 5/23=21% [placebo]) (53).

Colorectal surgery – A 2014 systematic review on all aspects of SAP provided three head-to-head comparisons: anaerobic coverage with additional aerobic coverage *vs*. mainly anaerobic coverage alone (for example, metronidazole with cefuroxime *vs.* metronidazole alone); aerobic coverage with additional anaerobic coverage *vs*. mainly aerobic coverage alone (for example, cefotaxime with metronidazole *vs*. cefotaxime alone); and aerobic *vs.* anaerobic coverage alone (for example. cefazolin *vs*. metronidazole). Both the addition of aerobic coverage to mainly anaerobic coverage and the addition of anaerobic coverage to mainly aerobic coverage demonstrated a large decrease in the SSI risk (RR 0.44 [95% CI 0.29-0.68]; RR 0.46 [95% CI 0.30-0.69]). When aerobic coverage alone was compared to anaerobic coverage alone, no clear difference was detected (RR 0.84 [95% CI 0.30-2.36]) (54). A 2015 systematic review with a specific focus on the prevention of postoperative infections in the paediatric population provided a narrative description of the evidence concluding that cefazolin combined with metronidazole was the recommended first-line regimen for children, whereas metronidazole with ciprofloxacin was the alternative indicated in the case of a documented or suspected allergy to penicillins and cephalosporins (55).

Caesarean section – A broader systematic review on evidence-based surgery for caesarean section identified three RCTs comparing antibiotic regimens. None of the investigated regimens (ampicillin/sulbactam; a three-agent regimen comprised of ampicillin, gentamicin and metronidazole; penicillin and cephalothin) demonstrated improved outcomes compared with standard cephalosporin prophylaxis. No quantitative data were provided (56).

Hernia surgery – A 2017 network meta-analysis included first- (seven RCTs) and second-generation cephalosporins (two RCTs), beta-lactam/beta-lactamase inhibitors (six RCTs) and fluoroquinolones (two RCTs) with placebo as the most common comparator. The authors found that beta-lactam/beta-lactamase inhibitors and first-generation cephalosporins were both significantly superior to placebo (RR 0.44 [95% CI 0.25-0.75]; RR 0.62 [95%CI 0.42-0.92]), but none of the antibiotic regimens was significantly different from the others in terms of the SSI risk (57).

Combinations of procedures – A 2010 systematic review including cardiac, vascular, orthopaedic and neurosurgery trials compared glycopeptides to beta-lactams and found no significant difference in the SSI risk between the two regimens (RR 1.04 [95% CI 0.30-3.58]) (63). A 2015 systematic review limited to cardiovascular and orthopaedic surgery also found no difference in the SSI risk between these two regimens (RR 0.87 [95%CI 0.63-1.18]), although they did find a reduction in the risk of SSIs due to MRSA (RR 0.52 [95% CI 0.29-0.93]) and enterococci (RR 0.36 [95% CI 0.17-0.80]) in the glycopeptide group (58). A 2013 systematic review specifically on the prevention of SSI due to MRSA included a variety of regimens but concluded that no meta-analysis was possible due to data heterogeneity (59). A 2015 systematic review compared gentamicin/flucloxacillin *vs*. cefuroxime in cardiac and orthopaedic surgery and found no difference in the SSI risk between the two regimens (OR 0.86 [95% CI 0.63-1.20]) (60).

Gynaecological procedures – A 2013 systematic review on SAP regimens in benign gynaecological surgery other than hysterectomy provided a narrative description of 19 RCTs across six procedures and concluded that SAP may be beneficial in first-trimester suction curettage and laparotomy. No advantage was found for loop electrosurgical excision, hysteroscopy or laparoscopic gynaecological surgery. Newer procedures and vaginal surgery lack research and merit further study (61).

Plastic surgery – A 2015 systematic review on infection prevention in facelift surgery provided a narrative description of the evidence and concluded that the US surgical care improvement project (SCIP) guidelines for clean surgery, which recommend cefazolin as the first-line antibiotic, should apply also to cosmetic surgery (62).

Limitations

This systematic review (of systematic reviews) was conducted solely to identify potentially important new evidence published beyond the considered guidelines. We have objectively reported the findings from systematic reviews performed by others, with no appraisal of their quality. As recognized by the authors in some cases, these systematic reviews have limitations due to heterogeneity of antibiotic classes and doses, patient age, surgical procedures and variations in the local ecology and patient categories. For these reasons, the results collated from these reviews in the summary above are not necessarily meant to be considered as acceptable SAP regimens.

Technical expert group

The WHO IPC Global Unit convened a technical expert meeting to review the retrieved evidence and identify the antibiotics of choice for SAP to be included in the WHO EML. Experts were identified based on their specific expertise on the topic and their experience in surgery, infectious diseases and IPC in a wide range of settings, including in LMICs (see Appendix 4 for the list of participants).

The aims of the meeting were to: (1) discuss the criteria for the selection of the antibiotics of choice for SAP; (2) agree on specific antibiotics according to a list of surgical procedures; and (3) provide key considerations regarding critical issues related to SAP dosing, re-dosing, timing, discontinuation, AMR and implications for LMICs.

2. Guiding principles to identify antibiotics of choice for SAP to be included in the EML

The experts appraised the existing WHO recommendations on SAP included in the 2016 WHO *Global guidelines on the prevention of SSI* (9) and in the 2015 WHO *Recommendations for prevention and treatment of maternal peripartum infections* (43) (Box 1).

Box 1

WHO recommendation on optimal timing for preoperative surgical antibiotic prophylaxis (strong):

- Administer SAP prior to the surgical incision when indicated (depending on the type of operation) within 120 minutes before incision, while considering the half-life of the antibiotic.

WHO recommendation on SAP prolongation (strong):

- Do **not** prolong surgical antibiotic prophylaxis after completion of the operation.

WHO recommendations on SAP for caesarean section:

- Routine antibiotic prophylaxis is recommended for women undergoing elective or emergency caesarean section (**strong)**.
- For caesarean section, prophylactic antibiotics should be given prior to skin incision, rather than intraoperatively after umbilical cord clamping **(strong).**
- For antibiotic prophylaxis for caesarean section, a single dose of first-generation cephalosporin or penicillin should be used in preference to other classes of antibiotics **(conditional)**.

The experts agreed that the following factors need to be considered for appropriate SAP (Box 2). Cost and availability of antibiotics were discussed as additional considerations to improve access but not as selection criteria.

Box 2

1. **Antibiotic**
   - According to the surgical procedure, including considerations about reported or probable microorganisms involved and their local antibiotic resistance patterns
   - Route of administration
   - Dosing
   - Consideration of patient allergies
2. **Timing:** for SAP start and re-dosing prior to wound closure
3. **Duration**

Together with the WHO secretariat, the experts decided that the main goal of the SAP section in the EML document should be to indicate the list of specific antibiotics of choice according to a list of surgical procedures and that additional generic considerations on the other identified factors (Box 2) should be included.

The experts appreciated the extensive and thorough evidence review presented by WHO and agreed to consider in particular two guidelines as the reference for the discussion as they were comprehensive, evidence-based and/or recent (*Clinical practice guidelines for antimicrobial prophylaxis in surgery* by IDSA, ASHP, SIS and SHEA, and the *Australian guidelines on surgical antibiotic prophylaxis* produced by Therapeutic Guidelines Ltd., an independent not-for-profit organization) (10, 11). These two guidelines were also presented in more detail by experts attending the meeting who participated in their development.

The experts discussed the identification of the surgical procedure classification to be used for developing recommendations on SAP agents for inclusion in the EML.
The following lists of surgical procedures were considered:

- the operative procedure categories used by the US Centers for Disease Control and Prevention National Healthcare Safety Network (NHSN) (46);
- the NHSN shorter list of principal operative procedures;
- the list of 20 procedures used in a WHO survey on SAP conducted in 2014, based on a combination of the NHSN list (46, 64), the Scottish Intercollegiate Guidance Network guidelines (42) and the *Clinical practice guidelines for antimicrobial prophylaxis in surgery* (IDSA, ASHP, SIS, and SHEA) (10);
- the list included in the evidence-based *Clinical practice guidelines for antimicrobial prophylaxis in surgery* (IDSA, ASHP, SIS, and SHEA) (10);
- a priority surgical procedures' list developed by the Guidelines Development Group (GDG) that produced the WHO SSI prevention guidelines.

Participants agreed that the NHSN lists were not suitable because they were developed for SSI surveillance purposes. In addition, they are too detailed and some of the included procedures do not require any antibiotics. After discussion, a consensus emerged that the list developed by the WHO GDG, which includes surgical procedures requiring SAP that are commonly encountered globally, was the most appropriate starting point as it had already been thoroughly discussed and was found acceptable by stakeholders. In response to concerns that the list was incomplete and not presented in a user-friendly manner, the group agreed to supplement it with additional procedures and re-order the content according to anatomical considerations. The final agreed list of surgical procedures is shown in Box 3. Participants also emphasized the fact that a procedure is not on the list does not necessarily mean that SAP is not indicated as the purpose of the list is to cover only the most frequently-encountered surgical procedures worldwide, including in LMICs.

Box 3

- Neck surgery
  - Clean
  - Clean-contaminated
- Cardiac surgery (involving sternotomy or valve insertion)
- Thoracic surgery (non-cardiac)

- Breast surgery
- Upper gastrointestinal tract surgery (for example, surgery of the oesophagus and stomach)
- Hepato-pancreato-biliary surgery
- Cholecystectomy
- Hernia surgery
- Appendectomy
- Colorectal surgery
- Hysterectomy
- Caesarian section
- Central vascular surgery
- Peripheral vascular surgery
- Orthopaedic surgery (excluding arthroscopy)
- Bone fracture surgery
- Urologic surgery
    - Prostate surgery
    - Nephrectomy
- Neurosurgery
    - Cranium
    - Spine

In addition, the experts also advised using the surgical wound classification (Appendix 3) when selecting SAP regimens for different procedures (46).

For each procedure considered, one or two first-line recommended antibiotics, were identified, as well as a second-line antibiotic to be used in cases of known immediate severe or delayed severe penicillin hypersensitivity. First-line and second-line antibiotics can either be single agents or a combination of agents depending on the surgical procedure/situation. Within the first-line, the *first-choice* antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents with positive benefit–risk ratios and a low resistance potential. *Second-choice* (alternative choice) antibiotics are generally more broad-spectrum agents with a less favourable benefit–risk ratio and a higher resistance potential. These are intended for situations where the primary option is unavailable. *Second-choice* antibiotics have safety and similar efficacy profiles as the primary option and can be considered reasonable alternatives. Second-line antibiotics to be used in case of allergy are non–beta-lactam agents for patients with immediate severe or delayed severe penicillin hypersensitivity. These are more broad-spectrum agents, usually with a less favourable benefit–risk ratio and a higher resistance potential than first-line antibiotics. It is important to distinguish between immediate non-severe or delayed non-severe penicillin hypersensitivity, which usually does not involve cross-reactions between penicillins and cephalosporins (specifically cefazolin), and severe reactions to beta-lactams or true cephalosporin allergy. In the former, certain first-choice agents are often tolerated and can be given for SAP.

For each procedure considered, the experts identified one or two first-line antibiotics, as well as one or two second-line antibiotics to be used in cases of known allergies. During the discussion, the recommendations and antibiotic indications made in evidence-based

guidelines were cross-checked to ensure consistency as much as possible. The table below represents the final outcome of these discussions and decisions.

Table. First- and second-line antibiotics recommended for SAP according to the surgical procedure

PROCEDURE	**First-line**		**Second-line** (if proven/severe allergy to penicillins and/or cephalosporins)
	First-choice	**Second-choice = alternative**	
Neck surgery - Clean - Clean-contaminated	no SAP Cefazolin (or cefuroxime) plus metronidazole	no SAP Amoxicillin/ clavulanic acid	Clean: no SAP Clean-contaminated: clindamycin + gentamicin
Cardiac surgery in general	Cefazolin (or cefuroxime)	NA	Vancomycin
Thoracic surgery (non-cardiac)	Cefazolin (or cefuroxime)	NA	Vancomycin
Breast surgery	Cefazolin (or cefuroxime)	NA	Vancomycin
Upper gastrointestinal tract surgery	Cefazolin (or cefuroxime)	NA	Clindamycin + gentamicin
Hepato-pancreato-biliary surgery + Cholecystectomy*	Cefazolin (or cefuroxime)	Amoxicillin/ clavulanic acid	Gentamicin + metronidazole
Hernia surgery	Cefazolin (or cefuroxime)	NA	Vancomycin
Appendectomy	Cefazolin (or cefuroxime) and metronidazole	NA	Gentamicin + metronidazole
Colorectal surgery	Cefazolin (or cefuroxime) and metronidazole	Amoxicillin/ clavulanic acid	Gentamicin + metronidazole
Hysterectomy	Cefazolin (or cefuroxime)	Amoxicillin/ clavulanic acid	Clindamycin + gentamicin
Caesarean section	Cefazolin (or cefuroxime)	Amoxicillin/ clavulanic acid	Clindamycin + gentamicin
Central vascular surgery	Cefazolin (or cefuroxime)	NA	Vancomycin

Peripheral vascular surgery	Cefazolin (or cefuroxime)	NA	Vancomycin
Orthopaedic surgery (excluding arthroscopy)	Cefazolin (or cefuroxime)	NA	Vancomycin
Bone fracture surgery	Cefazolin (or cefuroxime)	NA	Vancomycin
Urologic - Prostate surgery - Nephrectomy	Cefazolin (or cefuroxime) Laparoscopic nephrectomy: no SAP Laparotomy nephrectomy and partial nephrectomy: cefazolin (or cefuroxime)	Gentamicin	Gentamicin Laparotomy nephrectomy and partial nephrectomy: gentamicin
Neurosurgery - Cranium/spine	Cefazolin (or cefuroxime)	NA	Vancomycin

*Biliary tract open surgery or endoscopic in high-risk patients: factors that indicate a high risk of infectious complications in laparoscopic cholecystectomy include emergency procedures; diabetes; long procedure duration; intraoperative gallbladder rupture; age >70 years; conversion from laparoscopic to open cholecystectomy;, American Society of Anesthesiologists classification of 3 or greater; episode of colic within 30 days before the procedure; re-intervention of less than one month for a non-infectious complication; acute cholecystitis; bile spillage; jaundice; pregnancy; non-functioning gallbladder; immunosuppression; and insertion of a prosthetic device. As a number of these risk factors are not possible to determine before the surgical intervention, it may be reasonable to give a single dose of antimicrobial prophylaxis to all patients undergoing laparoscopic cholecystectomy (10).
NA, not applicable

Rationale for antibiotic selection and key considerations

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.

Cefazolin is a beta-lactam antibiotic that shares no common side-chains with other beta-lactams and it is often tolerated in patients with a penicillin or cephalosporin hypersensitivity, that is, it can be used for patients with immediate non-severe or delayed non-severe penicillin hypersensitivity, provided that such a diagnosis is made appropriately (65). In most cases, other parenteral cephalosporins (for example, cefuroxime) may also be used for patients with immediate non-severe or delayed non-severe penicillin hypersensitivity. Ideally, second-line antibiotics should only be used in rare cases of a documented severe cephalosporin allergy. For patients with confirmed immediate severe or delayed severe penicillin hypersensitivity, a non–beta-lactam antibiotic must be used

instead. Experts emphasized that the second-line antibiotics listed are suboptimal and should only be used in cases of known or highly suspected allergies. However, they noted that the appropriate documentation of allergies prior to surgery is not common practice in all settings, particularly in LMICs, and should be improved.

It was agreed that there is no good reason to use ceftriaxone for SAP as it belongs to the antibiotic categories listed in the WHO *Access* and *Watch* groups (66). In addition, it is included in the WHO highest-priority, critically important antimicrobials (CIA) list (67) 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 *Access* and *Watch* lists (66) and are among the highest-priority antimicrobials in the CIA list (67), 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 USA 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 (68). 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 one high-income country. It will be important to monitor further developments in this area. If 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.

As mentioned above (Box 3), the experts agreed 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.

Regarding the recommended timing for administering SAP (that is, within 120 minutes before incision, according to the WHO *Global guidelines for the prevention of SSI* (9) (Box 1) , the experts remarked 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, cefoxitin and penicillins in general. In particular, anaesthesiologists suggested that SAP should be administered in the operating room before anaesthesia induction as an effective mechanism for timely delivery. However, they noted that there are insufficient data currently to establish a more precise window. In settings where surgery is often delayed, patients with contaminated wounds might benefit from receiving antibiotic administration as soon as it is available.

The group identified the following key considerations for dosing and re-dosing:

- 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.

A comprehensive literature review of pharmacokinetics and pharmacodynamics should be conducted in order to inform the development of future guidance documents. In addition, further research on weight-based dosing is needed, in particular to establish whether weight or body mass index is the best parameter to use.

The experts discussed AMR implications for SAP. First, they underlined that SAP was never intended to cover all potential pathogens with intrinsic or acquired resistance. Second, it was also emphasized that local SAP protocols should not be based upon AMR data derived from surveillance of all clinical samples (including blood cultures), but rather on AMR patterns of microorganisms causing SSIs.

Screening for *S. aureus* and identification of carriers is particularly important before cardio-thoracic surgery and any kind of hardware implantation, such as in orthopaedic or head/spine surgery. For patients who are carriers of *S. aureus*, WHO recommends pre-operative treatment with nasal mupirocin ointment (strong recommendation for patients undergoing cardio-thoracic surgery and a conditional recommendation for all other surgical procedures) (9). Regarding SAP for cardiac, thoracic, orthopaedic and spinal procedures, the group recommended that vancomycin should be used (±cefazolin) in known MRSA carriers. It was noted that many North American hospitals recommend the use of both vancomycin and cefazolin, even for patients who are at risk of MRSA, but who have not been screened. However, there is insufficient evidence to support recommending this practice in global guidelines. Further research on the combination of vancomycin and cefazolin for SAP is needed. The group raised a note of caution that vancomycin should not be used as primary SAP, based on a lack of reliable data on carriage, or in settings with a high MRSA prevalence. These considerations were based on the suboptimal pharmacokinetic/pharmacodynamic properties of vancomycin as a prophylactic agent and on the worse coverage of methicillin-sensitive *S. aureus* (69).

The group noted that the WHO guidelines do not contain sufficient evidence for suggesting alternative antibiotic choices for SAP in ESBL-colonized surgical patients. Similarly, the WHO

SSI prevention guidelines GDG decided not to formulate a recommendation regarding screening for ESBL colonization and its impact on antibiotic prophylaxis due to a lack of available evidence (9). More recent evidence suggests that ESBL colonization increases the risk of SSIs after colorectal surgery and that ertapenem usage may reduce the risk compared to cefazolin plus metronidazole (70). However, the evidence is not sufficiently strong to recommend a change in SAP procedures on a general level for ESBL-colonized patients. The group further noted that universal or targeted ESBL screening prior to colon surgery remains an unresolved issue that warrants further studies, including health economic evaluations.

Special considerations for settings with limited resources

The experts agreed that the following points should be recommended for the improvement of SAP in settings with limited resources:

- governments and national drug approval agencies should ensure access to agents included in the EML for standard SAP; this is aligned with the principle of achieving a global standard for universal health coverage;
- the cost of SAP should not be an out-of-pocket expense for patients;
- governments should include antibiotics of choice for SAP within the national EML; parallel procurement paths for antibiotics should be blocked;
- consideration should be given to the adoption of global regulations on drug availability and access;
- advocacy actions are needed, including the involvement of national drug approval agencies and pharmaceutical companies.

The experts recommended that SAP theory and practice guidance should be provided as part of all health care professional training. In addition, SSI surveillance and reporting, with an emphasis on appropriate SAP, should be included as part of the local IPC strategy. Consideration should be given to adopting surgical unit-based safety programmes as a front-line strategy and to linking good SAP practices to safe surgery checklists (71).

The group emphasized the need for tools to enable the rapid assessment of cephalosporin and penicillin allergies in low-resource settings. As most of the labelled cephalosporin and penicillin allergies are not confirmed, the risk of inappropriately choosing the second-line antibiotics is high (72-75). The development of a low-cost allergy test kit for cefazolin should be considered a high research priority.

The experts cautioned against the overuse of SAP in procedures where there is no need of SAP, as well as its prolonged administration in the postoperative period, to overcome the insufficient implementation of other measures for preventing SSI, which often happens in LMICs. It was emphasized that it would be preferable to devote resources to improving IPC, rather than relying on antibiotics when they are not indicated.

The group recommended that implementation tools be evaluated for their suitability in low-resource settings. Tools should be language-specific and developed with the support of local surgical, anaesthesia, obstetric and nursing groups. In addition, qualitative studies should be conducted on attitudes about antibiotics. Finally, the group emphasized the need for additional data on AMR in LMICs, including population point and facility-based prevalence

surveys of carriage and SSI caused by MRSA, ESBL and carbapenem-resistant microorganisms.

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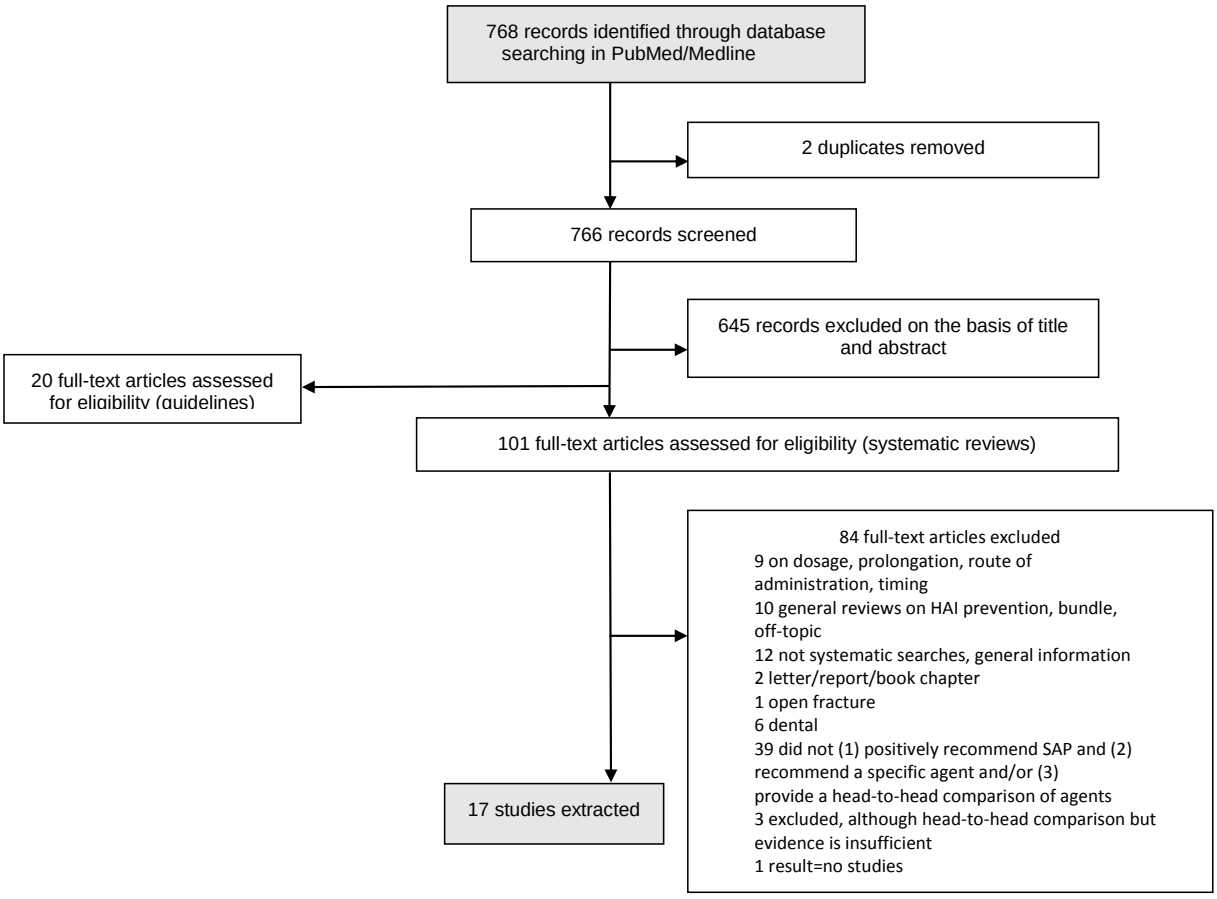
Appendix 1. Systematic review search strategy

23-10-2018, PubMed (Medline)		
1	Outcome	("Surgical Wound Infection"[Mesh] OR surgical site infection*[tiab] OR SSI[tiab] OR SSIs[tiab] OR surgical wound infection*[tiab] OR surgical infection*[tiab] OR post-operative wound infection*[tiab] OR postoperative wound infection*[tiab])
2	Intervention	("Antibiotic Prophylaxis"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR "Cefuroxime"[Mesh] OR "Metronidazole"[Mesh] OR "Cefazolin"[Mesh] OR "Levofloxacin"[Mesh] OR "Clindamycin"[Mesh] OR "Vancomycin"[Mesh] OR "Ciprofloxacin"[Mesh] OR "Ampicillin"[Mesh] OR "Aztreonam"[Mesh] OR "Cefotaxime"[Mesh] OR "Cefoxitin"[Mesh] OR "Cefotetan"[Mesh] OR "Ceftriaxone"[Mesh] OR "ertapenem" [Supplementary Concept] OR "Fluconazole"[Mesh] OR "Gentamicins"[Mesh] OR "moxifloxacin" [Supplementary Concept] OR "piperacillin, tazobactam drug combination" [Supplementary Concept] OR "sultamicillin" [Supplementary Concept] OR "Sulbactam"[Mesh] OR "Erythromycin"[Mesh] OR "Neomycin"[Mesh] OR antibacterial agent*[tiab] OR anti-bacterial agent*[tiab] OR antibacterial compound*[tiab] OR anti-bacterial compound*[tiab] OR antimicrobial[tiab] OR anti-microbial[tiab] OR antibiotic*[tiab] OR antiinfective agent*[tiab] OR anti-infective agent* [tiab] OR microbicides[tiab] OR bacteriocidal agent*[tiab] OR bacteriocides[tiab] OR antimycobacterial agent*[tiab] OR anti-mycobacterial agent*[tiab] OR cefuroxime[tiab] OR cephuroxime[tiab] OR metronidazole[tiab] OR cefazolin[tiab] OR cephazolin[tiab] OR cephazolin[tiab] OR levofloxacin[tiab] OR clindamycin[tiab] OR vancomycin [tiab] OR ciprofloxacin [tiab] OR ampicillin[tiab] OR aztreonam[tiab] OR cefotaxime[tiab] OR cefoxitin[tiab] OR cefotetan[tiab] OR ceftriaxone[tiab] OR ertapenem[tiab] OR fluconazole[tiab] OR gentamicin*[tiab] OR gentamycin*[tiab] OR garamycin*[tiab] OR garamicin*[tiab] OR gentacycol[tiab] OR moxifloxacin [tiab] OR piperacillin-tazobactam[tiab] OR ampicillin-sulbactam[tiab] OR sultamicillin*[tiab] OR erythromycin*[tiab] OR neomycin*[tiab])
3	Filter 1/2, Systematic reviews & Guidelines	(systematic[sb] OR "Meta-Analysis" [Publication Type] OR "Guideline" [Publication Type] OR "Practice Guideline" [Publication Type] OR systematic review*[tiab] OR metaanaly*[tiab] OR meta-analy*[tiab] OR guideline*[tiab]) NOT ("Letter" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Case Reports" [Publication Type] OR letter[ti] OR comment[ti] OR case report*[ti] OR editorial[tiab])
4	Filter 2/2, Publication date	("2010/06/01"[Date - Publication] : "3000"[Date - Publication])
5	#1 AND #2 AND #3 AND	("Surgical Wound Infection"[Mesh] OR surgical site infection*[tiab] OR SSI[tiab] OR SSIs[tiab] OR surgical wound infection*[tiab] OR surgical

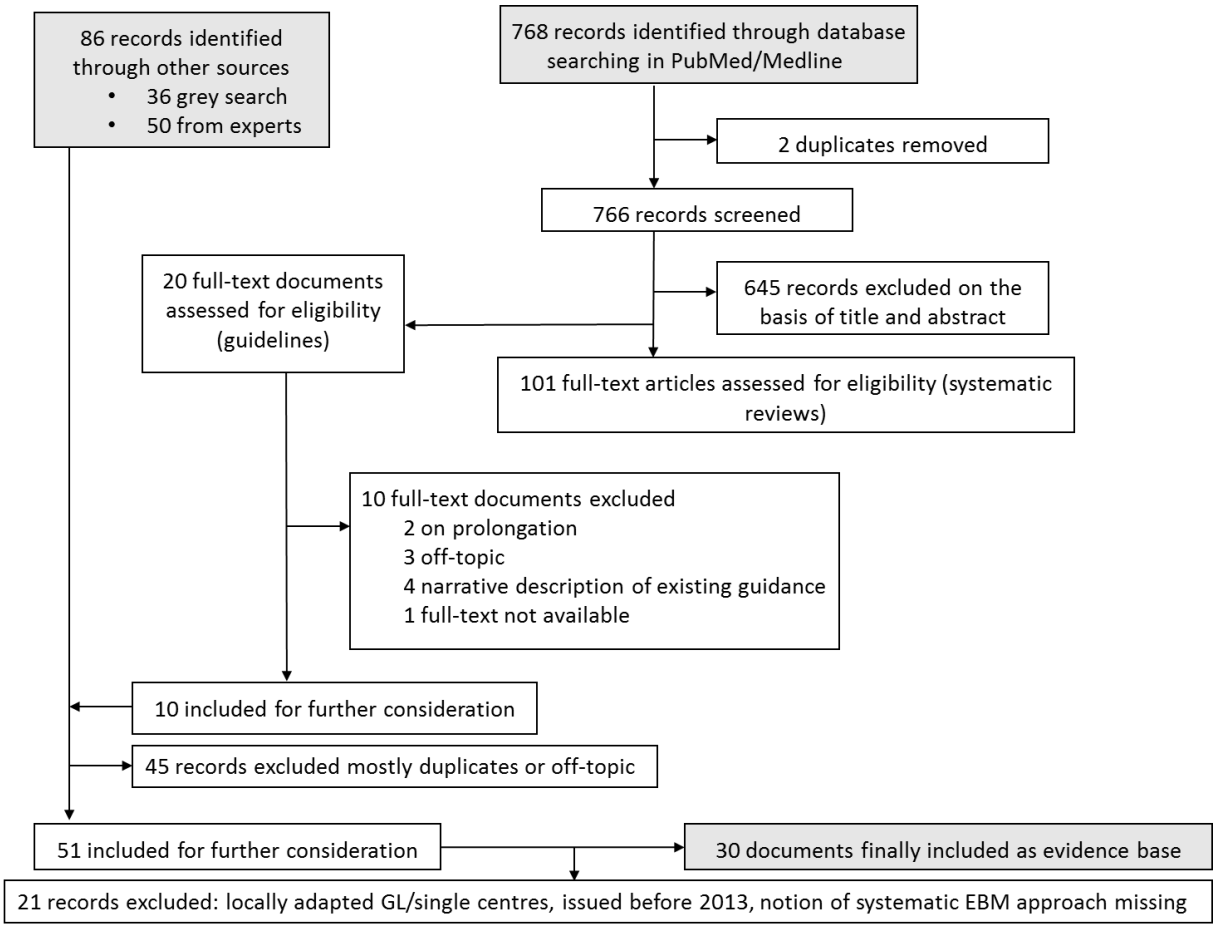
	#4	infection*[tiab] OR post-operative wound infection*[tiab] OR postoperative wound infection*[tiab]) AND ("Antibiotic Prophylaxis"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR "Cefuroxime"[Mesh] OR "Metronidazole"[Mesh] OR "Cefazolin"[Mesh] OR "Levofloxacin"[Mesh] OR "Clindamycin"[Mesh] OR "Vancomycin"[Mesh] OR "Ciprofloxacin"[Mesh] OR "Ampicillin"[Mesh] OR "Aztreonam"[Mesh] OR "Cefotaxime"[Mesh] OR "Cefoxitin"[Mesh] OR "Cefotetan"[Mesh] OR "Ceftriaxone"[Mesh] OR "ertapenem" [Supplementary Concept] OR "Fluconazole"[Mesh] OR "Gentamicins"[Mesh] OR "moxifloxacin" [Supplementary Concept] OR "piperacillin, tazobactam drug combination" [Supplementary Concept] OR "sultamicillin" [Supplementary Concept] OR "Sulbactam"[Mesh] OR "Erythromycin"[Mesh] OR "Neomycin"[Mesh] OR antibacterial agent*[tiab] OR anti-bacterial agent*[tiab] OR antibacterial compound*[tiab] OR anti-bacterial compound*[tiab] OR antimicrobial[tiab] OR anti-microbial[tiab] OR antibiotic*[tiab] OR antiinfective agent*[tiab] OR anti-infective agent* [tiab] OR microbicides[tiab] OR bacteriocidal agent*[tiab] OR bacteriocides[tiab] OR antimycobacterial agent*[tiab] OR anti-mycobacterial agent*[tiab] OR cefuroxime[tiab] OR cephuroxime[tiab] OR metronidazole[tiab] OR cefazolin[tiab] OR cephazolin[tiab] OR cephazolin[tiab] OR levofloxacin[tiab] OR clindamycin[tiab] OR vancomycin [tiab] OR ciprofloxacin [tiab] OR ampicillin[tiab] OR aztreonam[tiab] OR cefotaxime[tiab] OR cefoxitin[tiab] OR cefotetan[tiab] OR ceftriaxone[tiab] OR ertapenem[tiab] OR fluconazole[tiab] OR gentamicin*[tiab] OR gentamycin*[tiab] OR garamycin*[tiab] OR garamicin*[tiab] OR gentacycol[tiab] OR moxifloxacin [tiab] OR piperacillin-tazobactam[tiab] OR ampicillin-sulbactam[tiab] OR sultamicillin*[tiab] OR erythromycin*[tiab] OR neomycin*[tiab]) AND (systematic[sb] OR "Meta-Analysis" [Publication Type] OR "Guideline" [Publication Type] OR "Practice Guideline" [Publication Type] OR systematic review*[tiab] OR metaanaly*[tiab] OR meta-analy*[tiab] OR guideline*[tiab]) NOT ("Letter" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Case Reports" [Publication Type] OR letter[ti] OR comment[ti] OR case report*[ti] OR editorial[tiab]) AND ("2010/06/01"[Date - Publication] : "3000"[Date - Publication])

Appendix 2a: Study selection flow chart – systematic reviews



SAP, standard antibiotic prophylaxis; HAI, health care-associated infection

Appendix 2b. Study selection flow chart – guidelines



GL, guideline/s; EBM, evidence-based medicine.

Appendix 3. Surgical wound classification

Surgical wounds are divided into four classes (46).

1. Clean
refers to an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.

2. Clean-contaminated
refers to operative wounds in which the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

3. Contaminated
refers to open, fresh accidental wounds. In addition, operations with major breaks in sterile technique (for example, open cardiac massage) or gross spillage from the gastrointestinal tract and incisions in which acute, non-purulent inflammation is encountered, including necrotic tissue without evidence of purulent drainage (for example, dry gangrene), are included in this category.

4. Dirty or infected
includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Appendix 4
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