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Surgical antibiotic prophylaxis: Are you doing it right?

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Surgical site infection (SSI) places an enormous burden of disease on perioperative healthcare services. Its prevalence as a hospital-acquired infection (HAI) is second only to urinary tract infections.[1] The consequences in the short term include a protracted hospital stay, significantly increased healthcare costs and a higher mortality rate in certain types of surgery.[2] Patients who develop an SSI have a five-fold increase in hospital readmissions, are 60% more likely to be admitted to ICU and are twice as likely to die.[3] SSI incidence rates have thus become an important outcome measure of the quality of surgical care.[2]

Surgical antibiotic prophylaxis (SAP) is one component of broader strategies to prevent SSI. A comprehensive discussion on the prevention of SSI falls beyond the remit of this article which will focus solely on SAP.

Fundamental principles

An ideal agent for SAP should be able to minimise the risk of SSI and thereby the associated morbidity and mortality. It should reduce healthcare costs, have no adverse effects, have minimal effect on the patient's microbial flora and not contribute to selection of antibiotic-resistant microbial strains. On a practical level, the agent must have activity against the pathogens most likely to contaminate the wound, must be given in doses sufficient to achieve adequate tissue levels for the entire period of potential contamination and must be continued for the shortest effective duration.[4]

When is SAP indicated?

Some general rules about antibiotic prophylaxis can be made based on the type of operative wound as described by the Centers for Disease Control and Prevention (CDC)[5]:

CDC classification of operative wounds:
Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or urinary tract is not entered.
Clean-contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.
Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g. open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered.
Dirty: Old traumatic wounds with retained devitalised tissue and those that involve existing infection or perforated viscera. The organisms causing infection were present in the operative field before the operation.

Prophylaxis is indicated in procedures where there is a high associated rate of infection. These are clean-contaminated and contaminated wounds. It may also be indicated in certain clean procedures where the consequences of an SSI are particularly severe. These include procedures in which prosthetic material or implants are used.[4] The use of antibiotics in the presence of a dirty wound is defined as treatment of established infection and is thus not within the domain of prophylaxis.

Despite prophylaxis not being indicated in most clean procedures, there is evidence that the relative risk reduction of SSI from the use of SAP is similar in clean wounds as in clean-contaminated and contaminated procedures.[6] A pertinent question thus arises as to why prophylaxis is not indicated for all procedures regardless of wound type. The decision to use antibiotic prophylaxis is a balance of the cost of treating the SSI and its associated morbidity, with the costs of the prophylaxis and possible adverse effects thereof.

Adverse effects of SAP include drug allergy, anaphylaxis, antibiotic-associated diarrhoea, *Clostridium difficile* infection and antibiotic resistance. The contribution of prophylaxis to *C. difficile* infection is not clear, with rates of between 0.2% to 8% in patients who have received SAP, depending on procedure and patient-related factors.[7] Regarding antibiotic resistance, there is some evidence to suggest that use of SAP results in a greater risk of acquiring resistant strains, particularly with extended durations of prophylaxis.[2]

There are very few studies that have addressed the economic impact of SAP.[4] There are, however, suggestions that the cost of inappropriate SAP is significant. An audit in Great Britain and Ireland estimated that 20 000 doses of unnecessary antibiotic

prophylaxis are administered each year in laparoscopic cholecystectomies alone, at an extra cost of more than £100 000.[8] In keeping with the principles of antibiotic stewardship, it is thus necessary to have a rational and evidence-based approach to prophylaxis in surgery.[4]

SAP may however, be administered in procedures that don't typically require prophylaxis if there are other patient-related factors that predispose to a higher risk of SSI. These include poor nutritional status, obesity, diabetes, smoking, extremes of age, immune-system compromise, (e.g. corticosteroid therapy, HIV, chemotherapy or systemic illness) long duration of hospitalisation prior to the procedure and colonisation with specific bacterial strains.[4]

Choice of antibiotic

The chosen antibiotic should be active against the common pathogens causing SSI in the specific procedure. SSI in clean wounds is usually due to skin flora including *Staphylococcus aureus* or coagulase-negative staphylococci.[4] Clean-contaminated and contaminated wounds have various other pathogens depending on the flora of the specific mucous membranes involved. The common pathogens at each surgical site are detailed below[4]:

Cardiac: Gram-positives including *S. aureus* and coagulase-negative staphylococci.

Thoracic: Gram-positives predominantly.

Gastroduodenal: Coliforms (E*scherichia coli, Proteus* species, *Klebsiella* species), and Gram-positives (staphylococci, streptococci, enterococci).

Biliary tract: Gram-negatives and Gram-positives: *E. coli, Klebsiella* species, enterococci, streptococci and staphylococci.

Small-intestine: Gram-negatives predominantly.

Colorectal: Anaerobes (*Bacteroides fragilis*) and Enterobacteriaceae (*E. coli*).

Head and neck: *S. aureus*, streptococci (aerobic and anaerobic) and other anaerobes.

Neurosurgery: Gram-positives: *S. aureus* and coagulase negative staphylococci.

Gynaecological: Gram-positives, Gram-negatives and anaerobes.

Urological: *E. coli* and other Gram-negatives.

Over the past two decades, the causative organisms in SSI have shifted in many hospitals around the world and individual institutions must consider local patterns especially regarding resistant organisms such as methicillin-resistant *S. aureus* (MRSA).[4] Antibiotics with as narrow a spectrum as possible are preferred and agents that are used for treatment of infections are preferably avoided in order to minimise the risk of antibiotic resistance.

Cefazolin is used for prophylaxis in most surgical procedures. It has proven efficacy and has been studied extensively. Its spectrum, while relatively narrow, is active against staphylococci, some Gram-negatives and many other bacteria that are likely to contaminate the operative site. Its duration of action is sufficient for most procedures and it is reasonably safe and cheap.[4] Table I lists specific prophylaxis recommendations for a range of commonly performed surgical procedures.

Special patient populations

There is minimal data on antibiotic prophylaxis relating specifically to the paediatric population. SAP recommendations are generally the same as for adults except for the dose.[4]

Patients who are known to be colonised or recently infected with multi-drug resistant pathogens require unique consideration. Whether antibiotic cover needs to be extended to cover these pathogens will depend on the antibiotic sensitivity of the bacteria and the proximity of the probable site of colonisation to the surgical site. For example, in a patient with recent resistant Gram-negative infection, it would be prudent to extend prophylaxis for a gastrointestinal operation but not for a cutaneous procedure. In patients known to be colonised with MRSA, prophylaxis must be extended to cover this organism. Vancomycin should be reserved for these cases.[4] Some authorities recommend a course of eradication therapy in patients with known MRSA carriage prior to major surgery.[2]

Patients who are receiving antibiotics for an infection at a different site may also require some modification of their SAP. If their current antibiotic regimen covers the expected pathogens at the surgical site, administering an extra dose within 60 minutes of incision is acceptable. If this is not the case, the recommended prophylaxis for the procedure should be administered independent of their current antibiotic therapy.[4]

Timing of preoperative dose

The optimal timing of the dose of antibiotic has not been fully elucidated.[2] As the time interval from antibiotic administration to surgical incision starts to exceed 60 minutes, the rates of SSI start to increase.[4] Most guidelines recommend administration of the antibiotic within 60 minutes of skin incision.[2,4,9] Administration times closer to incision may possibly decrease the risk of SSI for certain procedures but the current evidence is weak and not consistent.[2]

Exceptions to this guideline are made for the fluoroquinolones and glycopeptides (e.g. vancomycin) which should be started 120 minutes before skin incision due to the need to administer them as an infusion over one to two hours.[4]

In women undergoing Caesarean section, advice has previously tended towards administering antibiotics after cord clamping, rather than pre-incision, in order to avoid unnecessary exposure of the neonate. Robust meta-analyses now show that pre-incision administration of prophylactic antibiotics reduces maternal infectious morbidity significantly with no evidence of adverse outcome in the neonate.[10,11]

Dose selection

Antibiotics need to be administered in doses that will attain sufficient blood and tissue concentrations for the duration of the

procedure in order to be effective. Pharmacokinetic properties of individual antibiotics as well as patient factors must thus be taken into account.[4]

Dosing of most antibiotics is based on weight in the paediatric population. In adults it is more convenient to use standardised doses. However, in obese patients this may result in sub-optimal tissue concentrations. Clear recommendations on dosing in obesity are not available due to the paucity of data available. It is unclear which weight scalar (actual, ideal or lean body weight) to use in these cases. Theoretically, using ideal body weight for lipophilic drugs such as vancomycin may result in sub-optimal tissue concentrations. Similarly, using total body weight for hydrophilic antibiotics such as gentamicin or cefazolin could possibly result in toxic blood and tissue levels.[4]

A recommendation is to use 1 g of cefazolin for adults weighing under 80 kg and increasing the dose to 2 g for patients over 80 kg and 3 g for patients over 120 kg.[4,12] Some hospitals use a standardised 2 g dose for all patients in order to simplify guidelines.[4] When using gentamicin, it is suggested to use ideal body weight plus 40% of the difference between total and ideal body weight.[4] There is insufficient evidence available for other prophylactic antibiotics to make firm recommendations regarding dosing in the obese population.

In patients with renal and liver dysfunction, antibiotic prophylaxis does not need to be modified when only a single preoperative dose is used.[4]

Recommended doses of commonly used antibiotics for SAP are shown in Table II.

Re-dosing

Administration of further doses of antibiotic will be required if the duration of the procedure is longer than two half-lives of the drug in order to maintain therapeutic tissue concentrations.[2,4] Re-dosing should also be done in cases of more than 1 500 ml blood loss. Patients with renal dysfunction will require consideration of a longer interval till re-dosing.[4]

Route of administration

Antibiotics for prophylaxis should all be administered IV with the exception of ophthalmic surgery where topical administration is the preferred route. Serum antibiotic levels after oral administration depend on the rate of absorption from the gastrointestinal tract which varies between individuals and is therefore not reliable.[2] Oral fluoroquinolones achieve similar serum levels compared to IV administration and some authorities deem oral administration of fluoroquinolones to be acceptable, particularly in urological surgery.[2,13]

There is limited good quality data regarding the use of topical antibiotics outside of ophthalmic surgery. Studies from the early 1980s showed that topical antibiotics are superior to placebo but not to IV antibiotics and provide no further benefit in combination with IV antibiotics. While there is some interest in the use of topical gentamicin in cardiac and colorectal surgery, high quality studies are lacking and as such cannot be recommended.[4]

Use of antibiotic-impregnated bone cement has become common during arthroplasty procedures. Although the evidence looks largely favourable, its use has not been endorsed by all guidelines at this time.[4]

Duration of prophylaxis

There is consistent evidence that prophylaxis for the duration of the procedure only is sufficient. Longer durations of prophylaxis provide no added benefit.[2]

The practice of continuing prophylaxis in cardiothoracic procedures for 48 hours is not supported by evidence and remains controversial.[4] Appropriate prophylaxis in these procedures should be for the duration of the procedure[4] although some guidelines do state that it may be continued for up to 24[12] or 48 hours.[2]

The continuation of antibiotic prophylaxis for 24 hours postoperatively for hip and knee arthroplasty is regarded by many as the gold-standard of care. A recent systematic review, however, found no evidence to support its practice and recommended conducting further large, multicentre randomised controlled trials (RCTs).[14] Nonetheless, the practice is supported by many guidelines.

The risks of prolonged antibiotic prophylaxis are the same as for unnecessary prophylaxis which has been described above. A systematic review[15] of the literature on prophylaxis prolongation identified five studies which reported an increase in adverse events when prophylaxis was extended beyond the duration of surgery. These included *C. difficile* enterocolitis, rashes, hypotension, phlebitis, pruritus and gastrointestinal disturbances. Eighteen other studies reported no increase in adverse events.[15] No meta-analysis was done for adverse events, leaving their significance unknown. There were no studies that assessed the impact of prolonged prophylaxis on antibiotic resistance but intuitively it remains a concern.[15]

Conclusions

SAP is a simple and cost-effective intervention that has the potential to greatly improve perioperative outcomes. Its importance in perioperative care is exemplified by its inclusion in the WHO Surgical Safety Checklist.[16] Understanding the underlying principles helps make its implementation straightforward in the majority of cases. There are many published guidelines on the subject, albeit with some generally minor differences between them. This is mainly because guideline development depends on many local factors, including patient population, availability of antibiotics and local resistance patterns. Where available, it is recommended to consult with your hospital's local guideline.

Table I. Recommended prophylaxis regimens for commonly performed procedures

Operation	Prophylaxis recommendation	Recommended agent	Alternative for beta-lactam allergy
Neurosurgery			
Craniotomy	Recommended	Cefazolin	Clindamycin, vancomycin
CSF shunt	Recommended	Cefazolin	Cindamycin, vancomycin
Spinal surgery	Recommended	Cefazolin	Clindamycin, vancomycin
Facial surgery			
Mandible fracture ORIF	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Replace cefazolin with clindamycin
Clean facial surgery	Not recommended		
Facial plastic surgery	Should be considered	Cefazolin	Clindamycin, vancomycin
Ear nose and throat – benign			
Ear surgery (clean/ clean-contaminated)	Not recommended		
Endoscopic sinus surgery	Not recommended		
Tonsillectomy and adenoidectomy	Not recommended		
Head and neck			
Clean, benign	Not recommended		
Clean, malignant; neck dissection	Should be considered	Cefazolin	Clindamycin, vancomycin
Contaminated/ clean-contaminated	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Replace cefazolin with clindamycin
Thorax			
Breast cancer	Should be considered	Cefazolin	Clindamycin, vancomycin
Breast surgery with implant	Recommended	Cefazolin	Clindamycin, vancomycin
Breast reshaping	Should be considered	Cefazolin	Clindamycin, vancomycin
Open heart surgery	Recommended	Cefazolin	Clindamycin, vancomycin
Lung resection	Recommended	Cefazolin	Clindamycin, vancomycin
Upper GIT surgery			
Oesophageal surgery	Recommended	Cefazolin	Clindamycin, vancomycin
Stomach and duodenal surgery	Recommended	Cefazolin	Clindamycin, vancomycin
Hepatobiliary surgery			
Bile duct surgery	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin + gentamicin
Pancreas surgery	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin + metronidazole
Liver surgery	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin + metronidazole
Laparoscopic cholecystectomy	Not recommended; should be considered if complicated		
Lower GIT			
Appendicectomy	Recommended	Amoxycillin/clavulanate	Clindamycin +- metronidazole
Colorectal	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin + gentamicin/ ciprofloxacin
Abdomen			
Hernia repair (with/without mesh)	Not recommended		
Diagnostic endoscopy	Not recommended		
ERCP	Should be considered	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin + gentamicin
Obstetrics and gynaecology			
Hysterectomy (all)	Recommended	Cefazolin	Clindamycin, vancomycin
Caesarean section	Recommended	Cefazolin	Clindamycin, vancomycin
Evacuation of incomplete miscarriage	Not recommended		

Table I. Recommended prophylaxis regimens for commonly performed procedures

Operation	Prophylaxis recommendation	Recommended agent	Alternative for beta-lactam allergy
Urology			
Endoscopic stone fragmentation	Recommended	Gentamicin	
Transrectal prostate biopsy	Recommended	Ciprofloxacin	
Transurethral prostate resection	Recommended	Ciprofloxacin or gentamicin	
Transurethral bladder tumour resection	Not recommended		
Circumcision	Not recommended		
Limb surgery			
Open fracture	Considered treatment		
Closed fracture	Recommended	Cefazolin	Clindamycin, vancomycin
Arthroplasty	Recommended	Cefazolin	Clindamycin, vancomycin
Orthopaedic surgery without implant	Not recommended		
Lower limb amputation	Recommended	Cefazolin + metronidazole or amoxycillin/clavulanate	Clindamycin, vancomycin
Vascular surgery	Recommended	Cefazolin	Clindamycin, vancomycin

(Adapted from: The Scottish Intercollegiate Guideline Network (SIGN) – Antibiotic Prophylaxis in Surgery[2]; The South Australia Expert Advisory Group on Antimicrobial Resistance (SAAGAR) – Surgical Antibiotic Prophylaxis Guideline[12]; The American Society of Health-systems Pharmacists (ASHP) – Clinical practice guidelines for antimicrobial prophylaxis in surgery[4]; and The Gauteng Provincial Antimicrobial Stewardship Committee – Antibiotic Surgical Prophylaxis.[13])

Table II. Doses and re-dosing intervals for commonly used antibiotics

Antibiotic	Adult dose	Paediatric dose	Re-dosing interval (hours)
Amoxicillin/clavulanate	1.2 g	30 mg/kg of amoxycillin component	4
Cefoxitin	2 g	40 mg/kg	2
Cefazolin	2 g ≥ 80 kg, 3 g ≥ 120 kg	25–30 mg/kg	4
Ciprofloxacin	400 mg	10 mg/kg	NA*
Clindamycin	900 mg ≥ 70 kg 600 mg < 70 kg	10 mg/kg	6
Fluconazole	400 mg	6 mg/kg	NA*
Gentamicin	5 mg/kg	2.5–5 mg/kg	NA*
Levofloxacin	500 mg	10 mg/kg	NA*
Metronidazole	500 mg–1 g	15 mg/kg	NA*
Piperacillin-tazobactam	4.5 g	Infants 2–9 mo: 80 mg/kg of piperacillin component Children > 9 mo 100 mg/kg of piperacillin component	2
Vancomycin	15 mg/kg	15 mg/kg	NA*

*NA – Not applicable due to prolonged half-life of the drug
(Adapted from The American Society of Health-systems Pharmacists (ASHP) – Clinical practice guidelines for antimicrobial prophylaxis in surgery[4] and The Gauteng Provincial Antimicrobial Stewardship Committee – Antibiotic Surgical Prophylaxis.[13])

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