Clinical pharmacology

Antimicrobial prophylaxis in surgery

Infection is the most common complication of surgery. Surgical site infections (SSIs) occur in approximately 3 - 6% of patients and prolong hospitalisation by an average of 7 days, which in the USA has a direct annual cost of 5 - 10 billion dollars.

Prophylactic administration of antibiotics decreases the risk of infections after many surgical procedures and represents an important component of care for the surgical population.

Antibiotics administered before the contamination of previously sterile tissues are deemed prophylactic antibiotics. The goal of therapy is to prevent the development of an infection.

Presumptive antibiotic therapy is administered when an infection is suspected, but not yet proven. The clinical areas where this is employed include acute cholecystitis, open compound fractures and acute appendicitis of less than 24 hours' duration. In these situations, if signs of perforation or infection are absent during surgery, then routine prophylactic rather than presumptive therapy is warranted. However, an operative finding of a gangrenous gallbladder or a perforated appendix is suggestive of an established infection process, and therefore a therapeutic antibiotic regimen is required.

SSIs can be categorised as incisional (i.e. wound infection) or organ/space (e.g. peritoneal cavity). By definition these SSIs must occur within 30 days of surgery; however, if a prosthetic implant is involved, an organ/space infection can be reported up to 1 year from the date of surgery.

Risk factors

These depend on both procedure- and patient-related factors. The risk traditionally has been stratified by surgical procedure in a classification system developed by the National Research Council (NRC) in the USA. The NRC classification system proposes that the risk of an infection depends on the microbiology of the surgical site, presence of a pre-existing infection, likelihood of contaminating previously sterile tissue during surgery, and drains during and after the surgical procedure. A patient's NRC procedure classification is the primary determinant of whether antibiotic prophylaxis is warranted.

Patient risk

Pre-existing infections increase the risk and should be resolved before surgery where possible. Diabetic patients have an increased risk, especially if preoperative glucose exceeds 11 mmol/l. Smoking has been identified as an independent risk factor for infections as nicotine has a deleterious effect on wound healing. The preoperative use of immunosuppressants, including corticosteroids, may increase infection risk. Other factors shown to increase the risk of infection include age, length of preoperative hospital stay and obesity.

Two large epidemiological studies have been published that quantify the infection risk based on specific patient- and procedure-related factors. The Study on the Efficacy of Nosocomial Infection Control (SENIC) assessed more than 100 000 surgery cases to identify and validate risk factors for infection. Abdominal surgery, operations lasting longer than 2 hours, contaminated procedures, and more than three underlying medical conditions, were each associated with an increase in the infection incidence.

The National Nosocomial Infections Surveillance (NNIS) system was an analysis of 84 000 surgical cases. It attempted to simplify the SENIC system by quantifying intrinsic patient risk using the American Society of Anesthesiologists (ASA) preoperative assessment score. An ASA score of ≤ 3 was found to be a strong predictor of the development of an infection.

All hospitals should implement a comprehensive infection control programme to minimise infections. Although antibiotic prophylaxis is most commonly relied upon, other measures also reduce the risk of infection.

Length of hospital stay is associated with increased colonisation and infection with nosocomial bacteria and leads to a higher incidence of infection. Surgery should be postponed if a patient is hospitalised for an unrelated medical problem. Shaving the incision site with a razor the day before surgery is associated with a higher infection rate; therefore, the site should instead be clipped just before surgery. Preoperative showering with chlorhexidine soap, while reducing bacteria colony counts, has not been shown to reduce infection risk.

Bacteriology

The organisms involved in SSIs are acquired either endogenously or exogenously (from contamination during the surgical procedure). For the majority of SSIs the source of the pathogen is the endogenous flora from skin/mucous membrane/hollow viscera. The commonest organisms involved are Gram-positive cocci, notably *Staphylococcus aureus*. Based on this knowledge and the risk of SSI the appropriate antibiotic choices should be made.

S. aureus, coagulase negative staphylococci, enterococci, *Escherichia coli* and *Pseudomonas aeruginosa* are the pathogens most commonly isolated. With the widespread use of broad-spectrum antibiotics, however, *Candida* spp. and methicillin-resistant *S. aureus* are becoming more prevalent.

Factors that affect the ability of an organism to induce SSI depend on organism load, virulence and host immune competency. Opportunistic organisms are usually kept in 'check' by normal flora and are rarely problematic unless they are found in large numbers. Loss of these protective flora, through the use of broad-spectrum antibiotics, may allow pathogenic bacteria to proliferate and infection to occur. If normal flora are transferred to a normally sterile tissue or site during a surgical procedure, they can become pathogenic. For example, *S. aureus* or *S. epidermidis* may be transferred from the skin surface to deeper tissue or *E. coli* from the colon to the peritoneal cavity, bloodstream, or urinary tract.

Impaired host defence reduces the number of bacteria needed to establish an infection. A breach of normal host defence through a surgical intervention may potentiate the ability of organisms to cause infection. The loss of specific immune factors, e.g. complement activation, cell-mediated response and phagocytic function, can greatly increase the risk of SSI development. Hypovolaemia can affect blood flow to the surgical site, thus diminishing host defence mechanisms against microbial invasion.

Table I. Prophylactic antibiotics for various surgical procedures

Type of surgery	Consensus position
Abdominal or vaginal hysterectomy	Cefazolin or cefoxitin. Metronidazole monotherapy is also used. If the patient has a (-lactam allergy, use clindamycin combined withgen tamicin
Hip or knee arthroplasty	Cefazolin If the patient has a (-lactam allergy use vancomycin or clindamycin
Cardiothoracic and vascular surgery	Cefazolin If the patient has a (-lactam allergy, use vancomycin or clindamycin
Colon surgery	Use cefoxitin, or cefazolin plus metronidazole If the patient has a (-lactam allergy, use clindamycin combined with gentamicin

Adapted from: Bratzler DW, *et al. Clin Infect Dis* 2004; 38.

The introduction of a foreign body during a surgical procedure reduces the number of colony-forming bacteria required to cause an SSI. A study examining *S. aureus*-contaminated wound infections demonstrated a 10 000-fold reduction in the number of organisms required to establish a wound infection if sutures are not present.

Antibiotic administration

Basic principles for the use of antimicrobial surgical prophylaxis include:

- the agent should be delivered to the surgical site before the initial incision
- bactericidal antibiotic concentrations must be maintained at the surgical site throughout the procedure.

It is usual to administer a single dose of an antibiotic. Subsequent doses may be indicated if the surgery is prolonged, depending on the half-life of the antibiotic, e.g. 2 - 5 hours for cefazolin and 6 - 8 hours for metronidazole.

Antibiotics should be administered with anaesthesia just before the initial incision. If given too early this may result in concentrations below the minimal inhibitory concentration (MIC) towards the end of the operation, while if administered too late it leaves the patient unprotected at the critical time – the initial incision.

Antimicrobial choice

The choice of agent depends on the surgical procedure, the most frequent pathogens seen in SSIs associated with the procedure, the safety and efficacy of the antimicrobial agent, the current literature evidence to support its use, and the cost. The most important of these factors is the evidence from randomised controlled trials. It is essential that the antimicrobial therapy has Gram-positive coverage, especially against the key pathogen *S. aureus.* The decision to broaden prophylaxis to agents with Gram-negative and anaerobic activity depends on both the surgical site and whether the operation will transect a hollow viscus or mucous membrane that may contain resident flora.

Cephalosporins are the most commonly prescribed agents for surgical prophylaxis. They have a broad antimicrobial spectrum, favourable pharmacokinetic profile, low incidence of side-effects, and are relatively cheap. Cefazolin, together with metronidazole for procedures where anaerobes are important, is the best studied agent and the preferred choice for most surgical procedures. It is interesting to note that cefazolin, which is a first-generation cephalosporin with a relatively narrow spectrum of activity, is so effective that it is generally used as the comparator in studies of antimicrobial prophylaxis for the prevention of SSIs and is seldom surpassed. It is also the most commonly recommended antibiotic in national and international guidelines for the prevention of SSIs.

Allergic reactions are the most common side-effects associated with the cephalosporins. The incidence of cross-sensitivity to the penicillins is less than 5%.

Inappropriate prophylactic antibiotic use may induce antibiotic resistance and be cost-ineffective. Potential sources of inappropriate antibiotic use include the use of broad-spectrum antibiotics when a narrow-spectrum agent is warranted and extending the duration of prophylaxis.

Individualised institutional guidelines that take into account best literature evidence and institution-based antibiotic susceptibility data are important tools to rationalise antibiotic prophylaxis. The use of vancomycin for prophylaxis should generally be discouraged as it has to be given by slow infusion and, more importantly, it is the key antimicrobial for resistant Gram-positive infections. Widespread use will select for resistance. Table I provides a guide to the choice of prophylactic antibiotic for various surgical procedures (evidence-based US guidelines).

Further reading

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