The Evidence Behind Prophylaxis and Treatment of Wound Infection After Surgery

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Abstract

Surgical site infections (SSIs) represent a serious post surgical complication. They are the leading cause of healthcare-related infections in developing countries and the second most common healthcare-related infection in developed countries. Here we discuss the epidemiology of and risk factors for SSIs together with the current evidence supporting the use of antibiotic prophylaxis for the prevention of wound infection after surgery.

11.1 Introduction

In the early nineteenth century, Ignez Semmelweis demonstrated that washing hands in the obstetrical clinic resulted in a dramatic reduction in the rate of puerperal sepsis, and then he published a book ''Etiology, Concept and Prophylaxis of Childbed Fever'' of his findings [1]. Afterwards, Louis Pasteur and Joseph Lister revolutionized the concept of wound infection prevention using antiseptic procedures in surgery. Antibiotic prophylaxis was established in the 1960s, when it was demonstrated that antibiotics cause maximum suppression of infection if given before bacteria gain access to tissue [2]. Since then, many advances have developed to prevent and control wound infection after surgery.

Because of the increasing number of operative procedures, and despite strict infection control policies, SSI remains a leading cause of morbidity and mortality in modern health care settings. It is the second most common type of health care–associated infection (HAI) after urinary tract infection in developed countries, while it is the leading cause of HAI in developing countries [3, 4]. SSI occurs in 2–5 % of patients undergoing inpatient surgery in the United States [3, 5]; and its reported prevalence varies between 1.13 infections per 100 procedures in developed countries to 5.6 per 100 surgical procedures in developing countries, of which 48 % are complex SSI [4–6]. Previously published reports have shown that patients who develop SSIs, in comparison to those with non-infected surgeries, are up to 60 % more likely to spend time in the ICU, five

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times more likely to be readmitted to the hospital, and have a twofold increase risk of death [7]. In addition, 77 % of deaths in patients with SSI are attributed directly to SSI [8].

Infection of surgical wounds is defined as infection following a surgical procedure that occurs within 30 postoperative days, if no implant was placed, and up to 1 year if an implant was placed [8]. SSI is classified according to the degree of microbial contamination into the following [8, 9]:

a. Clean: Closed, uninfected wound with no evidence of acute inflammation. This includes an uninterrupted viscus (respiratory, gastrointestinal, biliary, or urinary tracts) during a clean procedure.
b. Clean contaminated: Elective entry of a viscus (respiratory, gastrointestinal, biliary, or urinary tracts) under controlled conditions with minimal spillage, and no evidence of infection under aseptic conditions.
c. Contaminated: Includes gross spillage from gastrointestinal tract, open accidental wounds, and major breaks in aseptic conditions. Usually associated with acute, nonpurulent inflammation.
d. Dirty: Includes preoperative perforation of viscera with retained tissue or foreign material, or fecal contamination, or presence of old penetrating traumatic wound. Usually associated with the presence of purulent inflammation.

The rate of SSI increases significantly from 7.6 % episodes per 100 surgical procedures in clean wounds to 39.2 episodes per 100 surgical procedures in dirty wounds [4]. In addition, the rate of SSI varies widely by the type of surgical procedure. It is highest with intra-abdominal operations followed by cardiovascular surgeries [10].

11.2 Aetiology of SSI

Infection of surgical wounds is mainly caused by the patient's endogenous flora, and it is believed that infection is acquired at the time of surgery by direct inoculation. The most common single pathogen contributing to SSI is *Staphylococcus aureus*, causing 20–37 % of all SSI [5, 11, 12]. Of these, 49–54 % are *methicillin-resistant S. aureus* (MRSA) strains; making MRSA the single most common pathogen isolated from SSI in community hospitals, with an increasing trend over recent years [4, 5, 11]. *Gram negative bacilli (Escherichia coli, Pseudomonas aeruginosa, Enterobacter species, Klebsiella species, Acinetobacter species and Proteus mirabilis)* are also considered major players, causing just under half of all SSIs [4, 13]. Other organisms causing SSI include *Coagulase negative staphylococci, Enterococci, Streptococci, Candida species,* and *anaerobic organisms* [5, 11, 13]. Infection with endogenous gut flora when surgery involves opening a viscus, and the infection is usually polymicrobial. Exogenous contamination of the wounds can rarely be acquired from the operating room personnel or the operation room environment [14, 15].

11.3 Risk Factors for SSI

Patient-related risk factors (such as diabetes, obesity, smoking, and known colonisation with resistant organisms) are well known predisposing risk factors for SSI. These, together with the surgical characteristics (introduction of foreign material, amount of tissue damage, duration of surgery, shaving) and pathogen characteristics (degree of contamination, microbial burden and virulence) form a complex relationship posing patients to higher likelihood of SSI [12, 13, 16]. Thus many important factors should be considered perioperatively to minimize the risk of surgical site infection. These include prophylactic antimicrobial administration, use of aseptic surgical techniques and proper surgical site cleaning, proper hair removal using clippers if required and the avoidance of shaving, cessation of smoking 30 days before surgery, ensuring proper oxygenation during surgery, blood sugar control and avoiding hyperglycemia in patients undergoing cardiac surgeries, and avoidance of

hypothermia in patients undergoing colorectal surgeries [8, 12, 13, 17–24]. While all are important, the current evidence behind prophylactic antimicrobial administration in surgical patients will be discussed in more details in the following section.

11.4 Perioperative Antimicrobial Prophylaxis

The use of perioperative antimicrobial prophylaxis is a proven intervention to reduce the risk of SSI in elective surgical procedures [25–28]. This aims to reduce the burden of possible pathogens at or in close proximity to the surgical incision at a critical time. The main principles that should be followed to maximise the benefit of antimicrobial prophylaxis include [8, 13] (i) using antimicrobial prophylaxis in elective surgeries with a high risk for infection or if SSI would have a high risk of deleterious outcomes, (ii) using a prophylactic agent that is safe, inexpensive, and bactericidal with activity against the most probable infective pathogens in the surgical procedure, (iii) timing the infusion of the antimicrobial agent so that a bactericidal concentration of the drug is present in serum and tissue at the time of incision and, (iv) maintaining a therapeutic serum and tissue level of the antimicrobial agent throughout the operation and until the incision is closed.

11.4.1 Indications for Perioperative Antimicrobial Prophylaxis

The National Institute of Health Service and Clinical Excellence (NICE) in the United Kingdom recommends antimicrobial prophylaxis to be given before clean surgeries that involve placement of a prosthesis or implant, clean-contaminated surgeries, and contaminated surgeries [29]. Antimicrobial prophylaxis for surgery should be used if evidence from clinical trials is available, in which the surgery requires entry into a viscus or implantation of a prosthetic device, and in operations where SSI would pose major consequences [8, 17]. However, a recent meta-analysis demonstrated that prophylactic antimicrobial therapy is significantly associated with reduced risk of post-operative wound infection in 23 different types of surgeries, but the relative risk of wound infection did not vary between the different levels of surgery cleanliness; suggesting that prophylactic antimicrobial use is effective in reducing the risk of wound infection for all types of surgery including the ones with no available evidence from clinical trials [25]. Yet, the use of antimicrobial prophylaxis is associated with cost, potential adverse events, and possible development of antibiotic resistance; so this has to be well considered when using prophylactic antibiotics in clean surgeries.

Cardiothoracic surgeries are generally considered as clean surgeries, but they usually involve placement of implants. In addition, deep infection after cardiac surgeries is usually associated with catastrophic outcomes. Antimicrobial therapy in the settings of dirty wounds is considered part of the treatment because infection is already established [29]. In surgeries involving total hip and knee replacement, 13 patients need to be treated with antimicrobial prophylaxis in order to prevent one case of SSI [27].

For surgical intra-abdominal infections (IAIs), the current Canadian practice guidelines recommend antimicrobial prophylaxis in clean-contaminated abdominal surgeries for colorectal resection; small intestinal surgeries; oesophageal surgeries (obstruction, dilation, or sclerotherapy for varieces); high risk gastro-duodenal surgery (cancer, active bleeding, low gastric acidity, obstruction, obesity); high risk biliary-tract surgeries (acute cholecystitis, cholelithiasis or obstructive jaundice, open billiary-tract surgeries, old age, diabetes or obesity); and perforated, gangrenous or necrotising appendicitis [17]. However, a meta-analysis on antimicrobial prophylaxis for prevention of postoperative infection after appendectomy recommended prophylaxis in all patients undergoing operation for appendicitis with no apparent difference in the nature of the removed appendix [30].

Table 11.1 Suggested prophylactic antimicrobial regimens according to the type of surgery and infective pathogens

Type of surgical procedure	Infective pathogen	Prophylactic agent	Adult dose[a]	Timing of the infusion[b]	Duration (h)	Comments
Cardiac surgery [12, 31, 32, 37, 38, 44, 47]	*S. aureus* and CONS[c]	Cefazolin or Cefuroxime	1–2 g IV, 1.5 g IV	Within 60 min before incision	24–48	Vancomycin as an acceptable alternative if a prosthetic material is used
						β-lactam or penicillin allergy: vancomycin + aminoglycoside
						High risk for MRSA infection[d]: vancomycin (1 g IV) + cephalosporin
						If an aminoglycoside is given, do not repeat the dose
Non-cardiac thoracic surgery [8, 12, 31, 32]	*S. aureus*, CONS, *Streptococcus pneumonia*, and GNB	Cefazolin or cefuroxime	1–2 g IV, 1.5 g IV	Within 60 min before incision	≤24	High risk for MRSA infection[d]: vancomycin (1 g IV) + aminoglycoside
Abdominal surgery: [8, 12, 17, 28, 31, 32, 42, 54]						
Esophageal, gastroduodenal or biliary tract surgery	GNB, Gram positive cocci	Cefazolin	1–2 g IV	30–60 min before incision	≤24	β-lactam or penicillin allergy: clindamycin with either an aminoglycoside or a fluoroquinolone, High risk for MRSA infection[d]: vancomycin (1 g IV) + aminoglycoside
Colorectal surgery	GNB, *Enterococci*, and anaerobes	(IV): Cefazolin +, metronidazole or cefoxitin or cefotetan or ampicillin/sulbactam	1–2 g IV, 500 mg IV, 2 g IV, 1–2 g IV, 3 g IV	30–60 min before incision	≤24	
Appendectomy	GNB, and anaerobes	(PO): Neomycin + erythromycin base	1–2 g IV, 500 mg IV, 2 g IV, 1–2 g IV, 3 g IV	30–60 min before incision	≤24	
		Cefazolin +, metronidazole or cefoxitin or cefotetan or ampicillin/sulbactam				
Orthopaedic surgery [8, 12, 31, 32, 45, 48, 49, 55–57]	*S. aureus*, CONS, *Streptococci*, and GNB	Cefazolin or cefuroxime or teicoplanin	1–2 g IV, 1.5 g IV, 10 mg/kg IV	No tourniquet: 30 min before surgery, Tourniquet:10 min before surgery	≤24	Vancomycin as an acceptable alternative if a prosthetic material is used, β-lactam or penicillin allergy: vancomycin or clinamycin [58] IV)
Urologic surgery [8, 12, 31, 32]						
Open surgeries or laparoscopy	GNB and *Enterococci*	Cefazolin	1–2 g IV	Within 60 min of incision	≤24	High risk for MRSA infection[d]: vancomycin (1 g IV) + aminoglycoside
Cystoscopy[e] or upper urinary tract instrumentation	GNB and *Enterococci*	Ciprofloxacin or TMP/SXT	500 mg PO or 400 mg IV, 1 DS tablet			

Table 11.1 (continued)

Type of surgical procedure	Infective pathogen	Prophylactic agent	Adult dose[a]	Timing of the infusion[b]	Duration (h)	Comments
Neurosurgeries [12, 31, 32, 59]	*S. aureus*, CONS	Cefazolin or cefuroxime	1–2 g IV, 1.5 g IV	Within 60 min of incision	≤24	High risk for MRSA infection[d]: vancomycin (1 g IV)

GNB Gram-negative bacilli, *CONS* coagulase-negative staphylococci, *MRSA* Methicillin-resistant *S. aureu*s, *TMP/SXT* Trimethoprim/Sulfamethoxazole

[a]Repeat dose intraoperatively if prolonged surgery more than 4 h (every 3–4 h for cefuroxime and cefazolin, every 8 h for vancomycin and metrronidazole, and every 6 h for clindamycin)

[b]Two hours are allowed for the administration of vancomycin and fluoroquinolones. If vancomycin is used in cardiac surgeries, the dose should be administered within 60–16 min prior to incision

[c]Gram-negative bacilli are rarely reported in SSI after cardiac surgery, contamination occurs during the saphenous vein harvesting [60]

[d]High risk for MRSA infection: known MRSA colonization or coming from facilities with high prevalence of MRSA infection

[e]This includes any cystoscopy with manipulation, or high risk cystoscopy with positive urine cultures, transrectal prostatic biopsy, or preoperative urine catheter

11.4.2 Choice of Prophylactic Antimicrobial Regimens

The choice of prophylactic antibiotic regimen depends on the nature of surgery and the infective pathogens likely to cause the infection. In general, the chosen prophylactic agent should be safe, cost-effective, have good tissue penetration and bactericidal against expected pathogens [8, 17].

Table 11.1 summarises the recommended prophylactic antimicrobial regimens according to the type of surgery and the likely infective pathogens. In intra-abdominal surgical procedures, antimicrobial prophylaxis should include coverage for *S. aureus, Gram-negative bacilli* and *anaerobes* from the distal gastrointestinal tract [17, 31]. First generation cephalosporin (cefazolin) is effective in most procedures [31]. Metronidazole should be added in distal surgical procedures to cover anaerobic organisms [17, 28, 31]. Alternative regimens include cefoxitin, cefotetan or ampicillin/sulbactam alone [31, 32]. A recent meta-analysis on antimicrobial prophylaxis in colorectal surgeries demonstrated that the addition of aerobic coverage to anaerobic coverage and vice versa both resulted in statistically significant improvements in SSI rates, which supports the current recommended regimens [28]. Interestingly, the study also demonstrated that SSI was significantly lower when giving combined oral and intravenous antibiotic prophylaxis compared to intravenous alone, or oral alone [28]. The use of mechanical bowel preparation is currently not recommended before colorectal surgeries, as there is lack of evidence to support its use in preventing postoperative infectious complication, and it can be associated with rare but serious complications [33].

A meta-analysis of 28 placebo-controlled trials of cardiothoracic prophylaxis demonstrated that second-generation cephalosporins (cefamandole and cefuroxime) resulted in an approximate one and one-half-fold lower rate of SSI compared to cefazolin [26]. However, subsequent trials failed to discriminate between the different cephalosporins [34–36]. Because of this and the fact that Cefazolin has better activity against Staphylococci, as well as its availability and lower cost, it is the recommended prophylactic antimicrobial agent in cardiac surgeries [37].

In the era of community-associated MRSA (CA-MRSA), patients at high risk for MRSA infection (known MRSA colonisation or coming from facilities with high prevalence of MRSA infection) should receive perioperative vancomycin prophylaxis for prevention of MRSA infection [17, 37, 38].

Decolonisation with nasal mupirocin 5 days before surgery was examined in many presurgi-

cal patients. A meta-analysis showed that mupirocin prophylaxis in nasal *S. aureus* carriers was associated with significantly lower rate of nosocomial infections due to *S. aureus* among surgical patients, but secondary analysis restricted to SSIs only showed non significant results. The rate of infections caused by microorganisms other than *S. aureus* was also significantly higher in the treatment group. The authors suggested that in people who are nasal carriers of *S. aureus*, the use of mupirocin ointment results in a statistically significant reduction in *S. aureus* infections [39]. Another meta-analysis supported mupirocin use in non general surgery cases (e.g., cardiothoracic surgery, orthopedic surgery, and neurosurgery), but no benefit was found in general surgical cases [40]. Until rapid screening tests for *S. aureus* colonisation are widely available, mupirocin is currently recommended as a routine prophylactic measure for all patients undergoing cardiac surgical procedures [37]. Mupirocin use for decolonisation is still a controversial topic, as increasing incidence of mupirocin resistance is a potential issue. Moreover, it is not clear how many surgical patients need to be treated with prophylactic mupirocin in order to prevent one case of SSI, and it is not clear if prophylactic mupirocin should be administered to all pre-surgical patients or only to those colonised with *S. aureus*.

11.4.3 Timing of Perioperative Prophylactic Antimicrobial Infusion

The timing and dosing of the antibiotic infusion should be adjusted to attain peak serum and tissue concentrations at the critical moment of incision [17]. In 1992, Classen et al. demonstrated in a prospective study of 2,847 subjects that the lowest rates of SSIs occurred in the group of patients who received antimicrobial prophylaxis within 2 h of incision [41]. Afterwards, Weber and colleagues examined in a prospective cohort study the rate of SSI by the timing of surgical prophylaxis after cefuroxime (and metronidazole in colorectal cases) infusion in 3,836 surgical procedures. They found that the most effective time for prophylactic antimicrobial infusion is between 30 and 60 min before surgery, while there was a significantly higher odds of SSI when pre-operative antimicrobial prophylaxis was administered less than 30 min (adjusted OR = 1.95; 95 %CI, 1.4–2.8; $p < 0.001$), or between 60 and 120 min (adjusted OR = 1.74; 95 %CI, 1.0–2.9; $p = 0.035$) before surgery [42]. The association between the prophylaxis timing and the occurrence of SSI was also assessed prospectively in a multicenter study involving 4,472 randomly selected cardiac, hip/knee arthroplasty, and hysterectomy cases. Results showed that the best protection was seen when the antibiotic was given within 30 min of incision [43].

The effect of timing of the prophylactic vancomycin infusion on the incidence of SSI was evaluated in 2,048 patients undergoing cardiac bypass graft or valve replacement surgery. Patients who received vancomycin 16–60 min before the beginning of surgery had a lower rates of postoperative infection than those who received vancomycin 0 and 15 min minutes preoperatively. Reduction in the rate of SSI was also noticed among those who received vancomycin 16–60 min before surgery compared to the ones who received it 61–120 min, 121–180 min, and more than 180 min before surgery, but this reduction was not statistically significant [44].

Administration of perioperative antibiotics 30–60 min prior to incision is the current recommended timing in the Canadian practice guidelines for surgical intra-abdominal infections [17]. The Society of Thoracic Surgeons Practice Guidelines recommend prophylactic antibiotics to be administered in cardiac surgery patients within 60 min of skin incision [37]. This timing is also recommended by the Surgical Infection Prevention Project that is developed by the Centers for Medicare & Medicaid Services in collaboration with the Centers for Disease Control and Prevention [32].

In aseptic orthopaedic surgeries, prophylactic antibiotics should administered within 30 min before incision and at least 10 min before tourniquet inflation [45]. Development of SSI does

not differ significantly if the prophylactic antibiotic is given before inflation of the tourniquet or shortly after inflation of the tourniquet [46].

11.4.4 Duration and Frequency of Perioperative Antimicrobial Prophylaxis

Therapeutic serum and tissue levels should be maintained throughout surgery and ideally until closure of the incision; thus in cases of prolonged surgical procedures (more than 3–4 h), prophylactic antibiotics may need to be readministered intraoperatively [17, 31]. Additional intraoperative doses are to be given at intervals 1–2 times the half-life of the drug, with the exception of aminoglycosides, when the dose should not be repeated [24, 31, 37]. In the absence of an established infection, or bowel perforation, or a penetrating bowel trauma operated within 12 h, antimicrobial prophylaxis should be limited to 24 h or less [17].

A recent meta-analysis of 12 studies involving 7,893 adult patients undergoing open heart surgery compared short-term (<24 h) with longer-term antibiotic prophylaxis (≥24 h). Longer-term antibiotic prophylaxis reduced the risk of sternal SSI by 38 % (risk ratio 1.38, 95 % confidence interval (CI) 1.13–1.69) and deep sternal SSI by 68 % (risk ratio 1.68, 95 % CI 1.12–2.53), with no significant differences in mortality, infections overall and adverse events. This suggests that perioperative antibiotic prophylaxis of ≥24 h may be more efficacious in preventing sternal SSIs in patients undergoing cardiac surgery compared to shorter regimens [47].

It was demonstrated in a meta-analysis of antimicrobial prophylaxis in colorectal surgery that there is no advantage to longer antibiotic dosing [28]. Sub-group analysis of three studies that specifically compared a single preoperative dose of antibiotic to either a second intraoperative dose, or early postoperative dose, or both, also showed no advantage with extended dosing. This suggests that a single dose of antimicrobial prophylaxis is equivalent to multiple perioperative doses in the prevention of SSI, which questions the recommendation of giving a second dose in longer operations [28].

The use of a single dose of antimicrobial prophylaxis was shown to be effective in many other trials. A prospective randomised study evaluated the efficacy of single versus multiple doses of teicoplanin as antimicrobial prophylaxis for arthroplasties in 616 patients. Single dose teicoplanin was found to be more effective as prophylaxis for total hip or knee arthroplasty compared with multiple doses [48]. Another study also demonstrated no difference in the rate of postoperative SSI after clean orthopedic surgery when comparing single dose versus multiple doses of prophylactic antibiotics [49]. Furthermore, data from 23 studies that included 8,447 subjects undergoing surgery for closed fracture fixation showed that single dose antibiotic prophylaxis was as effective as multiple doses in reducing the rate of deep SSI [50].

11.5 Outcome of Antimicrobial Prophylaxis

The Surgical Infection Prevention and the Surgical Care Improvement Projects aim to decrease the morbidity and mortality associated with postoperative surgical site infections. The project's antimicrobial prophylaxis performance measures suggested that (i) prophylactic antimicrobial should be given within 1 h of surgical incision (or within 60–120 min for fluoroquinolones and vancomycin); (ii) prophylactic antimicrobial choice should be consistent with published guidelines; (iii) prophylactic antimicrobials should be discontinued within 24 h of surgery [32]. Hospitals that improve compliance with the different components of appropriate antimicrobial prophylaxis reported decrease in the rates of SSI [51, 52]. The Surgical Infection Prevention Project performed a large study that included 35,543 surgical cases from 56 hospitals on the impact of improved infection control and antimicrobial prophylaxis process measures. Implementation of these measures resulted in a 27 % reduction in the average rate of SSI in the first 3 months after surgery [51]. In contrast, non adherence to the Surgical

Site Infection Prevention Guidelines in elective general surgical, neurological, and orthopedic procedures with more than two errors in antibiotic prophylaxis measures was significantly associated with increased rate of SSI (odds ratio 4.030; 95 % CI, 1.02–15.96) [53]. Furthermore, implementing a comprehensive infection control program for prevention of SSI after cardiac surgery demonstrated that prophylactic antimicrobial administration was a protective factor against deep sternal SSI [52].

11.6 Summary

SSI is a leading cause for healthcare associated infections worldwide. As discussed in this review, SSI can be prevented by implementing the recommended infection control measures. Perioperative antimicrobial prophylaxis is one of the most well studied measures with proven benefits in preventing SSI. The current recommendations are to provide prophylactic antibiotics according to the recommended guidelines. The chosen antibiotic should have activity against the pathogens likely to be encountered in the procedure. The prophylactic antibiotic should be administered within one hour of surgical incision (within 30–60 min in general surgeries), and be discontinued within 24 h of the surgery. An exception is in cardiac surgeries, for which most guidelines recommend discontinuation 24–48 h after the surgery.

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