

## Chapter 20. Prevention of Surgical Site Infections

**Andrew D. Auerbach, MD, MPH**

University of California, San Francisco School of Medicine

### Subchapter 20.1. Prophylactic Antibiotics

#### **Background**

Surgical site infections (SSI) include superficial incisional infections, infections of the deep incision space and organ space infections.<sup>1,2</sup> A large body of evidence supports the premise that SSIs can be prevented through administration of appropriate prophylactic antibiotics. Two national organizations, the Federal Centers for Disease Control and Prevention (CDC) and the American Society for Health System Pharmacists (ASHP), have recently synthesized this vast literature to produce comprehensive guidelines regarding the administration of prophylactic antibiotics across a broad range of procedures.<sup>3,4</sup> Because of the breadth of this literature, we limited the focus of this review of strategies to prevent SSIs to adult surgery and procedures that typically occur in the operating room (as opposed to procedures such as endoscopy, interventional cardiology, or radiology procedures).

#### **Practice Description**

Antimicrobial prophylaxis refers to a brief course of an antimicrobial agent administered just before an operation begins in order to reduce intraoperative microbial contamination to a level that will not overwhelm host defenses and result in infection.<sup>4</sup> To maximize the benefits of antimicrobial prophylaxis, the agent used should be safe, inexpensive, and bactericidal with an *in vitro* spectrum that covers the most probable contaminants for the operation.<sup>4</sup> Administration, usually by intravenous infusion, should be timed so that a bactericidal concentration is present in serum and tissues by the time the skin is incised.<sup>5</sup> This practice is now standard of care and recommended by professional societies.<sup>6</sup> Therapeutic levels in serum and tissues should be maintained until, at most, a few hours after the incision is closed in the operating room.<sup>4</sup>

#### **Prevalence and Severity of the Target Safety Problem**

Surgical site infections are a common complication of care, occurring in 2-5% of patients after clean extra-abdominal surgeries (eg, thoracic and orthopedic surgery) and in up to 20% of patients undergoing intra-abdominal procedures.<sup>7-12</sup> Studies following patients into the post-discharge period have reported even higher rates of postoperative infection.<sup>13-16</sup> These complications increase morbidity for patients and consume substantial additional resources.<sup>17-21</sup>

#### **Opportunities for Impact**

Approximately 80-90% of surgical patients receive some kind of antibiotic prophylaxis, though recent studies have shown that choice of regimen, timing of administration or duration of prophylaxis is inappropriate in approximately 25-50% of cases.<sup>22-27</sup>

## Study Designs and Outcomes

As previously noted, the literature on prophylactic antibiotics is extensive. Therefore, the review was limited to evidence from Level 1A study designs. We identified 9 relevant studies examining the use of prophylactic antibiotics to prevent surgical site infections: 7 meta-analyses and 2 systematic reviews.<sup>28-36</sup> (Tables 20.1.1 and 20.1.2) These reviews were of high quality and limited their source material to randomized controlled trials. Although additional randomized trials have been published since these reviews were performed, updating the results of each review was beyond the scope of this project. All studies examined measured rates of site infection directly (Level 1), using previously published definitions to allow comparability. In addition, the rates of sepsis, length of stay, and physiologic measures were reported. One meta-analysis<sup>31</sup> and one systematic review<sup>33</sup> combined rates of several relevant infectious outcomes.

## Evidence for Effectiveness of the Practice

All studies showed a marked reduction in the odds or relative risk of SSI when antibiotic prophylaxis was employed. None of the meta-analyses reviewed explicitly examined the timing of prophylaxis, although many studies pooled data from investigations of antibiotic regimens administered in the immediate preoperative period, (ie, within minutes to an hour of initial incision). Two meta-analyses in our review<sup>29,31</sup> suggested a trend towards lower rates of infection with use of broader-spectrum antibiotic prophylaxis, such as third generation cephalosporins. When compared with single dose prophylaxis, multiple dose prophylaxis generally did not result in significant additional benefit.<sup>29,30,35</sup> In fact, Tanos et al found the odds of SSI were significantly less with single dose prophylaxis.<sup>31</sup> Gillespie et al reported a greater relative risk of infection with single dose prophylaxis with a short-acting antibiotic when compared with multiple dose prophylaxis.<sup>36</sup> However, the risk of infection with single dose prophylaxis using long-acting antibiotics did not differ significantly from that seen with multiple-dose regimens.

## Potential for Harm

None of the meta-analyses analyzed reported rates of adverse events (such as allergic reactions or nosocomial infections) associated with antibiotic prophylaxis of any type or duration. Both of the systematic reviews<sup>33,36</sup> noted a trend towards more frequent adverse events with the use of antibiotic prophylaxis. Authors of both systematic reviews observed that these events were reported rarely and that variation in the definition of “adverse events” across studies made pooling results difficult.

Infection with *Clostridium difficile* affects a large number of hospitalized patients and has significant clinical and economic implications. As many as 16% of *C. difficile* colitis cases in surgical patients can be attributed to prophylaxis alone,<sup>37</sup> with higher risk for this complication among patients receiving broad-spectrum antibiotics or prolonged courses of therapy. Shortening the duration of antibiotic administration may reduce potential risks of prophylaxis (see Chapter 14). Emergence of other types of resistant pathogens is an additional theoretical concern of inappropriate antibiotic prophylaxis; our literature search found no data describing effect of antibiotic prophylaxis on population-level incidence of these pathogens.

## Costs and Implementation

A number of studies have evaluated strategies for improving compliance with recommended practices for perioperative antibiotic prophylaxis. These include chart audit with feedback,<sup>38</sup> computerized decision support,<sup>23, 39-42</sup> dissemination of guidelines,<sup>43</sup> total quality management (TQM) and continuous quality improvement (CQI) techniques,<sup>44-47</sup> provider education programs,<sup>48,49</sup> and comprehensive efforts by an infection control team.<sup>50</sup> Another promising and easily implemented method is to delegate the administration of prophylactic antibiotics to the anesthesia team or the holding room nursing staff.<sup>22, 25, 48</sup>

Costs for systems to increase appropriate use of antibiotics will likely be offset by savings due to prevented infections. However formal analyses of the cost-effectiveness of specific programs to improve prophylaxis have not been reported.

## Comment

For many surgical procedures there is clear evidence supporting the use of antibiotic prophylaxis, administered in a timely manner, to prevent surgical site infections. The reviews suggest that broader spectrum antibiotics may be superior to limited-spectrum antibiotics for intra-abdominal or gynecologic surgeries. In addition, single-dose antibiotic prophylaxis appears to be at least as effective as multiple-dose regimens for a broad range of surgical procedures and may pose less risk to patients in terms of adverse events (eg, *C. difficile* colitis) and less risk to the population in terms of microbial resistance.

Future research will continue to address what prophylactic regimens are most effective for various surgical procedures. Investigation should also focus on methods to improve compliance. The optimal strategies for implementation will likely vary from institution to institution.

**Table 20.1.1. Meta-analyses examining antibiotic prophylaxis\***

Study	Trials Included	Surgical Procedures, Antibiotics	Results: Odds Ratio or Relative Risk of Infection (95% CI)
Kreter, 1992 <sup>35</sup>	28	Cardiothoracic surgery; cephalosporins	<ul style="list-style-type: none"> <li>▪ Cefazolin vs. placebo: OR 0.2 (0.10-0.48).</li> <li>▪ Cefazolin vs. cefuroxime or cefamandole: OR 1.6 (1.03-2.45)</li> <li>• Single dose vs. multiple dose regimen: no significant difference</li> </ul>
McDonald, 1998 <sup>30</sup>	28	Multiple types of surgery; multiple antibiotics	<ul style="list-style-type: none"> <li>▪ Single dose vs. multiple dose antibiotics (all studies): OR 1.06 (0.89-1.25)</li> <li>▪ Duration of multiple dose regimen &lt;24 hours: OR 1.02 (0.79-1.32)</li> <li>• Duration of multiple dose regimen &gt;24 hours: OR 1.08 (0.86-1.36)</li> </ul>
Meijer, 1990 <sup>29</sup>	42	Biliary surgery; cephalosporins	<ul style="list-style-type: none"> <li>▪ Antibiotic vs. placebo: OR 0.30 (0.23-0.38)</li> <li>▪ Cephalosporin I vs. cephalosporin II or III: OR 1.18 (0.69-2)†</li> <li>• Single dose vs. multiple dose regimen: OR 0.80 (0.4-1.6)</li> </ul>
Mittendorf, 1993 <sup>28</sup>	25	Abdominal hysterectomy; multiple antibiotics	<ul style="list-style-type: none"> <li>▪ Antibiotic vs. placebo (all studies): OR 0.35 (0.27-0.5); p&lt;0.00001‡</li> <li>▪ Cefazolin vs. placebo: OR 0.32 (0.18-0.6); p=0.0002‡</li> <li>• Metronidazole vs. placebo: OR 0.24 (0.08-0.8); p=0.015 ‡</li> </ul>
Sharma, 2000 <sup>34</sup>	6	Percutaneous gastrostomy; multiple antibiotics	<ul style="list-style-type: none"> <li>▪ Antibiotic vs. placebo (all studies): RR 0.73, NNT 5.7</li> <li>• Single dose regimens: RR 0.78, NNT 6.1</li> </ul>
Tanos, 1994 <sup>31</sup>	17	Abdominal hysterectomy; cephalosporins	<ul style="list-style-type: none"> <li>▪ Antibiotic vs. placebo (all studies): OR 0.35 (0.3-0.4)</li> <li>▪ Cephalosporin I vs. placebo: OR 0.4 (0.3-0.5)</li> <li>▪ Cephalosporin II vs. placebo: OR 0.37 (0.2-0.8)</li> <li>▪ Cephalosporin III vs. placebo: OR 0.26 (0.1-0.5)</li> </ul>

			<ul style="list-style-type: none"> <li>• Single dose vs. multiple dose regimen: OR 0.37 (0.3-0.5)</li> </ul>
Wilson, 1992 <sup>51</sup>	21	Multiple types of surgery; multiple antibiotics	<ul style="list-style-type: none"> <li>▪ Amoxicillin-clavulanic acid vs. other antibiotics (all studies): OR 0.84 (0.68-1.04)</li> <li>▪ Trend favoring amoxicillin-clavulanic acid for biliary and gynecologic surgery</li> </ul>

\* CI indicates confidence interval; NNT, number needed to treat; OR, odds ratio, and RR, relative risk.

† Roman numerals I, II, III indicate generation of cephalosporin antibiotics.

‡ P values were reported in article; OR were approximated based on figures.

**Table 20.1.2. Systematic reviews of antibiotic prophylaxis\***

Study	Trials Included	Surgical Procedures; Antibiotics	Results: Relative Risk of Infection (95% CI)
Gillespie, 2000 <sup>36</sup>	48	Long bone fractures; multiple antibiotics	<p><u>Single dose antibiotic vs. placebo</u></p> <p>Deep wound infection: RR 0.40 (0.24-0.67)            Superficial wound infection: RR 0.69 (0.50-0.95)            Urinary tract infection: RR 0.63 (0.53-0.76)            Pneumonia: RR 0.46 (0.33-0.65)</p> <p><u>Multiple dose antibiotic vs. placebo:</u></p> <p>Deep wound infection: RR 0.36 (0.21-0.65)            Superficial wound infection: RR 0.48 (0.28-0.81)            Urinary tract infection: RR 0.66 (0.4-1.0)            Pneumonia: RR 0.81 (0.41-1.63)            Adverse events: RR 1.83 (0.96-3.50)</p> <p><u>Single dose short-acting antibiotic vs. multiple doses same agent up to 24 hours after surgery</u></p> <p>Deep wound infection: RR 7.98 (1.01-62.0)            Superficial wound infection: RR 4.82 (1.08-21.6)            Urinary tract infection: RR 1.81 (1.01-3.23)</p> <p><u>Single dose long-acting antibiotic vs. any multiple dose regimen lasting more than 24 hours</u></p> <p>Deep wound infection: RR 1.10 (0.22-5.34)            Superficial wound infection: RR 0.57 (0.17-1.93)</p> <p><u>Multiple doses administered over 24 hours or less vs. longer therapy</u></p> <p>Deep wound infection: RR 1.1 (0.22-5.34)            Superficial wound infection: RR 0.57 (0.17-1.93)</p> <p><u>Oral vs. parenteral prophylaxis</u></p> <p>Insufficient data (single underpowered study)</p>
Smaill, 2000 <sup>33</sup>	66	Cesarean section; multiple antibiotics	<p><u>Impact of antibiotic prophylaxis on ...</u></p> <p><u>-Combined outcomes of fever, wound infection, sepsis and endometritis:</u></p> <p>Elective Cesarean section: RR 0.25 (0.11-0.55)            Emergent Cesarean section: RR 0.39 (0.33-0.46)            Unspecified/nonelective: RR 0.37 (0.32-0.42)</p>

			<p>All Cesarean section: RR 0.37 (0.33-0.42)</p> <p><u>-Maternal side effects:</u> RR 1.96 (0.86-4.49)</p> <p><u>-Length of stay:</u> 0.34 fewer days in hospital (0.17-0.52)</p>
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\* CI indicates confidence interval; RR, relative risk.

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## Subchapter 20.2. Perioperative Normothermia

### **Background**

The body temperature of patients may fall by 1 to 1.5°C during the first hour of general anesthesia.<sup>1</sup> Regional anesthesia also typically causes core hypothermia.<sup>2</sup> Intraoperative hypothermia impairs immune function (especially oxidative killing by neutrophils) and results in dermal vasoconstriction and reduced blood flow to surgical sites, which further increases the risk of surgical site infection by lowering tissue oxygen tension.<sup>3</sup> Hypothermia also results in reduced platelet function, shivering associated with patient discomfort and activation of the sympathetic nervous system, and adverse cardiac events.<sup>2</sup>

### **Practice Description**

Normal core temperature can be maintained during surgery through use of active measures including warmed intravenous fluids and inspired gases, as well as forced air warming. The latter involves an air blanket placed over the patient that circulates air warmed to 40°C. Water blankets may also be used, but are not as effective in maintaining body temperature.<sup>4</sup> Patient temperature is monitored using conventional thermometer probes, with active measures adjusted to maintain core temperature near 36.5°C. Any method or combination of methods that maintains the target core temperature appears to have the same effect.<sup>2</sup>

### **Prevalence and Severity of the Target Safety Problem**

See Subchapter 20.1.

### **Opportunities for impact**

Attention to patient temperature is standard of care in intraoperative anesthesia management.\* However, there are no data on the extent to which active warming measures are currently used perioperatively.

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\* The American Society of Anesthesiologists' *Standards for Basic Anesthesia Monitoring* notes "Every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected."<sup>5</sup>

## Study Designs and Outcomes

We identified one randomized controlled trial<sup>3</sup> and one retrospective cohort study<sup>6</sup> evaluating the effect of active warming interventions on the rate of wound infection (Level 1 outcome). (Table 20.2.1). Wound infection was either defined as “suppuration requiring removal of sutures”<sup>3</sup> or as in previously published definitions.<sup>7</sup>

## Evidence for Effectiveness of the Practice

Kurz et al performed a randomized controlled trial of active warming in the intraoperative care of patients undergoing elective colectomy. All patients received aggressive perioperative hydration and intravenous opioids for pain relief, in an effort to maximize wound perfusion. Patients in the normothermia arm experienced a 68% reduction in the rate of wound infection, lower wound infection scores (as defined by the elements of the acronym ASEPSIS: **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, and duration of inpatient **S**tay), and shorter length of hospitalization.<sup>3</sup> While the relatively high infection rate (19% of control group in this university-based population with a substantial degree of underlying disease) and suboptimal antibiotic prophylaxis (antibiotics continued for about 4 days postoperatively; see Subchapter 20.1) do not invalidate the study results, they do limit their generalizability.

In a retrospective cohort study based on chart reviews of 150 patients undergoing elective colectomy, Barone et al noted no independent association between intraoperative hypothermia (defined as temperature less than  $<34.3^{\circ}\text{C}$ ) and the incidence of wound infections, or the length of stay. Explanation for differences in the findings of the two studies may relate to confounding due to the retrospective design of the study by Barone, or in differences in defining wound infections by the authors (suppuration requiring removal of sutures).<sup>8</sup>

Other potential benefits of maintaining perioperative normothermia have been reported in randomized controlled trials. Frank et al found the risk of morbid cardiac events (combined outcome of angina, myocardial ischemia or infarction, and ventricular arrhythmia) was significantly decreased among patients in the normothermia group (1% intervention vs. 6% control,  $p=0.02$ ).<sup>9</sup> Maintaining normothermia has also been associated with decreased blood loss and transfusion requirements among patients undergoing elective colectomy<sup>3</sup> and hip arthroplasty.<sup>10,11</sup> Postoperative shivering, thermal discomfort, time to extubation, and duration of post-anesthesia recovery are all significantly reduced.<sup>2,12</sup>

## Potential for Harm

None of these studies reported an adverse effect directly related to these practices. Sigg et al observed a higher rate of wound bacterial colonization with the reuse of forced air coverlets.<sup>13</sup>

## Costs and Implementation

Equipment for monitoring temperature is readily available in operating rooms. Kruz et al estimated the direct cost of fluid and forced air warming at \$30 per case.<sup>9</sup> Studies have not formally assessed all relevant costs, including additional physician time required. It is likely that added costs are largely offset by savings due to reduced surgical site infections and associated decreases in length of stay.

## Comment

Given the evidence of effectiveness, the low potential for harm, and the simplicity of the intervention (including the ready availability of the equipment), maintenance of perioperative normothermia seems a promising practice to improve patient safety. The methodologically stronger of the 2 studies reviewed showed clear benefits. However, some of its benefits may not be generalizable to patient populations undergoing other procedures. For example, intraoperative hypothermia may have little impact on wound infections in patients undergoing cesarean section.<sup>14</sup> Thus, additional study of the practice is needed in other settings. Furthermore, for some procedures hypothermia is likely to protect patients. Core temperature is often intentionally reduced to protect the myocardium and central nervous system during certain cardiac and neurosurgical procedures.<sup>2,12,15</sup> In such cases the potential benefits of normothermia may not outweigh the associated risks.

**Table 20.2.1. Summary of studies reporting effectiveness of perioperative normothermia\***

Study	Study Population; Intervention	Study Design, Outcomes	Results
Kurz, 1996 <sup>3</sup>	200 patients (104 normothermia, 96 hypothermia) undergoing, elective colectomy in multicenter study; warmed gases, fluids and forced arm during operation vs. usual care	Level 1, Level 1	Wound infection rate: 6% vs. 19% (p=0.009) ASEPSIS score: 7 vs. 13 (p=0.002) Days to sutures out: 9.9 vs. 10.9 (p=0.002) Taking nutrition orally: 5.6 vs. 6.5 days (p=0.006) Length of stay: 12 vs. 15 days (p=0.001)
Barone, 1999 <sup>6</sup>	150 patients (101 normothermia, 49 hypothermia) undergoing elective colectomy at a single community hospital; no formal intervention (retrospective chart review, warming devices were used in 90% of patients)	Level 3, Level 1	Wound infection rate: 12% in both groups Multivariate models: no significant association between hypothermia and wound infection or length of stay

\* ASEPSIS indicates **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, and duration of inpatient **S**tay.<sup>7</sup>

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### Subchapter 20.3. Supplemental Perioperative Oxygen

#### Background

Low oxygen content in devitalized tissues predisposes them to bacterial colonization, which is thought to be a key pathophysiologic step in the initiation of surgical site infections.<sup>1</sup> Administration of high concentrations of oxygen increases wound oxygen tension, allowing for more effective neutrophil function and the potential for reduced infection rates.<sup>2</sup>

#### Practice Description

The practice of perioperative oxygen supplementation involves administration of 80% oxygen and 20% nitrogen by endotracheal tube intraoperatively and by sealed mask and manifold system or conventional non-rebreather mask for the first two hours of recovery. Oxygen is increased to 100% immediately before extubation, with the concentration returned to 80% as soon as deemed safe by the anesthesiologist.<sup>3</sup>

#### Prevalence and Severity of the Target Safety Problem

See Subchapter 20.1.

## **Opportunities for Impact**

Administration of oxygen is a routine part of perioperative care. However the frequency with which high oxygen concentrations (as described above) are administered is not known.

## **Study Designs and Outcomes**

We identified one randomized controlled trial evaluating the effect of high concentration oxygen supplementation on surgical site infections (Table 20.3.1).<sup>3</sup> The primary outcome was incidence of wound infection within 15 days after surgery (Level 1). Wounds were considered infected when bacteria were cultured from pus expressed from the incision or aspirated from a loculated collection within the wound.<sup>3</sup>

## **Evidence for Effectiveness of the Practice**

The clinical characteristics of the intervention and control groups were similar at baseline, including risk of infection as assessed by a modified Study on the Efficacy of Nosocomial Infection Control (SENIC) score ( $p=0.8$ ) and National Nosocomial Infection Surveillance System (NNISS) score ( $p=0.86$ ). The incidence of wound infection was significantly less in the intervention group (13/250, 5%) than in the control group (28/250, 11%,  $p=0.014$ ). The results remain statistically significant when the study definition of “infection” is broadened to include wounds with pus but no bacterial growth on culture (7% vs. 14%,  $p=0.012$ ). Perioperative administration of high levels of oxygen was associated with a 54% relative risk reduction (95% CI: 12%-75%) of wound infection within 15 days of surgery. ASEPIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of deep tissues, Isolation of bacteria, and duration of inpatient Stay<sup>4</sup>) scores were also significantly better with high levels of oxygen (3 vs. 5,  $p=0.01$ ). Although longer follow-up might have identified additional wound infections, the authors argue that it was unlikely that these events would take place preferentially in one group as the proposed therapeutic effect of oxygen appears limited to the immediate perioperative period.<sup>3</sup> Admission to the intensive care unit and death were less frequent in the intervention group, but the difference failed to achieve statistical significance.

Two additional randomized controlled trials of perioperative supplemental oxygen were identified.<sup>5,6</sup> Both found a significant reduction in postoperative nausea and vomiting, but neither study evaluated the effect on wound infections.

## **Potential for Harm**

The study by Greif et al reported no adverse affects related to the intervention. Several potential risks of high oxygen concentrations should be noted. High oxygen concentrations may present a fire hazard when heated surgical instruments (eg, lasers) are introduced into the airway.<sup>7-11</sup> Such concentrations can also induce lung injury in certain vulnerable patients<sup>12</sup> or precipitate atelectasis in patients at risk.<sup>3,13,14</sup> Hyperoxic mixtures may increase oxidative myocardial injury in patients undergoing cardiopulmonary bypass.<sup>15</sup> Finally, patients who undergo resuscitation with 100% oxygen may have worsened neurologic outcomes, possibly also as a result of increased oxygen free-radical generation.<sup>16,17</sup>

## **Costs and Implementation**

The incremental direct costs associated with administering high oxygen concentrations are minimal, as oxygen delivery systems are elements of routine perioperative care and employ equipment readily available in operating rooms.

## Comment

Administration of perioperative oxygen in high concentrations seems a promising adjunctive therapy: the practice is simple, the equipment needed is readily available, and a multicenter randomized trial has demonstrated its efficacy.

However, there are significant questions about the generalizability of the approach to expanded populations of surgical patients. All patients in the Grief et al study had core temperature maintained at 36°C, were aggressively hydrated, and had postoperative pain treated with opioids in order to maximize wound perfusion. To what degree the effectiveness of the practice is affected by changes in these “co-interventions” has not been assessed. There is reason for concern regarding use of high concentrations of oxygen in patients undergoing procedures associated with low blood flow (eg, cardiopulmonary bypass), or in whom local production of oxygen free radicals may cause further organ injury (eg, patients with head trauma).

Additionally, questions remain regarding whether modifications to the protocol used would impart similar or greater benefit. For example, would oxygen administration by nasal cannula at 10 LPM be as effective as oxygen delivered by a sealed mask? Would longer duration of therapy impart additional benefit? These questions should be answered in future trials.

**Table 20.3.1. Randomized controlled trial of supplemental perioperative oxygen\***

Study	Study Population	Intervention	Results†
Greif, 2000 <sup>3</sup>	500 patients undergoing colorectal resection; multicenter study, 1996-98	80% oxygen, 20% nitrogen during surgery and the first 2 hours of recovery	Wound infection: ARR 0.06 (95% CI, 0.018-0.102) RR 0.46 (95% CI, 0.25-0.88) ASEPSIS <sup>§</sup> score: 3 vs. 5 (p=0.01) ICU admission: 2.0% vs. 4.8% (p=0.14) Mortality: 0.4% vs. 2.4% (p=0.13)

\* ARR indicates absolute risk reduction; CI, confidence interval; ICU, intensive care unit; and RR, relative risk. The ASEPSIS scoring system incorporates **A**dditional treatment, **S**erous discharge, **E**rythema, **P**urulent exudate, **S**eparation of deep tissues, **I**solation of bacteria, and duration of inpatient **S**tay<sup>4</sup>.

† Outcomes within 15 days of surgery, expressed as rates in intervention vs. control groups.

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#### Subchapter 20.4. Perioperative Glucose Control

##### Background

Diabetes is a well-known risk factor for perioperative medical complications. Poor glucose control is an independent risk factor for surgical site infections<sup>1-5</sup> in a range of surgical procedures. Increased risk for infection is thought to result from a combination of clinically apparent effects of longstanding hyperglycemia (eg, macro- and microvascular occlusive disease) and subtle immunologic defects, most notably neutrophil dysfunction.<sup>6-12</sup> Hyperglycemia may also impair the function of complement and antibodies, reducing the opsonic potential of these factors and impairing phagocytosis, further reducing barriers to infection.<sup>13,14</sup> Although many of the clinically apparent manifestations of diabetes are not easily reversed in the perioperative period, there is a small literature that suggests that improving glucose control can improve immunologic function and reduce the incidence of surgical site infections (SSI).<sup>6-8,12</sup>

Perioperative management of glucose for diabetic patients commonly includes withholding or administering a reduced dose of the patients' usual hypoglycemic agent(s) and commencing a low-rate intravenous glucose infusion while patients are NPO prior to surgery. The infusion is continued postoperatively until the patient is able to eat and resume outpatient diabetes therapy. Often a sliding scale insulin regimen, a schedule of subcutaneous regular insulin dosage contingent on capillary blood glucose measurements, is also continued through the perioperative period. However, use of a sliding scale may result in wide variations in serum glucose,<sup>15</sup> opening the rationale of this method to question.<sup>16-18</sup>

### **Practice description**

Aggressive glucose control in the perioperative period can be achieved using a *continuous intravenous insulin infusion* (CII). Nursing staff monitor fingerstick (or arterial line drop-of-blood sample) glucose measurements and adjust the infusion rate based on a protocol intended to maintain serum glucose within a certain range. For example, the target range for the original Portland Protocol was between 151 and 200 mg/dL.<sup>16,19,20</sup> In the most recent version, the range is between 125 and 175 mg/dL.<sup>21</sup>

### **Prevalence and Severity of the Target Safety Problem**

Little evidence exists to describe the practice of CII in prevention of surgical site infections in broad surgical practice. The small amount of evidence available describes its use in patients undergoing cardiac surgery, primarily coronary artery bypass grafting (CABG). Diabetes is a well-described risk factor for sternal wound infections, a catastrophic complication of median sternotomy.<sup>19,22-25</sup> Sternal wound infections occur in 0.8% to 2% of unselected patients undergoing median sternotomy and CABG.<sup>20,22,23</sup> Diabetic patients, who comprise between 17 and 20% of all patients undergoing CABG, have been reported to have an incidence of sternal wound infections as high as 5.6%.<sup>26</sup> Such infections are associated with marked increases in morbidity and costs. Furnary et al reported that patients with sternal wound infections had an average increased length of stay of 16 days and a higher mortality rate (19% vs. 3.8% in patients without sternal wound infections).<sup>20</sup> (See also Subchapter 20.1).

### **Opportunities for Impact**

More than 700,000 Americans underwent open-heart surgery in 1998 alone.<sup>27</sup> Up to 20% of these patients may be candidates for continuous insulin infusion. Although CII is included in the recent ACC/AHA Guidelines for CABG Surgery,<sup>28</sup> there are no data on the extent to which the measure is currently used during cardiac or other surgical procedures.

### **Study Designs and Outcomes**

We identified one prospective before-after study that compared rates of deep sternal wound infections (DSWI) in diabetic patients undergoing CABG before and after implementation of an aggressive CII protocol.<sup>20</sup> DSWI included infections involving the sternum or mediastinal tissues, including mediastinitis. An older study from the same authors was not reviewed as it reported findings at an earlier point in the same trial.<sup>19</sup> Additional studies examined the use of CII in perioperative patients but did not report Level 1 clinical outcomes relevant to patient safety (eg, mortality, wound infection) and were also not reviewed.<sup>29</sup>

## **Evidence for Effectiveness of the Practice**

Furnary et al found that aggressive glucose control with CII was associated with a reduction in deep sternal wound infections.<sup>20</sup> The effect of the intervention remained statistically significant in a logistic regression model adjusting for multiple potential confounding variables. Furthermore, the demographic characteristics were generally biased against the CII group, which had a significantly higher percentage of patients with hypertension, renal insufficiency, and obesity but fewer patients with congestive heart failure. However, the authors did not adjust for long-term markers of glucose control such as glycosylated hemoglobin, nor did they describe other changes in patient care systems that resulted from changing patients to insulin infusions. Continuous insulin infusions require closer attention by nursing staff both for monitoring of infusion equipment and for frequent measurements of blood glucose. It is possible that the improved outcomes were due to closer overall attention to the patient. Although 74% of DSWI occurred after initial discharge (raising the concern that the shorter length of stay in the sliding scale insulin group may have resulted in some infection not being detected), the authors reported that they directly followed-up all diabetic patients for one year from the time of surgery.<sup>30</sup> The personnel, equipment, surgical techniques, and use of prophylactic antibiotics were similar throughout the study period.<sup>31</sup> Nonetheless, it is likely that secular trends in the care of patients undergoing cardiac surgery account for some of the impact attributed to CII.

## **Potential for Harm**

Hypoglycemic episodes are the most concerning adverse event associated with intensive glucose management with intravenous insulin. These episodes result in a range of medical complications, from delirium to myocardial infarction resulting from increased sympathetic activity. Furnary noted that, using the standardized protocol in their study, no cases of symptomatic hypoglycemia occurred in either group of patients.<sup>30</sup> However, CII protocols intended to maintain normoglycemia in surgical patients have been associated with high rates (40%) of postoperative hypoglycemia requiring treatment (<60 mg/dL glucose).<sup>32</sup>

## **Costs and Implementation**

The equipment and personnel required to administer intravenous insulin are readily available. Although a formal cost-effectiveness analysis of the practice has not yet been performed, limited data are available. Furnary et al estimate the additional expense of CII at \$125-150 per patient.<sup>33</sup> While this likely includes direct costs of CII such as infusion equipment and additional nursing care for more frequent monitoring of glucose and adjustment of insulin infusion rates, it may underestimate the true costs of the practice at other sites, particularly during early phases of implementation. Furnary reported that the practice required a significant period of time for staff to gain familiarity and expertise with CII, and that by the end of the study they had in place a system that required no significant changes in care patterns for CII to be administered.<sup>34</sup> In early phases of implementation there may be additional costs related to excess time spent by patients in ICU or high-level care areas (ie, stepdown units) rather than regular wards. The start-up costs in terms of training and system changes, and whether the approach is easily adaptable to sites that lack the capability to administer CII in numerous inpatient settings, have yet to be determined.

It seems likely that savings from averted infections may substantially compensate for the incremental direct costs of CII. Based on Furnary's findings and cost assumptions, the average DSWI was associated with \$26,000 in additional charges (not costs). Of 1499 patients in the

intervention group, the number of DSWIs prevented was 10 (95% CI: 4-21) and the average cost to prevent one DSWI was approximately \$21,000 (95% CI: \$10,000-\$52,500). Of course, these figures do not incorporate the potential effects of the intervention on other sites of infection, mortality, adverse events, and patients' preferences (utilities) for these possible health states.

### **Comment**

An increasing body of evidence demonstrates that tight control of blood glucose improves overall outcomes of patients with diabetes.<sup>35-37</sup> Emerging data, coupled with an increasing appreciation of the deleterious effects of hyperglycemia on immune function, strongly support the supposition that aggressive control of perioperative glucose reduces the incidence of surgical site infections. Although the practice has been implemented at a number of institutions and is also being used in diabetic patients undergoing non-cardiac surgeries,<sup>34</sup> studies of its effectiveness in these settings have not yet been published. Until additional evidence is available, preferably from blinded randomized controlled trials, the intervention can be considered promising but not yet proven to be causally associated with improved outcomes.

**Table 20.4.1. Prospective, before-after study of aggressive perioperative glucose control\***

Study	Study Population	Comparison Groups	Results†
Furnary, 1999 <sup>20</sup>	2467 diabetic patients undergoing cardiac surgery at a community hospital	968 patients treated with sliding scale SQ insulin (1987-91) 1499 patients treated with CII to target glucose of 150-200 mg/dL until POD 3 (1991-97)	Deep surgical wound infections Unadjusted: 1.9% vs. 0.8% (p=0.011) Adjusted RR 0.34 (95% CI: 0.14-0.74) Mortality: 6.1% vs. 3.0% (p=0.03) Length of Stay: 10.7d vs. 8.5d (p<0.01)

\* CI indicates confidence interval; CII, continuous intravenous insulin; POD, postoperative day; and RR, relative risk.

† Results reported as pre-intervention (sliding scale SQ insulin) vs. post-intervention (CII).

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