

2017

## Surgical site infection research opportunities

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### Recommended Citation

Itani, Kamal M. F.; Dellinger, E. Patchen; Mazuski, John; Solomkin, Joseph; Allen, George; Blanchard, Joan C.; Kelz, Rachel; and Berrios-Torres, Sandra I., "Surgical site infection research opportunities." *Surgical Infections*. 18, 4. 401-408. (2017).  
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# Surgical Site Infection Research Opportunities

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## Abstract

Much has been done to identify measures and modify risk factors to decrease the rate of surgical site infection (SSI). Development of the Centers for Disease Control and Prevention (CDC) Core recommendations for the prevention of SSI revealed evidence gaps in six areas: Parenteral antimicrobial prophylaxis, glycemic control, normothermia, oxygenation, antiseptic prophylaxis, and non-parenteral antimicrobial prophylaxis. Using a modified Delphi process, seven SSI content experts identified nutritional status, smoking, obesity, surgical technique, and anemia as additional areas for SSI prevention research. Post-modified Delphi process *Staphylococcus aureus* colonization and SSI definition and surveillance were also deemed important topic areas for inclusion. For each topic, research questions were developed, and 10 were selected as the final SSI research questions.

**Keywords:** anemia; antibiotic prophylaxis; glucose control; guideline; surgical site infection

**T**HE CENTERS for Disease Control and Prevention (CDC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) *Guideline for the Prevention of Surgical Site Infection* (SSI) was developed using evidence-based methodology with key questions provided by external SSI content experts. This guideline is a targeted update to the *Guideline for the Prevention of Surgical Site Infection, 1999* [1]. The Core section recommendations were crafted using randomized controlled trials (RCTs) and systematic reviews of RCTs, across surgical specialties. The prosthetic joint arthroplasty-specific section recommendations focused solely on the evidence available for this single high-volume, high-burden procedure. The evidence was rigorously evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [2]. Final recommendations for both sections are presented in the 2017 guideline [3].

The purpose of this article is to propose SSI research questions based on both evidence gaps identified during the Core section guideline development process and additional

questions proposed by the content experts. Content experts agreed that new research should also include a cost-effectiveness assessment of any preventative measure studied. The SSI research opportunities specific to prosthetic joint arthroplasty procedures are addressed by the arthroplasty content experts in a separate article [4].

## Identifying SSI Research Areas

Potential SSI research areas and questions were derived from two sources: (1) evidence gaps identified during the Core section guideline development process and (2) additional research areas and questions proposed by content experts (Fig. 1).

### *SSI research areas based on guideline evidence gaps*

In the updated CDC and HICPAC categorization scheme for recommendations [5,6], key questions for which there is either no evidence or low to very low-quality evidence with uncertain trade-offs between benefits and harms are

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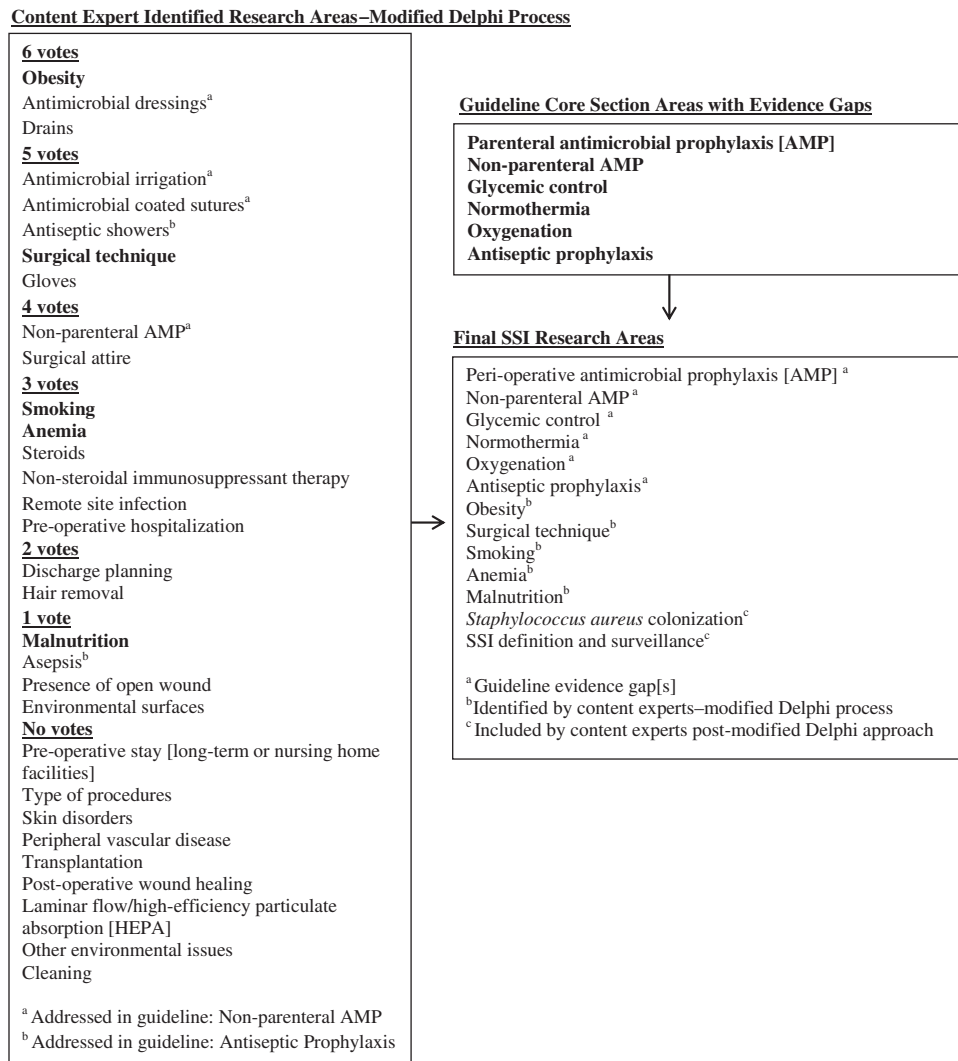
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**FIG. 1.** Surgical site infection research areas.

categorized as “No recommendation/unresolved issue” and can be deemed to represent “evidence gaps.” All six Core section key topics (parenteral antimicrobial prophylaxis [AMP], non-parenteral AMP, glycemic control, normothermia, oxygenation, and antiseptic prophylaxis) had some evidence gaps (Fig. 1).

#### *Additional SSI research areas proposed by the content experts*

The content experts initially identified 31 areas for SSI research (Fig. 1) and prioritized them using a modified Delphi process [7]. Twenty-two areas received at least one vote. Of the 10 areas that received at least four votes, consensus was reached to eliminate eight (five already addressed as guideline evidence gaps and three suggested by the content experts), leaving obesity (6 votes) and surgical technique (5 votes) as research areas. There was also consensus to include smoking and anemia (3 votes each) and malnutrition (1 vote). Post-modified Delphi process, *Staphylococcus aureus* colonization (a topic originally suggested for inclusion in the guideline) and SSI definition and

surveillance (which impact SSI rates and reporting) were included in the final 13 research areas (Fig. 1).

#### *Identifying research questions*

Fifty-two questions were crafted in 13 research areas (Tables 1 and 2). Those questions receiving three or more votes were selected as final SSI research questions (Table 1). Eight questions represent guideline Core section evidence gaps, and two were identified from research areas identified by the content experts. The 42 remaining questions represent additional SSI research opportunities (Table 2).

#### **Final SSI Research Areas**

##### *Parenteral AMP: Timing, dosing, re-dosing, duration*

There are many outstanding questions surrounding the timing of antimicrobial agents before surgery and how improving this timing for particular classes or agents used for specific surgeries might reduce SSI further. A recent large retrospective study confirmed that the current practice of administering parenteral AMP within 60 minutes of incision

TABLE 1. FINAL SURGICAL SITE INFECTION RESEARCH QUESTIONS

## Parenteral antimicrobial prophylaxis (AMP)\*

- What is the optimal timing of pre-operative parenteral AMP that reduces the risk of surgical site infection (SSI)?\*
- What are the criteria for intra-operative re-dosing of parenteral AMP that reduce the risk of SSI?\*

## Non-parenteral AMP\*

- How safe and effective is intra-operative antimicrobial irrigation in reducing the risk of SSI?\*

## Glycemic control\*

- How do pre-operative hemoglobin A1C levels impact the risk of SSI and what are their optimal pre-operative target levels in diabetic and non-diabetic patients?\*

## Normothermia\*

- What are the most effective strategies for achieving and maintaining peri-operative normothermia?\*

## Oxygenation\*

- What is the optimal target fraction of inspired oxygen [FiO<sub>2</sub>] to reduce the risk of SSI; how and when should it be administered?\*
- What is the relevant role of each: Optimal oxygenation, normothermia, normovolemia, and type of anesthesia (neuraxial versus general) in the risk of SSI?

## Antiseptic prophylaxis\*

- For pre-operative bathing or showering, what is the optimal agent, timing, number of product applications at each session, and frequency of showers/baths that reduce the risk of SSI?\*

## Smoking

- What is the optimal timing of pre-operative smoking cessation that results in substantial reduction in the risk of SSI?\*

## Surgical technique

- What is the optimal subcutaneous tissue closure (e.g., suture type, spacing, etc.) that reduces the risk of SSI in various patients (e.g., surgical procedures, obese patients, etc.)?\*

\*From the *Centers for Disease Control and Prevention and Healthcare Infection Control Practices Advisory Committee's Guideline for the Prevention of Surgical Site Infection, 2017.*

for all antimicrobial agents and across specialties might not be optimal [8]. The need for and optimal timing of intra-operative parenteral AMP re-dosing and whether subsequent doses should be the same as the initial pre-operative dose in obese versus non-obese patients have not been studied [9]. Whether discontinuation of parenteral AMP beyond skin closure in the operating room is appropriate in clean contaminated cases is also poorly studied [10,11].

*Non-parenteral AMP: Antimicrobial irrigation, ointments, powders, dressings*

According to the guidelines, no antimicrobial agent such as ointments, solutions, powders, or sealants should be applied to the wound. Irrigation of the deep and subcutaneous tissues with aqueous iodophor solution can be considered. No recommendation could be made regarding antimicrobial dressings applied immediately after primary wound closure in the operating room. Opportunities for prevention of SSI by local prevention as opposed to systemic administration continue to exist as new agents and delivery system evolve.

*Glycemic control: Peri-operative glycemic control; hemoglobin A1C levels and risk of SSI*

While avoidance of severe hyperglycemia is recognized as key to the care of all hospitalized patients and important in the prevention of SSI, the degree to which hyperglycemia should be controlled to prevent SSI remains unclear [12,13]. The frequency and post-operative duration of peri-operative glucose monitoring has not been evaluated rigorously. The degree to which hyperglycemia should be controlled has been subject to a number of investigations but has proven extremely controversial [14,15]. Studies with less rigorous de-

signs have shown that maintenance of improved glycemic control (although not necessarily strict glycemic control) was associated with improved outcomes, including reduced rates of SSI in patients undergoing cardiac surgery [16–19]. High glucose variability has been associated with higher risk of acquired infection and death in patients in medical-surgical intensive care units; therefore, glycemic control focused on maintaining an absolute blood glucose target level at a single point in time might warrant re-evaluation [20].

Data regarding hemoglobin A1C levels as a marker of pre-operative glucose control and its association with SSI are also lacking. One hypothesis is that while elevated A1C levels are associated with a higher risk of hyperglycemia in the peri-operative period, the hyperglycemia itself is the important SSI risk factor, not the A1C level [21].

*Normothermia: Mechanism, lower limit, normothermia ratio, strategies to achieve and maintain*

It has been hypothesized that normothermia prevents SSI by reducing vasoconstriction, thereby improving oxygen delivery at the incision [22,23]. Whether normothermia, independent of oxygenation, optimizes metabolic and enzymatic activities essential in incision healing mechanisms and the killing of micro-organisms, thus reducing the risk of SSI, remains unknown, however. Also, whether systemic normothermia accurately reflects temperature at the incision warrants further study. In addition, hypothermia is associated with greater degrees of intra-operative blood loss that in many analyses is an additional risk factor for SSI [22,23].

The lower limit of temperature in normothermia and its duration post-operatively have been inconsistently defined. Research to identify a break point “normothermia ratio” for

TABLE 2. ADDITIONAL SURGICAL SITE INFECTION RESEARCH OPPORTUNITIES

## Parenteral antimicrobial prophylaxis (AMP)\*

- What is the optimal AMP dosing for various agents?

## Non-parenteral AMP\*

- How safe and effective are non-parenteral antimicrobial agents applied to the surgical incision?\*
- How safe and effective are antimicrobial dressings applied to the surgical incision following primary closure in the operating room?\*

## Glycemic control\*

- Should hemoglobin A1C levels be checked routinely on all patients undergoing elective surgical procedures?
- Is there a particular hemoglobin A1C level that would justify screening and intervention to prevent surgical site infection (SSI)?
- Is there a safe blood glucose value or range that should be targeted in the peri-operative period to prevent SSI in surgical patients?

## Normothermia\*

- What is the lower temperature limit of normothermia?\*
- What is the optimal timing and duration of normothermia?\*
- Identify a break point “normothermia ratio” for higher SSI.
- Does systemic normothermia reflect the same temperature as the wound?

## Oxygenation\*

- How does increased FiO<sub>2</sub> impact the risk of SSI in patients undergoing neuraxial anesthesia?\*
- Is FiO<sub>2</sub> a good surrogate of oxygen saturation at the wound?
- What is the best method and body location for measuring oxygen saturation?

## Antiseptic prophylaxis\*

- Are there specific patient groups that would benefit to a greater extent from pre-operative showers or bathing?
- Is antiseptic irrigation useful for all wound classes? Which antiseptic agent?
- Is there a role for application of antiseptic agents directly to the surgical incision?

## Nutritional status

- What is the best way of characterizing pre-operative nutritional status’ impact on SSI?
- How does pre-operative serum albumin level impact the risk of SSI?
- Does pre-operative specialized nutritional support decrease the risk of SSI?
- Are there patients or types of surgery where pre-operative specialized nutritional support would decrease the risk of SSI?

## Smoking

- What is the differential contribution to SSI of smoking duration and/or amount?

## Obesity

- What is the relative contribution to SSI of obesity alone versus obesity and other associated obesity co-morbid conditions and factors?
- How do we best quantify obesity in the prevention of SSI? Weight, body mass index, or other morphometric measurements?
- How does pharmacokinetics in obese patients affect the use of parenteral and non-parenteral antimicrobial and antiseptic agents?
- Does subcutaneous tissue perfusion in obese patients contribute differently to SSI than non-obese patients?

## Surgical technique

- What is the correlation between the amount of electrocautery use on the skin and subcutaneous tissue and risk of SSI?
- What is the correlation between the amount of tissue pressure and tension applied intra-operatively and risk of SSI?
- When should a drain be placed in the subcutaneous space and when should it be removed to reduce the risk of SSI?

## Anemia

- Is anemia a risk factor for SSI?
- Is blood transfusion a risk factor for SSI or is it a surrogate for other SSI risk factors such as operations that are more difficult, take longer, require more dissection, and therefore result in more blood loss?
- Is there a cutoff point for blood transfusion below which peri-operative transfusions should be done but above which they should be withheld in order to decrease the risk of SSI?
- Is the risk of SSI higher with “older” blood transfusions?
- How does parenteral iron, oral iron, or recombinant human erythropoietin used to correct pre-operative anemia impact the risk of SSI?

*Staphylococcus aureus* (SA) colonization

- Is SA colonization an independent risk factor for SA SSI?
- Does SA decolonization reduce risk of SSI?
- Does parenteral AMP with vancomycin in patients colonized with methicillin-resistant *S. aureus* (MRSA) reduce the risk of MRSA SSI?
- Should all surgical patients undergo screening for SA (MRSA/methicillin-sensitive *S. aureus*)?

## SSI surveillance

- Does diagnosis of SSI by the attending physician or surgeon introduce bias in reporting?
- Could responsibility for SSI surveillance shift to personnel who are not familiar with surgical wounds?
- Could SSI surveillance shift to monitoring by natural language processing of electronic medical records and how would it compare to surveillance using administrative databases?
- Will the implementation of ICD-10 coding allow for SSI surveillance using administrative databases?
- Should subjective criteria such as Celsian signs and quality of wound discharge be substituted by an objective scoring system for the diagnosis of SSI?

\*From the Centers for Disease Control and Prevention and Healthcare Infection Control Practices Advisory Committee’s Guideline for the Prevention of Surgical Site Infection, 2017.

higher SSI rates would be important. The denominator for that ratio is the duration of time (min) from arrival to the operating room up to a defined time post-operatively to be determined (2–5 h). The numerator for that ratio would consist of the amount of time (min) a patient's core temperature is above a pre-defined minimum temperature level for that period in the denominator. Finally, the most effective strategy to achieve and maintain peri-operative normothermia remains unknown.

#### *Oxygenation: Optimal delivery, measurement*

While multiple human and animal studies have demonstrated the relationship between higher oxygen levels and the increased ability of white blood cells to kill bacteria at the surgical wound [24–26], the best method and body location to measure oxygen saturation/tissue oxygenation has not been determined. The guideline recommendation states that: “For patients with normal pulmonary function undergoing general anesthesia with endotracheal intubation, administer increased fraction of inspired oxygen (FiO<sub>2</sub>) both intra-operatively and post-extubation in the immediate post-operative period. To optimize tissue oxygen delivery, maintain peri-operative normothermia and adequate volume replacement.” (Category IA-strong recommendation) [3]. Optimal delivery of oxygen to the wound site and the degree to which it is influenced by inspired oxygen fraction remains unknown, however.

#### *Antiseptic prophylaxis: Pre-operative bathing/showering, intra-operative skin preparation*

While commonly performed, the effectiveness of pre-operative bathing or showering with an antiseptic or non-antiseptic agent in reducing the risk of SSI has not been determined firmly. Variable results in this field may be because of differences in the agent used, timing, frequency, and method by which the agents are applied within and across trials. For intra-operative surgical site antiseptic skin preparation, the relative efficacy of iodophors compared with chlorhexidine gluconate and the relative contribution of alcohol to the efficacy of these agents warrant further investigation.

#### *Malnutrition: Optimizing pre-operative nutrition*

Malnourishment is a known risk factor for infection [27]. Some nutritional interventions could decrease the risk of SSI in malnourished patients undergoing elective surgical procedures [28,29]. Based in part on the results of a large United States Department of Veterans Affairs study published in 1991 [30], pre-operative parenteral nutrition is not recommended for most patients undergoing elective surgical procedures, unless they are moderately to severely malnourished. Studies of pre-operative enteral nutrition have given conflicting results. Based on a number of small studies, pre-operative enteral nutrition, particularly immunonutrition, has been endorsed in some guidelines and reviews [31–33].

Immunonutrition refers to immune-modulating nutrition products (hydrolyzed peptide-based protein formulas with some combination of fish oils such as eicosapentaenoic acid, and docosahexaenoic acid), arginine, nucleic acids, antioxidants believed to work by increasing cell membrane stability, improving gastrointestinal mucosal integrity, enhancing

cell-mediated immune responses, attenuating inflammatory responses to stress, and improving blood flow to poorly vascularized and ischemic tissue [34]. Many of the studies supporting pre-operative nutritional therapy have had significant methodologic flaws, the data have been heterogeneous, and all infectious complications, not SSI per se, have been the primary end point for many of them. A recent study of patients undergoing total gastrectomy for gastric cancer found that pre-operative immunonutrition did not impact the risk of SSI [35].

#### *Smoking: Optimizing pre-operative cessation*

While there is strong evidence that smoking is a major risk factor for SSI and that smoking cessation intervention reduces that risk [36], whether a smoking threshold for increased risk of SSI exists is not known. The optimal timing of pre-operative smoking cessation that results in substantial reduction in SSI is unknown.

#### *Obesity: Contribution to SSI risk, optimizing measurement*

Obesity, a known risk factor for SSI [37,38], is associated with multiple co-morbidities (e.g., diabetes mellitus, metabolic syndrome, increased American Society of Anesthesiologists class, tissue hypoperfusion, and prolonged surgical procedures); however, the relative contributions to SSI risk of obesity alone and obesity in combination with these factors is unknown. Obesity has been characterized by descriptors such as weight, body mass index, subcutaneous fat at the site of incision, excess body fat, percent body fat, and other morphometric body measurements, but the best measure as predictor of SSI risk remains elusive. While tissue penetration of parenteral antimicrobial agents at the site of incision has been shown to be dependent on dosing in obese patients, the differences in the pharmacokinetics of various antimicrobial agents between normal weight and obese patients have been studied poorly. The impact of the type of subcutaneous tissue closure, (including whether or not to use a drain), on the risk of SSI in obese patients, remains unknown. The amount of fat relative to capillary perfusion in animal models and the optimization of perfusion might elucidate issues related to hypoperfusion, improved oxygen tension, and antimicrobial tissue penetration.

#### *Surgical techniques: Electrocautery, tissue handling, subcutaneous and skin closure*

Surgical technique might impact operative time, blood loss, and intra-operative contamination, all of which in turn impact SSI risk. Although these factors have been used as surrogates, they are not a direct measure of surgical technique. Quantifying the use of electrocautery and the extent to which it devitalizes tissue and contributes to SSI should be studied. Similarly, tissue handling by measuring the amount of tension and pressure applied to tissue and its contribution to SSI should be investigated. The optimal type of subcutaneous and skin closure in obese and non-obese patients undergoing a variety of surgical procedures, skin closure versus no closure, size and spacing of fascial sutures, placement and timing of removal of drains should be explored further.

### Anemia: Peri-operative anemia, blood transfusion

The lower hemoglobin value to define anemia resulting in SSI is unknown. The association between pre-operative anemia and SSI risk differs between publications [39,40]. Anemia might reduce oxygen transport to the surgical incision, impairing antibacterial mechanisms and incision healing, increasing the risk of SSI. It might, however, simply be associated with other medical conditions that increase infection risk. Some studies have demonstrated an association between peri-operative blood transfusion and an increased risk of SSI [41–43]. In addition, patients with anemia are likely to be at increased risk of receiving a peri-operative blood transfusion [44]. The relative risks of anemia and transfusion are unknown.

### *S. aureus* colonization

*Staphylococcus aureus* is the micro-organism most commonly associated with SSI. In addition, the overall incidence of SSI because of both methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* (MRSA) strains is increasing [45]. Colonization with *S. aureus*, present in 25%–30% of persons in the community, is a recognized risk factor for SSI [46]. Thus, approaches to the identification and decolonization of *S. aureus* carriers could reduce the risk of *S. aureus* SSI. High-quality evidence on the decolonization of staphylococci from the nasopharynx and its effectiveness in reducing the risk of *S. aureus* SSI is limited. In a large meta-analysis of orthopedic and cardiac surgical patients, decolonization was associated with a lower incidence of gram-positive SSI [47]; however, decolonization appeared to be less effective in patients undergoing other surgical procedures [48].

In a large randomized double-blind placebo-controlled study, prophylactic intranasal application of mupirocin did not significantly reduce the rate of *S. aureus* SSI [49]. In a recent trial, combined pre-operative bathing with chlorhexidine gluconate and nasal decolonization resulted in a significant reduction in *S. aureus* SSI in a population in which MRSA was nearly absent [50]. Overall rates of SSI were not reported, however. There are significant logistic and cost-related issues associated with programs for screening and decolonization of *S. aureus* carriers and increasing concerns about emerging bacterial resistance to mupirocin [51]. Additional research to identify those patients who would most likely benefit from targeted screening and decolonization as well as the optimal means of performing both is warranted.

### SSI definition and surveillance

Differences in SSI rates reported for similar surgical procedures may reflect different interpretations of SSI definitions, inconsistent coding, or variability in the intensity of surveillance (particularly post-discharge surveillance). Although the CDC SSI surveillance definitions are the most widely used [52,53], many have called for improvement in both the definition and surveillance of SSIs.

Surgeons have questioned the categorization of SSI into superficial, deep incisional, and organ/space [54,55]. Superficial SSIs are the most common. While they are less likely to be associated with increased length of hospital stay and cost [54], they continue to be an outcome of major significance to the patient and surgeon. It has also been postulated that su-

perficial infections are the SSIs most likely to be identified after discharge from either outpatient or inpatient operations and thus potentially go undetected by surveillance mechanisms [55]. In contrast, deep incisional and organ/space SSIs are most commonly detected on admission and re-admission to the hospital and therefore are not subject to the variability in identification or post-discharge surveillance. For public reporting purposes, deep incisional and organ/space SSIs are combined into a single category. In select procedures, organ/space infections can result from a technical failure such as an anastomotic leak in bowel operations. Whether technical failure-related organ/space infections should continue to be combined with other organ/space infections for public reporting purposes remains a topic of discussion. More research will need to be performed to validate or refute these concepts. In addition, there needs to be uniform policies and support for those surveillance strategies that are deemed to be most effective.

### Conclusion

Over the years, important strides advancing our knowledge in the prevention of SSI have been made. Recommendations made in the accompanying *CDC and HICPAC Guideline for the Prevention of Surgical Site Infection* are based on RCT-level evidence and reveal substantial gaps that deserve our consideration for future research that will also address the cost-effectiveness of those measures. This article presents opportunities for SSI research focusing on prevention effectiveness and high-yield questions to help prioritize SSI research opportunities over the next few years.

### Author Disclosure Statement

No competing financial interests exist.

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