A Review of Some Selective Relevant Literature

APIC Grand Canyon Chapter 88

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MEDICAL COLLEGE OF WISCONSIN

Papers for Discussion

1. Jessica L. Seidelman, et al Surgical Site Infection Prevention: A Review. 250 JAMA 2023;329: 244-252.

2. Massimo Sartelli, et al. Surgical Antibiotic Prophylaxis: A Proposal for a Global Evidence-Based Bundle. Antibiotics 2024;13: 1-16 https://doi.org/10.3390/antibiotics13010100

3. David J. Leaper, et al. Assessment of the Risk and Economic Burden of Surgical Site Infection Following Colorectal Surgery Using a US Longitudinal Database: Is There a Role for Innovative Antimicrobial Wound ClosureTechnology to Reduce the Risk of Infection? Diseases of the Colon and Rectum 2020;63: 1628-1638.

4. Lauren T. Kerivan, et al. Closed Incisional Negative Pressure Wound Therapy is Cost-Effective at Reducing Superficial Surgical Site Infections. Surgical Infections 2025;26: 413-419.

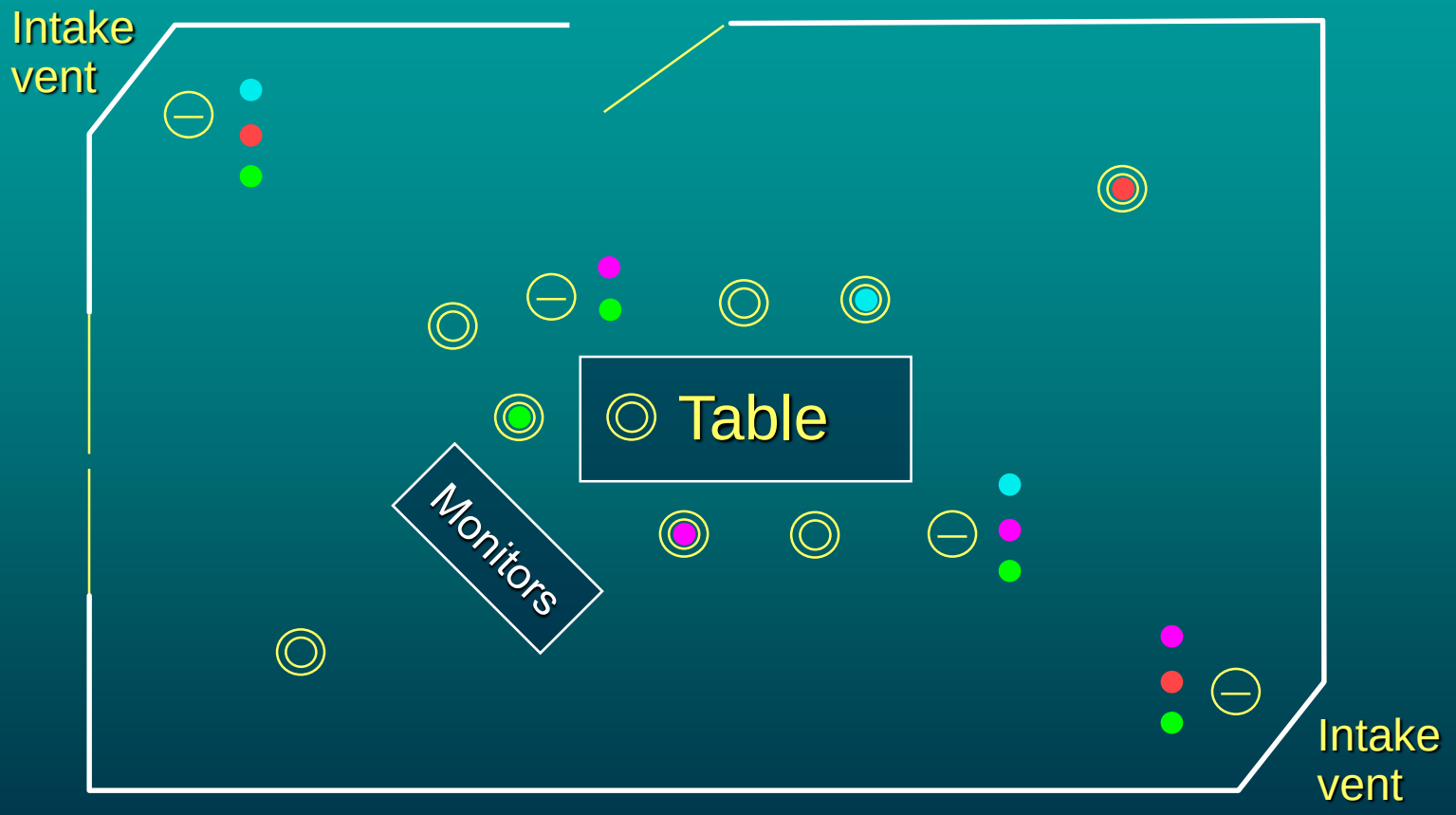

“It is not the air,
it is something in the air.”
Lister 1861

Coagulase-Positive Staphylococci Recovered From Operating Room Personnel

Source	Number of cultures	Coagulase-positive Staph. recovered: Number	Coagulase-positive Staph. recovered: Percent
Hospital 1	1,440	248	17.2
Hospital 2	2,888	388	13.4
Hospital 3	1,654	512	31.0
Hospital 4	1,514	287	19.0
Hospital 5	1,767	485	27.4
Totals	9,263	1,920	20.7

Ann Surg 1964; 160: 1-92

Vascular Operating Room

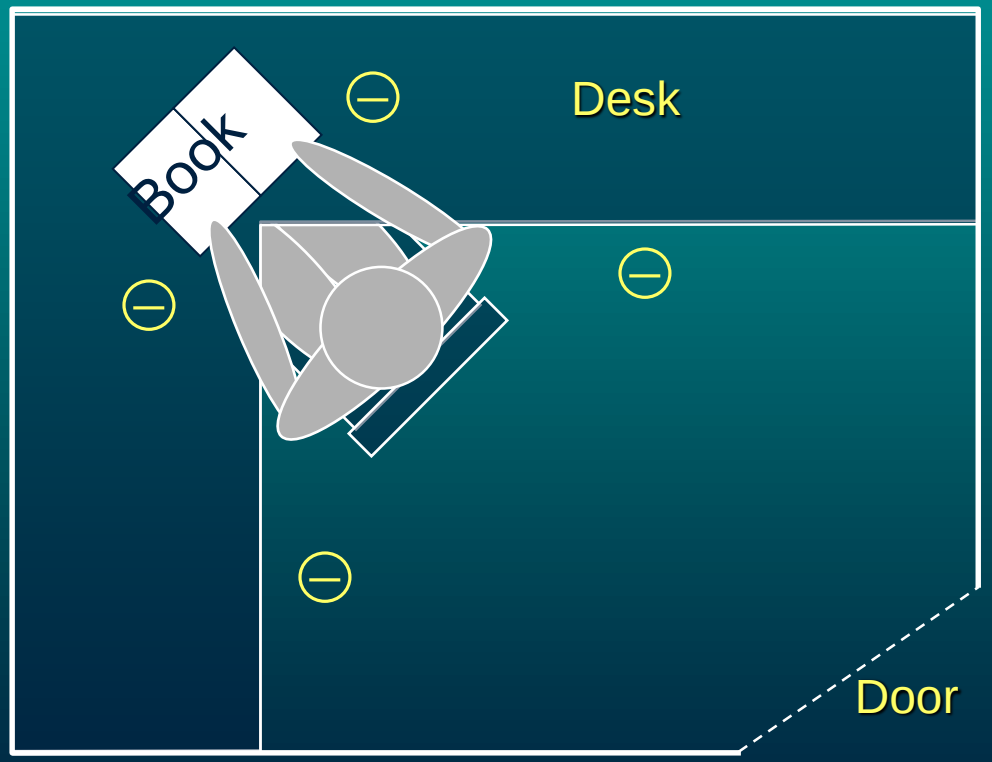


⊖ - Cascade Impactor

◎ - Personnel

• - Colored dots - *S. aureus* recovery from anterior nares

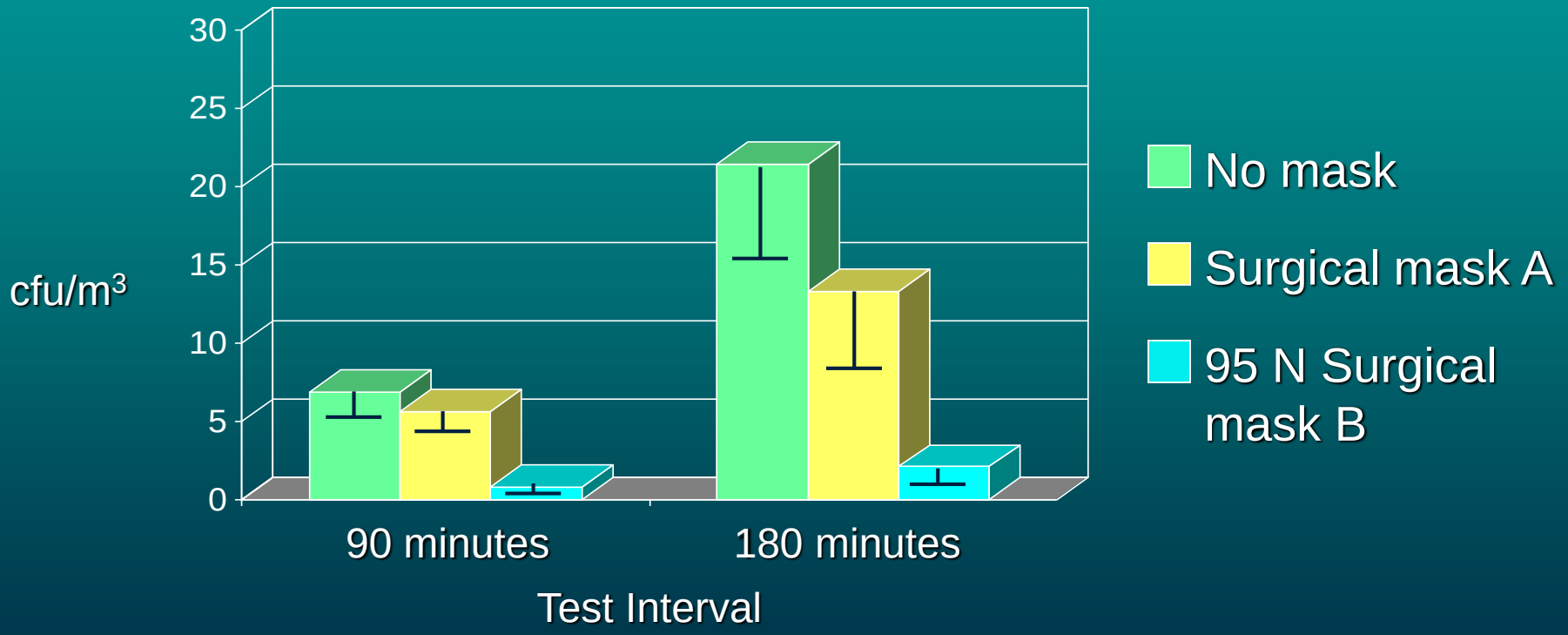
Impact of Surgical Mask on Prevention of Oral-Pharyngeal Shedding



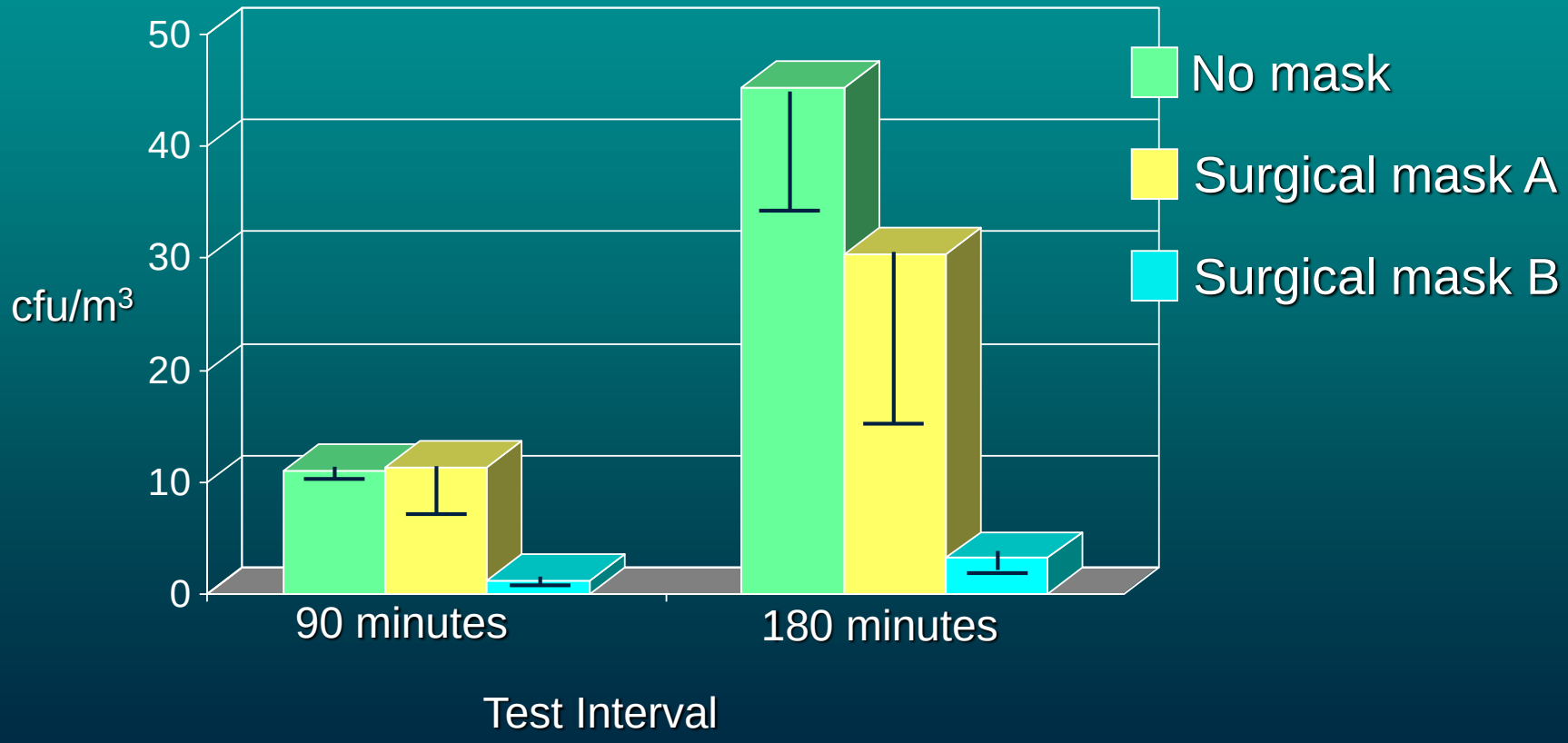
⊖ - Cascade Impactor

Area = ~50 sqft

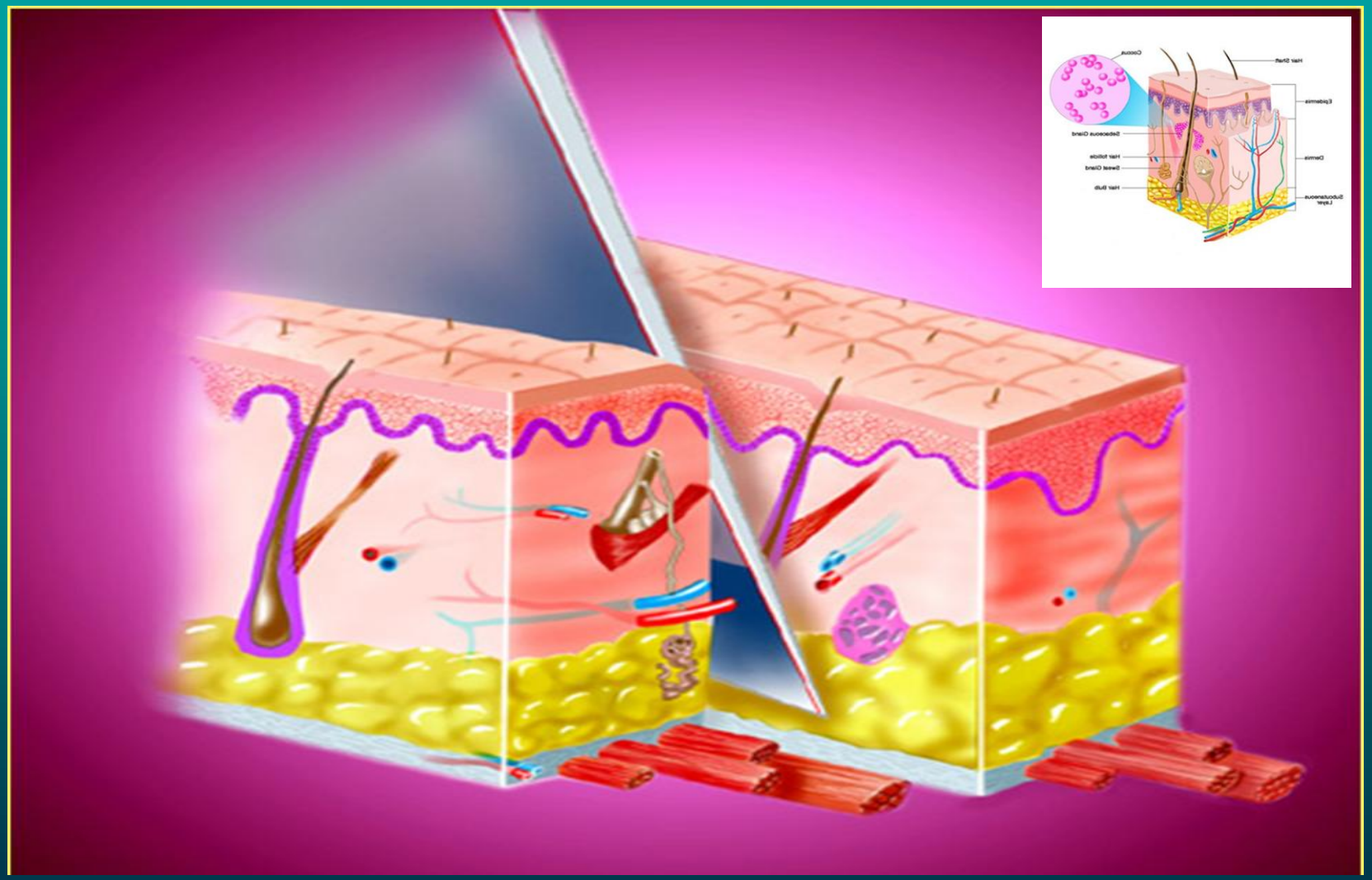
Impact of Surgical Masks on Prevention of Nasopharyngeal Shedding (N=20)



Impact of Rhinorrhea on Microbial Shedding (N=6)



It’s all about the surgical wound and comorbid risk



“….all surgical wounds are contaminated to some degree at closure – the primary determinant of whether the contamination is established as a clinical infection is host (wound) defense”

Belda et al., JAMA 2005;294:2035-2042; Wiley AM, et al. Clin Orthop Relat Res 1979;139:150-155

JAMA | Review

Surgical Site Infection Prevention
A Review

Jessica L. Seidelman, MD, MPH; Christopher R. Mantyh, MD; Deverick J. Anderson, MD, MPH

IMPORTANCE Approximately 0.5% to 3% of patients undergoing surgery will experience infection at or adjacent to the surgical incision site. Compared with patients undergoing surgery who do not have a surgical site infection, those with a surgical site infection are hospitalized approximately 7 to 11 days longer.

OBSERVATIONS Most surgical site infections can be prevented if appropriate strategies are implemented. These infections are typically caused when bacteria from the patient's endogenous flora are inoculated into the surgical site at the time of surgery. Development of an infection depends on various factors such as the health of the patient's immune system, presence of foreign material, degree of bacterial wound contamination, and use of antibiotic prophylaxis. Although numerous strategies are recommended by international organizations to decrease surgical site infection, only 6 general strategies are supported by randomized trials. Interventions that are associated with lower rates of infection include avoiding razors for hair removal (4.4% with razors vs 2.5% with clippers); decolonization with intranasal antistaphylococcal agents and antistaphylococcal skin antiseptics for high-risk procedures (0.8% with decolonization vs 2% without); use of chlorhexidine gluconate and alcohol-based skin preparation (4.0% with chlorhexidine gluconate plus alcohol vs 6.5% with povidone iodine plus alcohol); maintaining normothermia with active warming such as warmed intravenous fluids, skin warming, and warm forced air to keep the body temperature warmer than 36 °C (4.7% with active warming vs 13% without); perioperative glycemic control (9.4% with glucose <150 mg/dL vs 16% with glucose >150 mg/dL); and use of negative pressure wound therapy (9.7% with vs 15% without). Guidelines recommend appropriate dosing, timing, and choice of preoperative parenteral antimicrobial prophylaxis.

CONCLUSIONS AND RELEVANCE Surgical site infections affect approximately 0.5% to 3% of patients undergoing surgery and are associated with longer hospital stays than patients with no surgical site infections. Avoiding razors for hair removal, maintaining normothermia, use of chlorhexidine gluconate plus alcohol–based skin preparation agents, decolonization with intranasal antistaphylococcal agents and antistaphylococcal skin antiseptics for high-risk procedures, controlling for perioperative glucose concentrations, and using negative pressure wound therapy can reduce the rate of surgical site infections.

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Multimedia

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A surgical site infection is defined as infection following an operation at an incision site or adjacent to the surgical incision.[1] Infections occur in approximately 0.5% to 3% of patients undergoing surgery[2-4] and are among the most prevalent health care–acquired infections.[5-7] Surgical site infections are responsible for approximately $3.5 billion to $10 billion in US health care costs annually.[8,9] Compared with patients without surgical site infections, those with them remain in the hospital approximately 7 to 11 days longer[7,10]; 1 study involving 177 706 postsurgical patients reported that 78% were readmitted as a result of the infection.[11] This review summarizes current evidence-based interventions for prevention of surgical site infection that are applicable to the majority of operations (Box).

Methods

We searched PubMed, Google Scholar, and the Cochrane database for English-language studies of pathogenesis, clinical presentation, and prevention of surgical site infections published from January 1, 2016, when guidelines were most recently published by the World Health Organization, to September 15, 2022. In addition, we manually searched the references of selected articles for additional relevant publications. We prioritized randomized trials, systematic reviews, meta-analyses, clinical practice guidelines, and articles pertinent to general medical readership. Of 94 studies identified, 69 were included, consisting of 14 randomized trials, 19

Table 1. Modifiable and Nonmodifiable Patient-Related Factors Associated With Surgical Site Infections

Factor	Pathophysiology
Patient-related, modifiable	
Diabetes	Hyperglycemia impairs the innate immune system and promotes glycosylation of proteins, which compromises wound healing.[16] Diabetes can lead to higher perioperative glucose levels and hyperglycemia that is more difficult to treat.[17]
Immunosuppressive medications and conditions	Immunosuppressive clinical conditions or medications diminish the inflammatory phase of wound healing.[18,19]
Malnutrition	Malnutrition can decrease collagen synthesis, granulation formation in surgical wounds, and result in poor tissue healing. Hypoalbuminemia weakens innate immunity by prompting macrophage apoptosis and diminishing macrophage activation. Low albumin also accelerates the seepage of interstitial fluid into the surgical wound and promotes general tissue edema.[20]
Obesity	Adipose tissue has less blood flow, which inhibits the delivery of oxygen and antibiotics.[21-23]
Preoperative infections	Prior to elective surgery, recognize and treat all infections (even if they are distant from the surgical site).[24]
Tobacco use	Tobacco use causes vasoconstriction, which can progress to alterations in collagen metabolism, decreased inflammatory response, and relative ischemia.[25]
Patient-related, nonmodifiable	
Age	The skin's basement membrane and dermis thin with increasing age, and the skin loses its reserve of cutaneous blood vessels and nerves that diminish wound healing.[26,27]
History of prior skin and soft tissue infections	A history of skin and soft tissue infections may be indicative of issues with inherent immunity and propensity for infection.[28]
History of radiation therapy	Treatment with radiation induces underlying tissue injury and inhibits wound healing.

Table 2. Modifiable Operation–Related Factors Associated With Surgical Site Infections

Factor	Pathophysiology
Airborne contamination	Raising the amount of microorganisms in the operating room environment provides additional opportunity for surgical site infection. Most of the airborne pathogens are generated by persons in the operating room and their movements.[29,30]
Anticoagulation	Anticoagulants may generate continual oozing of the incision and slow wound healing.[31]
Blood transfusions	Blood transfusions impair macrophage activity and influence infection risk.[32]
Decreased tissue oxygenation	Diminished tissue oxygenation lends itself to decreased oxidative killing by neutrophils and impaired tissue healing from depleted epithelialization, neovascularization, and collagen formation. Low oxygen settings can curtail the efficacy of perioperative antibiotics.[33,34]
Foreign material	Foreign material stimulates inflammation at the surgical site and raises the risk of surgical site infection.[35,36]
Operation length	Longer operative time is associated with higher damage to wound cells, wound contamination, and exposure to the outside environment.[37]
Perioperative hypothermia	Perioperative hypothermia weakens immune system protection against surgical wound contamination: vasoconstriction leads to impaired tissue perfusion and less access for key immune cells, less motility of key immune cells, and decreased scar formation.[38]
Postoperative hyperglycemia	Cellular functions of bactericidal activity, leukocyte adherence chemotaxis, and phagocytosis are enhanced by insulin and glycemic control, suggesting a direct relation between elevated blood glucose and cellular function deficits.[39] This relationship is observed in patients with and without a diagnosis of diabetes.
Surgical technique	Wound healing is decreased by leaving behind devitalized tissues, inadvertent entry into hollow viscera, inadequate blood supply maintenance, rough manipulation of tissue, misplaced drains and sutures, and unsuitable postoperative wound care.[40]
Wound care	Wounds that remain uncovered following surgery can be contaminated, or uncontrolled drainage can diminish the integrity of the surrounding skin.[41,42]
Wound contamination from patient's own flora	Wound classification delineates the degree of contamination of a surgical wound at the time of the operation.[43] Skin preparation and perioperative antibiotic administration reduce but do not eliminate the introduction of microorganisms at the surgical site.[44,45] Shaving leads to microscopic cuts in the skin that can become niduses for bacteria to multiply.[40] Without appropriate drapes and barrier devices, bacteria from hair follicles and deeper skin layers can recolonize the surgical site.
Wound contamination from operating room personnel	Transition of microorganisms from the surgical personnel's shoes, mouths, or body can contaminate surgical wounds.[14] Microorganisms from the hands of health care workers in the operating room can move onto the patient and operating field if personnel do not perform appropriate handwashing or gloving.[14,46,47]
Wound contamination from surgical instruments	Sterilization eliminates all microorganisms on the surfaces of surgical instruments. Using insufficiently sterilized tools can lead to pathogen transmission.[48]

antibiotics

MDPI

Review

Surgical Antibiotic Prophylaxis: A Proposal for a Global Evidence-Based Bundle

Massimo Sartelli [1,*], Federico Coccolini [2], Francesco M. Labricciosa [3], AbdelKarim. H. Al Omari [4], Lovenish Bains [5], Oussama Baraket [6], Marco Catarci [7], Yunfeng Cui [8], Alberto R. Ferreres [9], George Gkiokas [10], Carlos Augusto Gomes [11], Adrien M. Hodonou [12], Arda Isik [13], Andrey Litvin [14], Varut Lohsiriwat [15], Vihar Kotecha [16], Vladimir Khokha [17], Igor A. Kryvoruchko [18], Gustavo M. Machain [19], Donal B. O'Connor [20], Iyiade Olaoye [21], Jamal A. K. Al-Omari [22], Alessandro Pasculli [23], Patrizio Petrone [24], Jennifer Rickard [25], Ibrahima Sall [26], Robert G. Sawyer [27], Orlando Téllez-Almenares [28], Fausto Catena [29] and Walter Siquini [1]

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Ideally, an antibiotic for SAP should be able to achieve the following:

- Prevent SSIs;
- Reduce SSI morbidity and mortality;
- Diminish healthcare duration and cost;
- Not produce any adverse effects;
- Have no aftermath for the patient's intestinal microbial flora or the healthcare facility.

To achieve these goals, an antibiotic administered for SAP should fulfill the following:

- Active against the most likely bacteria that can contaminate the surgical field;
- Provided in an appropriate dosage and time that ensures adequate serum and tissue concentrations amid the whole operation;
- Safe;
- Administered for the shortest effective period, minimizing adverse effects, opportunistic infections, antimicrobial resistance (AMR) development, and costs.

A global evidence-based bundle for surgical antibiotic prophylaxis

1. Administering the appropriate antibiotic
2. Administering the antibiotic at the correct time before the incision
3. Re-administering the antibiotic for prolonged procedures and in patients with severe blood loss
4. Discontinuing surgical antibiotic prophylaxis after surgery
5. Monitoring the implementation level of the suggested measures

SKIN MICROBIOME

Contribution of the patient microbiome to surgical site infection and antibiotic prophylaxis failure in spine surgery

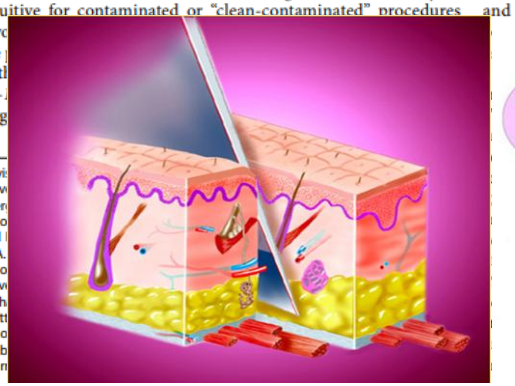
Dustin R. Long[1]*, Chloe Bryson-Cahn[2], Adam Waalkes[3], Elizabeth A. Holmes[3], Kelsi Penewit[3], Celeste Tavolaro[4], Carlo Bellabarba[4], Fangyi Zhang[4,5], Jeannie D. Chan[2,6], Ferric C. Fang[3,7,8], John B. Lynch[2], Stephen J. Salipante[3]

Despite modern antiseptic techniques, surgical site infection (SSI) remains a leading complication of surgery. However, the origins of SSI and the high rates of antimicrobial resistance observed in these infections are poorly understood. Using instrumented spine surgery as a model of clean (class I) skin incision, we prospectively sampled preoperative microbiomes and postoperative SSI isolates in a cohort of 204 patients. Combining multiple forms of genomic analysis, we correlated the identity, anatomic distribution, and antimicrobial resistance profiles of SSI pathogens with those of preoperative strains obtained from the patient skin microbiome. We found that 86% of SSIs, comprising a broad range of bacterial species, originated endogenously from preoperative strains, with no evidence of common source infection among a superset of 1610 patients. Most SSI isolates (59%) were resistant to the prophylactic antibiotic administered during surgery, and their resistance phenotypes correlated with the patient's preoperative resistome ($P = 0.0002$). These findings indicate the need for SSI prevention strategies tailored to the preoperative microbiome and resistome present in individual patients.

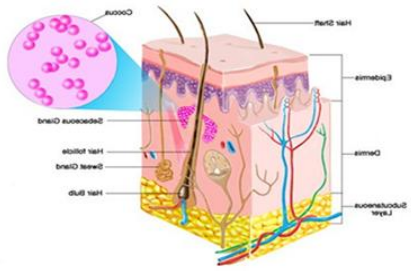
INTRODUCTION

Surgical site infection (SSI) is the most common and costly complication of modern surgery, affecting about 1 in 30 procedures (*1*). Compared with other hospital-acquired conditions, SSI rates have seen little improvement over recent reporting periods (*2*–*4*) despite wide adherence to standard infection prevention measures (*4*, *5*). Moreover, focused efforts to identify and correct deficiencies in established best practices for SSI prevention have not translated to reduced rates of infection (*6*), suggesting both the limited potential of current strategies to drive substantial further reductions in SSI and the need for new data to guide development of preventative approaches.

Future quality improvement in this arena remains limited by a poor fundamental understanding of both the origins of SSI and the high rates of resistance to prophylactic antimicrobial agents observed in these infections (*7*). Whereas the potential for surgical wounds to become inoculated with endogenous bacteria may be intuitive for contaminated or "clean-contaminated" procedures



cleaning, sterile processing, and operating room attire, which target "exogenous" sources of infection from nosocomial reservoirs. In contrast, prior microbiological studies (*13*–*15*) indicate that many wound infections may arise from "endogenous" reservoirs of colonizing microbiota carried by the patient. Yet, seminal studies on endogenous wound infection predate the era of next-generation sequencing and have largely been limited to *Staphylococcus aureus*, leaving unaddressed the broader range of pathogens, including Gram-negative and anaerobic organisms, that are commonly implicated in SSI (*16*). A more generalized model of SSI as an infectious process of predominantly endogenous origin (including in clean procedures and non-staphylococcal infections) has therefore not been widely adopted. Surgical culture, health care system initiatives, research studies, product development, legal proceedings, and many guidelines consequently continue to place emphasis on hospital-centered rather than patient-centered factors, such as operating room traffic, surgical attire, air flow, equipment decontamination, and interpersonal transmission (*17*–*23*). Only recently has there



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JAMA Surgery | Review

Preventing Surgical Site Infections in the Era of Escalating Antibiotic Resistance and Antibiotic Stewardship

Dustin R. Long, MD; Adam Cifu, MD; Stephen J. Salipante, MD, PhD; Robert G. Sawyer, MD; Kaylie Machutta, BS; John C. Alverdy, MD

IMPORTANCE According to the Centers for Disease Control and Prevention and governing bodies within the American College of Surgeons, the administration of antibiotics as prophylaxis against infection prior to a planned elective procedure is, with rare exception, routinely recommended. The goal of "getting to zero" infections remains a high priority for policymakers, practitioners, and certainly for patients.

OBSERVATIONS Despite the many advances in surgical technique, skin decontamination, sterile procedure, and enhanced recovery programs, surgical site infections continue to adversely affect procedures as diverse as dental implant surgery, joint arthroplasty, and major abdominal surgery. Although surgical site infection rates are at historically low levels, progress has stalled in recent reporting periods and such infections remain disabling, costly, and occasionally lethal. Stakeholders in the field, including surgeons, infectious diseases specialists, and industry, advocate for strategies emphasizing greater levels of intraoperative sterility or broader-spectrum antibiotic coverage as the most appropriate path forward.

CONCLUSIONS AND RELEVANCE The current emphasis on ever-increasing levels of intraoperative sterility and extended-spectrum antibiotic use are not sustainable long-term solutions. Continuing to escalate these approaches may contribute to unintended consequences including antimicrobial resistance. Principles of antimicrobial stewardship and microbiome sciences can be applied to inform a more effective and sustainable approach to infection prevention in the field of surgery.

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Surgeons' practices toward prophylactic antibiotic administration for elective surgery reflect a perspective that prophylactic antibiotics are both safe and effective and should therefore be maximally leveraged for the prevention of surgical site infections (SSIs).[1] Overall, routine preoperative antibiotic prophylaxis significantly reduces the incidence of SSIs compared with no,[2,3] or delayed,[4] systemic antibiotic prophylaxis in many procedures. However, in the decades since the first trials of routine surgical antibiotic prophylaxis were conducted, a new appreciation for the limitations and harms of antibiotic use has emerged and antibiotic administration for surgical prophylaxis has grown to comprise 1 in 5 of all inpatient antibiotic exposures.[5] Over the same period, the prevalence of bacteria resistant to common antibiotic agents has increased in our communities and health systems, such that now up to half of all SSIs in the US are estimated to be resistant to the recommended prophylactic agent, while national SSI rates have stopped decreasing.[6,7] In turn, several recent studies focused on high-risk procedures (ie, pancreas and colon surgery) have shown that use of additional and/or broader-spectrum prophylactic antibiotics can incrementally reduce SSI rates in this new context,[8-12] an effect specifically associated with the expanded coverage of bacteria resistant to more narrow-spectrum agents.[11,13] However, a high degree of inappropriate perioperative antibiotic use persists, both in the US and internationally.[5,14,15] Such expansions in the spectrum of, duration of, and indications for perioperative antibiotics by health systems and individual surgeons represent a natural response to the persistent problem of SSIs, but are in conflict with the growing reality of antimicrobial resistance and antibiotic stewardship programs intended to constrain harm associated with their overuse.[16] In this article, we review challenges, misconceptions, and opportunities in preventing SSIs in the era of escalating antibiotic resistance, and discuss the risks, benefits, and alternatives of current prophylactic antibiotic prescribing practices in the context of antimicrobial stewardship.

Discussion and Observations

Proposed Framework for Stewardship of Surgical Antibiotic Prophylaxis

Although the best approaches to optimizing antimicrobial use in surgery may vary appropriately between practice settings and procedure types, we propose a general 5-part framework (**Box**), based on a survey of current literature and priority areas in this field, by which the principles of antimicrobial stewardship and the sustained effectiveness of surgical antibiotic prophylaxis can be integrated.

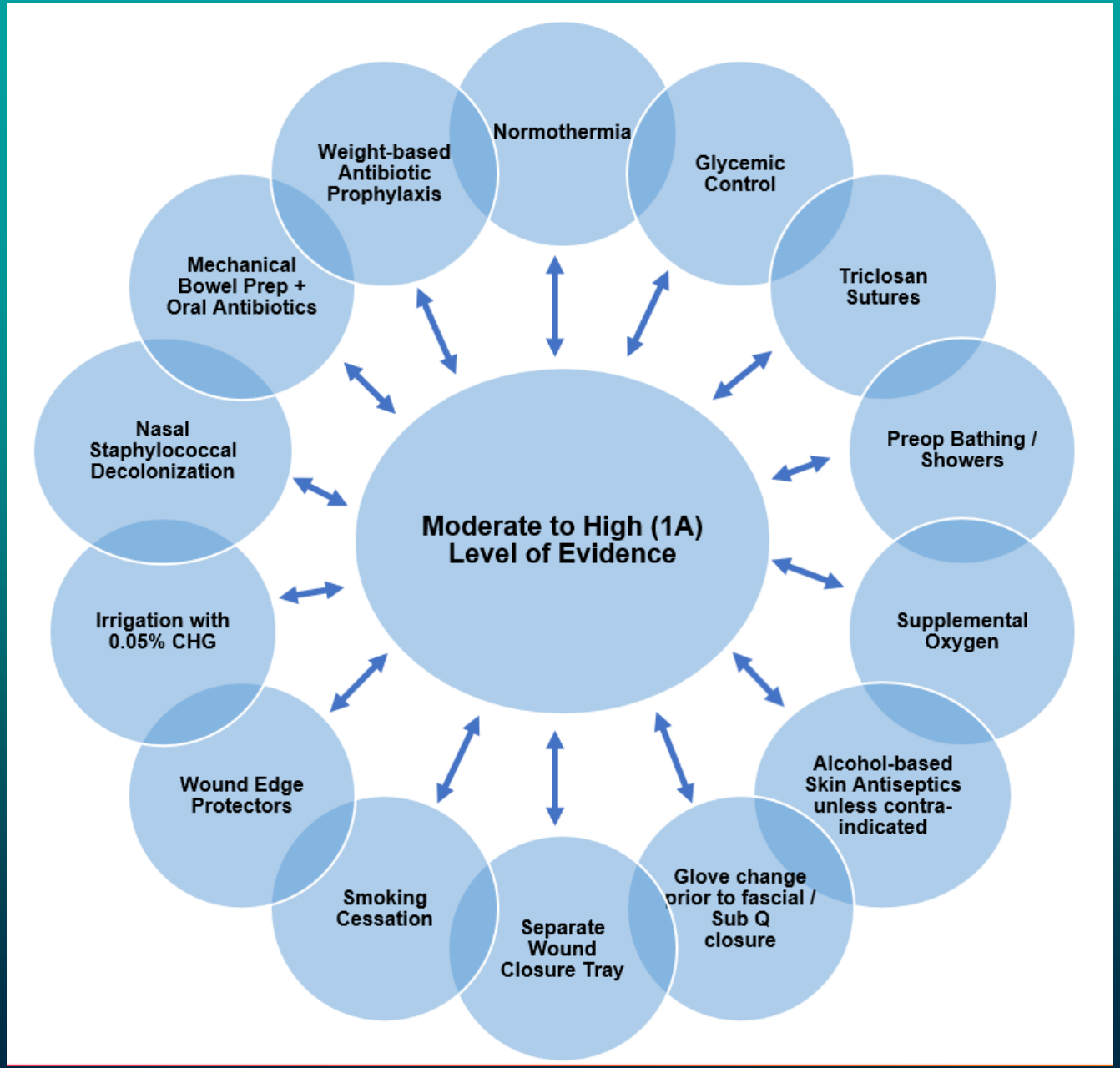
Long DR, et al. Sci Transl Med 2024 Apr 10;16(742):eadk8222

Long DR, et al. JAMA Surg. 2024;159:949-9560

What Do The Long Studies Tell Us?

- The Spinal Study results identify the patient microbiome as the primary reservoir for SSI.
- Most SSI isolates (59%) were resistant to the prophylactic antibiotic administered during surgery, and their resistance phenotypes correlated with the patient's preoperative resistome (*p=0.0002*).
- The anticipated global increase in colonization of healthy individuals with antimicrobial resistant organisms will be reflected in a rapidly changing microbial landscape within our hospitals and communities.
- These findings suggest that future efforts in infection prevention should enable, (1) more individualize and (2) patient-centered interventional strategies (BM) = bundle modification

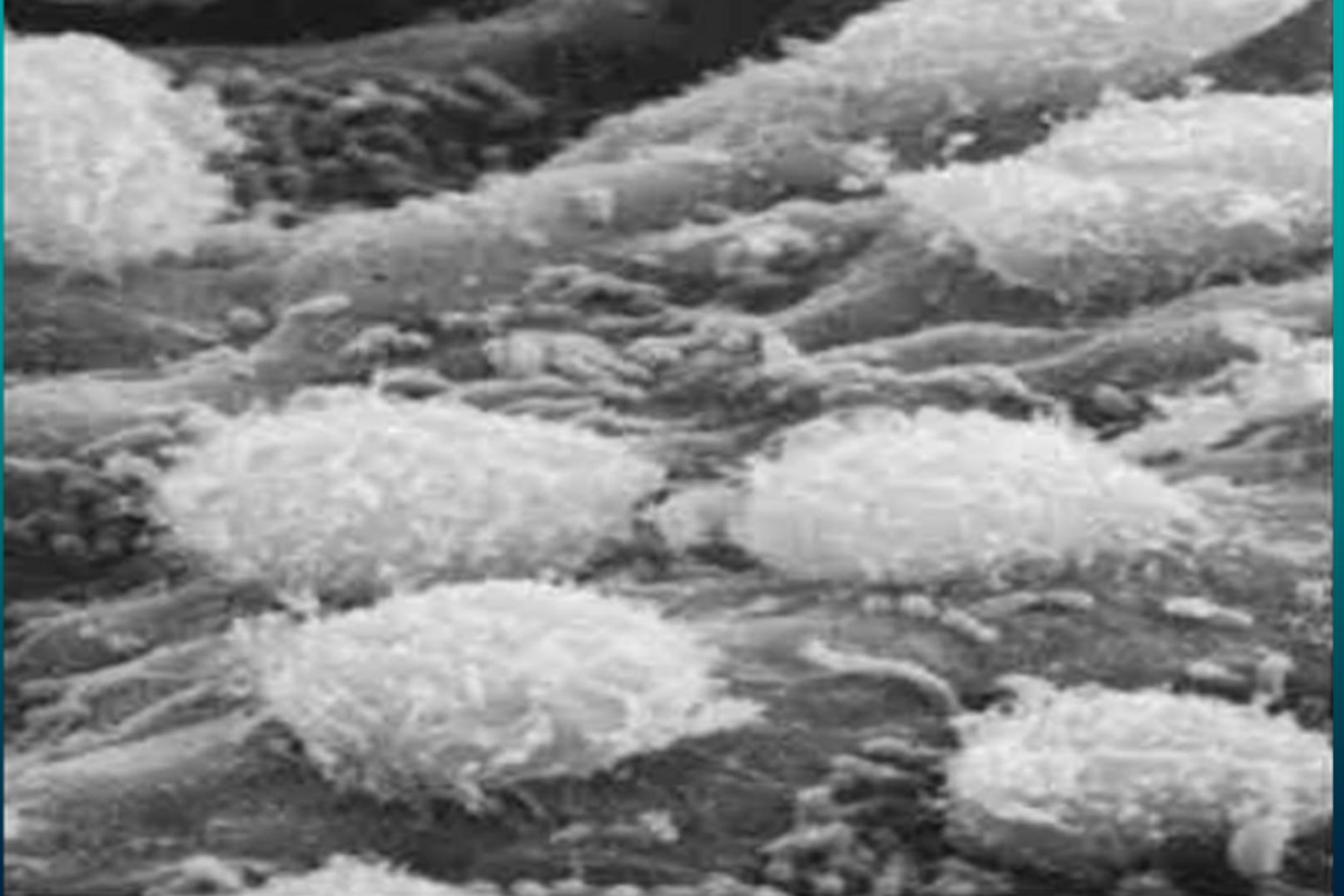
Selecting An Evidence-Based (EB) Surgical Care Bundle



Food For Thought

Remember, the human microbiome plays a role in both health and disease. As heathcare professionals, our ability to do harm to the microbiota is substantial, with uncertain short- and long-term impacts.

Antimicrobial stewardship programs have the potential to minimize this impact, align antibiotic usage practices with rational evidence-based strategies underpinned by data, and ultimately improve patient outcomes.



ORIGINAL CONTRIBUTION

Assessment of the Risk and Economic Burden of Surgical Site Infection Following Colorectal Surgery Using a US Longitudinal Database: Is There a Role for Innovative Antimicrobial Wound Closure Technology to Reduce the Risk of Infection?

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Abhishek Chitnis, Ph.D.[2] • Andrew Hogan, M.Sc.[4] • George W.J. Wright, Ph.D.[4]
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BACKGROUND: Colorectal surgical procedures place substantial burden on health care systems because of the high complication risk, of surgical site infections in particular. The risk of surgical site infection after colorectal surgery is one of the highest of any surgical specialty.

OBJECTIVE: The purpose of this study was to determine the incidence, cost of infections after colorectal surgery, and potential economic benefit of using antimicrobial wound closure to improve patient outcomes.

DESIGN: Retrospective observational cohort analysis and probabilistic cost analysis were performed.

SETTINGS: The analysis utilized a database for colorectal patients in the United States between 2014 and 2018.

PATIENTS: A total of 107,665 patients who underwent colorectal surgery were included in the analysis.

MAIN OUTCOME MEASURES: Rate of infection was together with identified between 3 and 180 days postoperatively, infection risk factors, infection costs over 24 months postoperatively by payer type (commercial payers and Medicare), and potential costs avoided per patient by using an evidence-based innovative wound closure technology.

RESULTS: Surgical site infections were diagnosed postoperatively in 23.9% of patients (4.0% superficial incisional and 19.9% deep incisional/organ space). Risk factors significantly increased risk of deep incisional/organ-space infection and included several patient comorbidities, age, payer type, and admission type. After 12 months, adjusted increased costs associated with infections ranged from $36,429 to $144,809 for commercial payers and $17,551 to $102,280 for Medicare, depending on surgical site infection type. Adjusted incremental costs continued to increase over a 24-month study period for both payers. Use of antimicrobial wound closure for colorectal surgery is projected to significantly reduce median payer costs by $809 to $1170 per patient compared with traditional wound closure.

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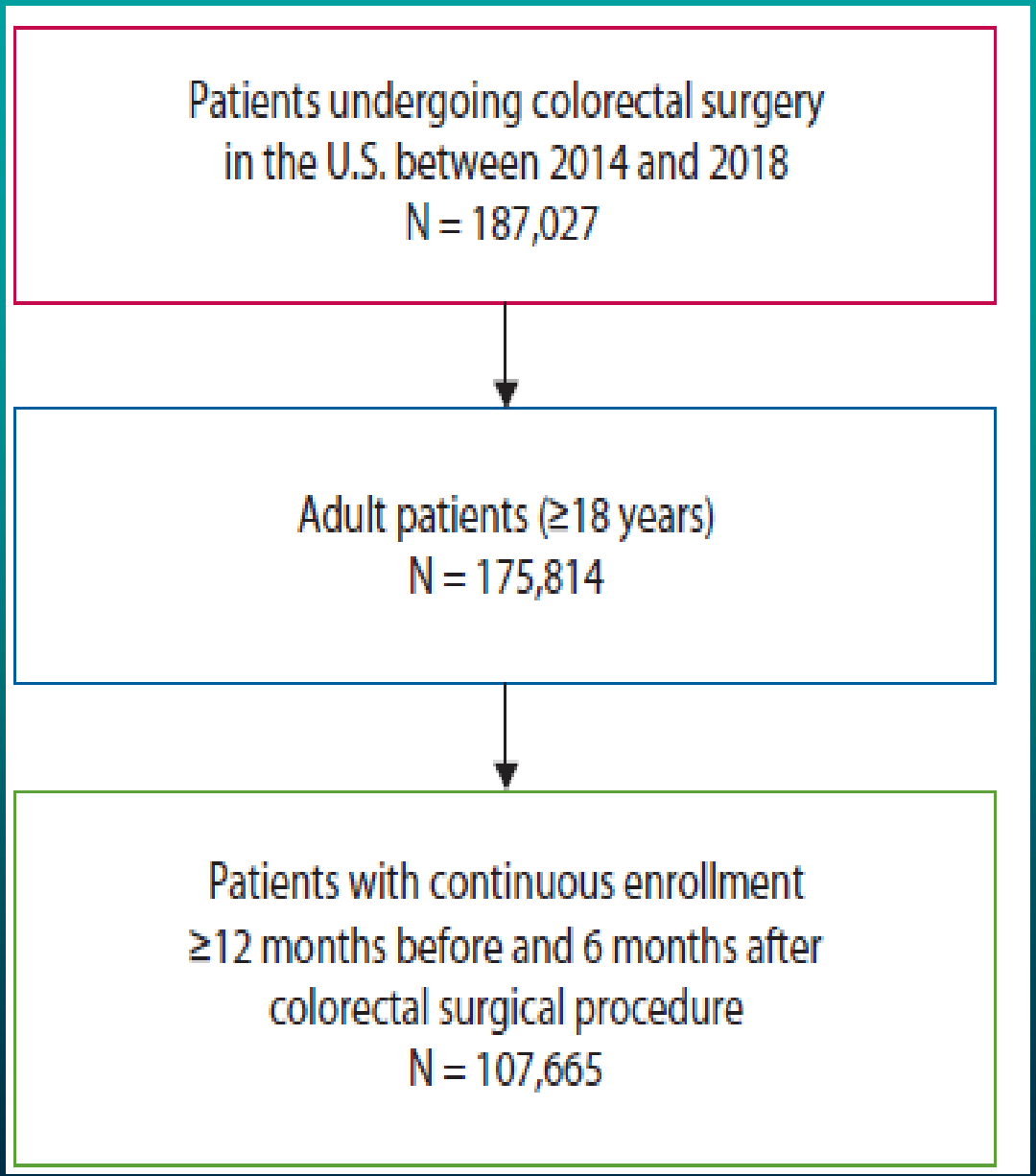

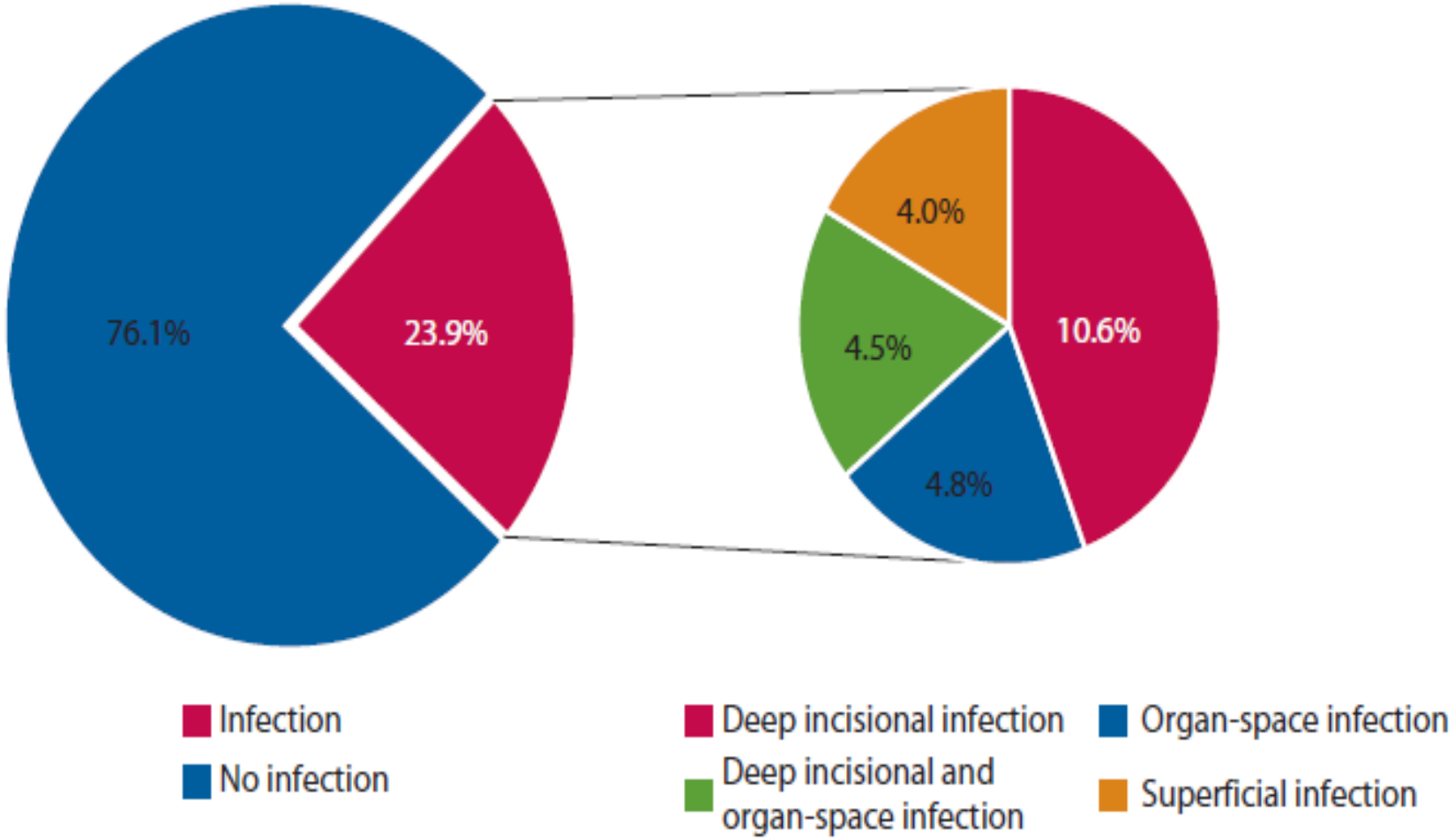

FIGURE 4. Surgical site infection rate at 6 months after the index colorectal surgery by infection type.

Cost of Superficial and Deep/Organ Space Colorectal SSIs

TABLE 3. Summary of SSI costs from the database analysis by infection type, payer, and time point

	Mean SSI cost (95% CI)			
Payers	*Deep incisional and organ-space*	*Deep incisional*	*Organ-space*	*Superficial*
Commercial payers				
6 months	$122,117 ($117,490–$127,007)	$43,490 ($42,120–$44,888)	$71,324 ($67,859–$74,904)	$28,866 ($26,690–$31,115)
12 months	$144,809 ($137,819–$152,062)	$52,628 ($50,633–$54,670)	$85,079 ($79,641–$90,747)	$36,429 ($33,085–$39,910)
24 months	$164,471 ($152,816–$176,759)	$64,563 ($61,143–$68,097)	$96,910 ($87,550–$106,844)	$44,281 ($38,538– $50,350)
Medicare				
6 months	$84,067 ($77,457–$91,069)	$25,387 ($22,884–$28,010)	$47,955 ($44,325–$51,764)	$16,026 ($12,884–$19,375)
12 months	$102,280 ($92,575–$112,670)	$32,456 ($28,832–$36,280)	$54,547 ($49,293–$60,111)	$17,551 ($13,040–$22,408)
24 months	$121,274 ($104,102–$140,169)	$45,771 ($38,679–$53,407)	$66,784 ($56,992–$77,402)	$20,758 ($12,538–$29,834)

SSI = surgical site infection.

Leaper DJ, Holy CE, Spencer M, Chitnis A, Hogan A, Wright GWJ, et al. Assessment of the Risk and Economic Burden of Surgical Site Infection Following Colorectal Surgery Using a US Longitudinal Database: Is There a Role for Innovative Antimicrobial Wound Closure Technology to Reduce the Risk of Infection? Diseases of the colon and rectum. 2020;63(12):1628-38.

Are We Missing Anything Here!

- Infection Rate (107,665 Colorectal Patients): 23.9%
- 50% of infections diagnosed at 3-25 days while 75% of infections diagnosed by/after 2 months
- CDC-NHSN & ACS-NSQIP closes the books on colorectal surveillance at 30-days
- We are missing 25%-30% of colorectal infections due to our current NHSN Surveillance Strategy

SURGICAL INFECTIONS
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Closed Incisional Negative Pressure Wound Therapy is Cost-Effective at Reducing Superficial Surgical Site Infections

Lauren T. Kerivan,[1] Katherine A. Vilain,[2] Terra M. Hill,[1] and Christopher A. Guidry[1]

Abstract

Background: Surgical site infections (SSIs) have a significant health economic burden, accounting for more than US $3.3 billion in costs, and lead to increased microbial resistance, prolonged hospital stays, elevated 30-day mortality rates, greater incidences of reoperation, and decreased quality of life. Recently, evidence has emerged suggesting that prophylactic closed incision negative pressure wound therapy (ciNPWT) may substantially reduce the risk of post-operative wound complications, specifically SSIs. This study aimed to evaluate whether ciNPWT is cost-effective compared with routine incision care for the prevention of superficial SSIs.
Hypothesis: We hypothesized that ciNPWT is cost-effective compared with routine incision care for the prevention of superficial SSIs.
Methods: A cost-effectiveness decision analytic model was created comparing the use and non-use of ciNPWT. Superficial SSI probabilities, cost of care for patients with and without post-operative infection, and quality of life Short Form (SF)-36 survey data were obtained from a literature review. Cost of ciNPWT was obtained from health administrative data. A decision tree was constructed using TreeAge Software Pro Version 2020 (TreeAge Software, Inc., Williamstown, MA). Deterministic and probabilistic sensitivity analyses were performed to evaluate the robustness and reliability of the model.
Results: One-way sensitivity analysis with a willingness-to-pay threshold of $5,000 demonstrated that above a baseline infection rate of approximately 6.4%, ciNPWT is cost-effective at reducing superficial SSI. Probabilistic sensitivity analysis indicated that even with uncertainty present in the parameters analyzed, the majority of simulations (95.4%) favored ciNPWT as the more effective tactic.
Conclusions: Despite the added device cost, ciNPWT is cost-effective for superficial SSI prevention across a variety of surgical infection risk profiles.

Keywords: cost-effectiveness; decision analysis; negative-pressure wound therapy; prevention; surgical site infections

Background

Surgical site infections (SSIs) have a significant health economic burden, accounting for more than US $3.3 billion in costs annually, and lead to prolonged hospital stays, elevated 30-day mortality rates, greater incidences of reoperation, and decreased quality of life.[1] In 2016, the World Health Organization (WHO) identified prevention of SSIs as an international high priority and published recommendations for a wide range of risk-reducing perioperative interventions.[2] Both the 2016 and 2018 editions of the WHO global guidelines conditionally recommended prophylactic use of closed incision negative pressure wound therapy (ciNPWT) for SSI prevention, despite noting overall low-quality evidence and lack of consensus with other national/specialty guidelines.[3,4] At least tentative recommendations have similarly been made by the World Society of Emergency Surgery, the Japan Society for Surgical Infection, the American College of Surgeons, and a joint recommendation from the Society for Healthcare Epidemiology and the Infectious Diseases Society of America.[5–8]

Recently, ciNPWT has been the subject of multiple randomized controlled trials, systematic reviews, and meta-analyses with accumulating moderate-to-high certainty evidence for its

[1]Department of Surgery, University of Kansas Medical Center, Kansas City, KS, USA.
[2]Saint Luke's Hospital Cardiovascular and Cardiothoracic Research, Kansas City, MO, USA.
Data from this article were presented as an oral presentation at the Surgical Infection Society Annual Meeting on June 6, 2024, in Miami, FL.

So, What Do We Know?

1. Negative pressure wound therapy (NPWT) accelerates healing by applying controlled suction to a wound, removing excess fluid, reducing bacteria, and stimulating tissue growth.

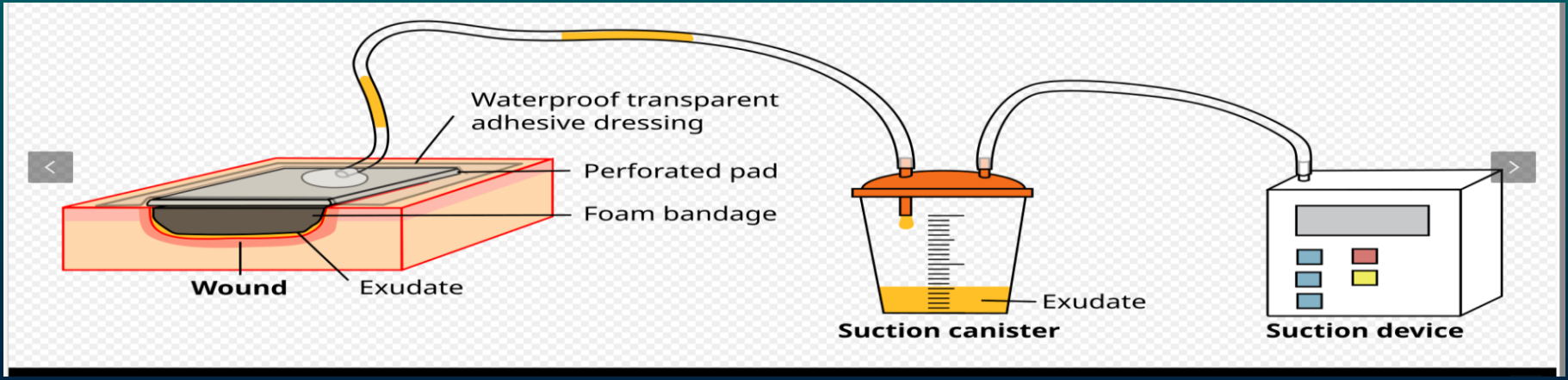
2. The therapy removes excess fluid (exudate) and reduces edema, which improves blood flow and oxygen delivery to the wound bed, creating a cleaner and healthier environment. The suction also pulls wound edges together, decreasing the wound size and promoting faster closure.

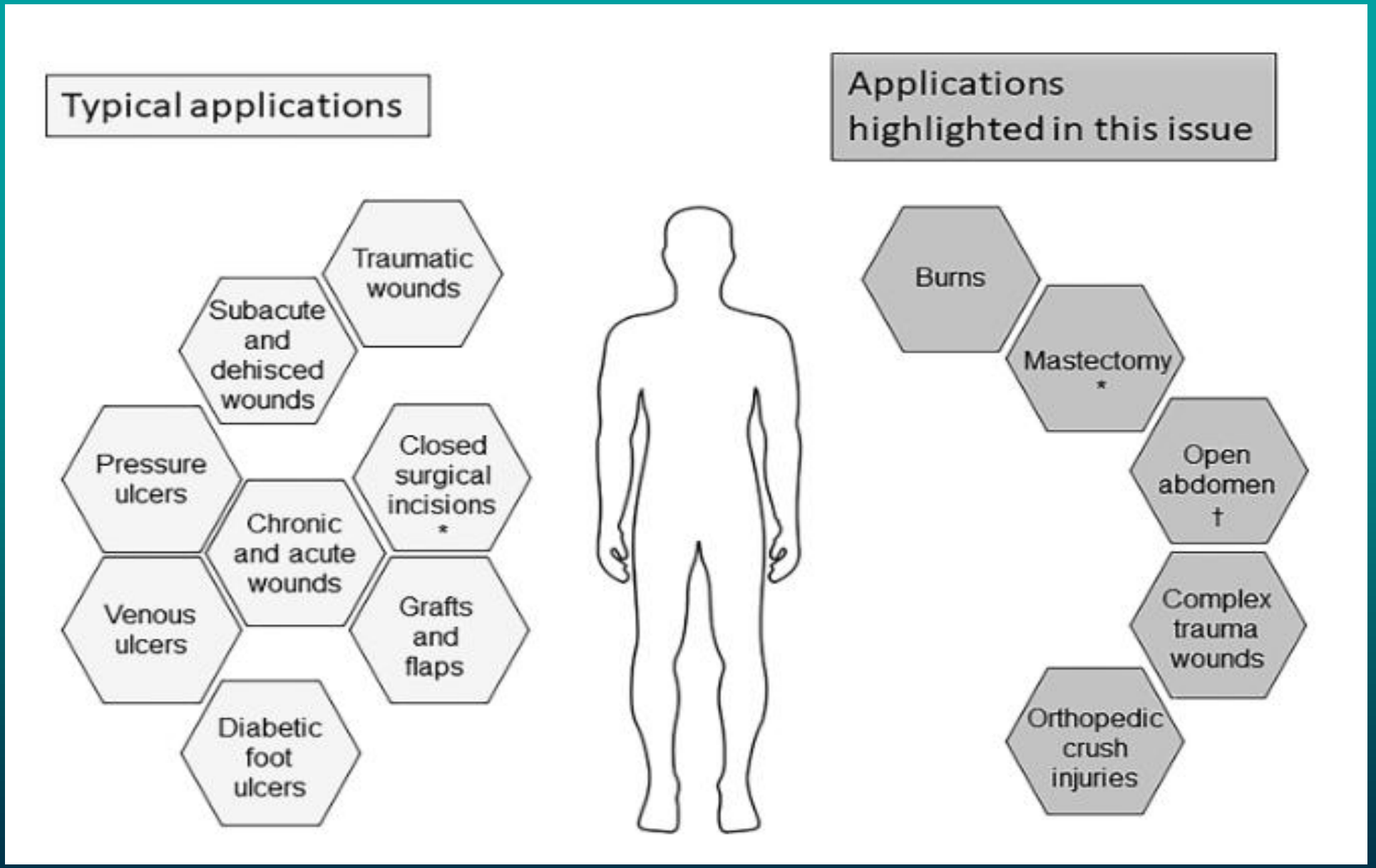
3. The negative pressure generates microstrain on the wound tissue, which stimulates cell proliferation and granulation tissue formation. This mechanical stress encourages new blood vessel growth (angiogenesis) and enhances perfusion, reducing the risk of tissue necrosis

Components of NPWT

A typical NPWT system includes:

1. Foam or gauze dressing: Placed directly on or in the wound to distribute negative pressure evenly and absorb fluid.
2. Adhesive film drape: Creates an airtight seal over the dressing to maintain suction and protect the wound from contamination.
3. Suction tubing and pump: Connects the dressing to a vacuum pump, which can be battery-powered or mains-operated, and collects wound exudate in a canister.
4. Some systems allow instillation of saline or antibiotics to irrigate the wound while maintaining negative pressure.





Stéphanie F. Bernatchez Advances in Wound Care 2024;14: https://doi.org/10.1089/wound.2024

Clinical Application

NPWT is used for acute, chronic, and complex wounds, including surgical wounds, pressure ulcers, diabetic foot ulcers, burns, and skin grafts

Its benefits include:

1. Faster wound closure and reduced healing time
2. Decreased bacterial load and infection risk
3. Reduced swelling and improved circulation
4. Enhanced formation of healthy granulation tissue
5. Ability to manage wounds that are difficult to close surgically

Questions – Comments?

SURGICAL INFECTIONS
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Results: One-way sensitivity analysis with a willingness-to-pay threshold of $5,000 demonstrated that above a baseline infection rate of approximately 6.4%, ciNPWT is cost-effective at reducing superficial SSI. Probabilistic sensitivity analysis indicated that even with uncertainty present in the parameters analyzed, the majority of simulations (95.4%) favored ciNPWT as the more effective tactic.
Conclusions: Despite the added device cost, ciNPWT is cost-effective for superficial SSI prevention across a variety of surgical infection risk profiles.

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efficacy in SSI prevention.[9–13] The latest Cochrane Review shows a relative risk reduction in superficial SSI of 0.70 (95% confidence interval [CI]: 0.53–0.92) with prophylactic ciNPWT application compared with standard dressings.[14] Similar results were also reported by James et al. (2024), who found a statistically significant improvement in superficial SSI outcomes for patients receiving ciNPWT (odds ratio [OR]: 0.30; 95% CI: 0.17–0.53) in a recent large meta-analysis.[15] Despite this evidence for clinical benefit, routine use of ciNPWT is not standard practice for many surgeons. We believe that a lack of robust cost-efficacy data may contribute to inconsistent implementation.

Inherent cost differences between ciNPWT and standard surgical dressings, as well as risk-stratified variation in clinical effectiveness data, highlight a critical need to identify groups of patients in whom this intervention is cost-effective. Thus, the purpose of this study was to assess the cost-effectiveness of ciNPWT compared with standard dressings for SSI prevention across a range of baseline infection rates, using the most up-to-date meta-analytic data. We hypothesized that use of ciNPWT would reduce healthcare costs in patients with a high baseline risk of superficial SSI.

Methods

A cost-effectiveness model was created from the perspective of a healthcare administrator. The model evaluates the development of superficial SSI at 30 days for two clinical pathways as follows: (1) with ciNPWT and (2) without ciNPWT. The model also assumes that all incisions are closed primarily regardless of contamination even if ciNPWT is not used. Modeling ciNPWT compared with open wounds designed to close by secondary intent (regardless of augmentation by other forms of NPWT) is beyond the scope of this study.

All data included in the model are listed in Table 1. The model assumes a baseline superficial SSI rate of 15% with a range from 1% to 30%, reflecting a surgical cohort with wide range of superficial SSI risk. Modulating this baseline superficial SSI rate is the primary way that the model evaluates differing levels of infection "risk" with low-risk patients/wounds corresponding to low baseline infection rates (clean cases, etc.) and high-risk patients corresponding to greater baseline rates (dirty/infected wounds, etc.). We chose to model the risk of infection directly rather than using subjective wound classifications. The ORs reflecting the use of ciNPWT on 30-day superficial SSI were taken from the James et al. meta-analysis.[15] The probability of superficial SSI in patients with ciNPWT was modeled by converting baseline infection rates into odds, multiplying the resulting new odds by the ciNPWT OR, and then converting back to a probability.[16] Cost of ciNPWT was the acquisition cost for the ciNPWT system used at our institution (3M™ Prevena™ Incision Management System). The model assumes that the cost of a "standard" dressing is negligible. Costs of managing superficial SSI were taken from published literature and inflated to 2024 dollars.[17,18] Considering that data on quality adjusted life years for superficial SSIs are limited, published data using the physical component of the SF-36 for patients with and without superficial SSI were used to model effectiveness.[19] For the purposes of the analysis, the authors calculated ranges of ±5% for the SF-36 values. Differences in the SF-36 of 4–7 points are considered a reasonable threshold for minimal clinically important difference.[20]

The model is illustrated in Figure 1. The model was constructed using TreeAge Software Pro Version 2020 (TreeAge Software, Inc., Williamstown, MA). Cost-effectiveness analysis was conducted, with one- and two-way sensitivity analyses performed on superficial SSI rate and the OR for ciNPWT. Probabilistic sensitivity analysis was conducted, and cost-effectiveness was assessed at $5,000 and $50,000 willingness-to-pay (WTP) thresholds.[16] Because of uncertainty related to scarcity of evidence for model inputs, all parameters in probabilistic sensitivity analyses were assumed to have a uniform underlying distribution, therefore making any value within the range as likely as any other. In addition, the model was created assuming that ciNPWT would not *increase* wound infection rates; therefore, the OR for ciNPWT was allowed to range from 0 to 1, but not above 1. This range is far outside of the bounds of ORs reported by the reference meta-analysis.[15] This choice allows us to determine the OR threshold below, which ciNPWT might be cost-effective, even if this threshold is outside of that reported in the literature.

Results

Base case decision analysis identified ciNPWT as the optimal tactic. With an average cost of $1,532.29 and average SF-36 score of 46.81, ciNPWT was both less expensive and more effective than ("dominant" over) standard dressings ($2,930.49 and 46.40). Probabilistic sensitivity analysis of 100,000 iterations demonstrated that ciNPWT was the optimal tactic in 95.4% of cases at a WTP threshold of $5,000 and 99.7% at a WTP threshold of $50,000. A scatterplot of the incremental cost-effectiveness as calculated by probabilistic sensitivity analysis is included as Figure 2.

One-way sensitivity analysis of SSI rate demonstrated that ciNPWT was the most cost-effective option above an infection rate of 6.4% at a WTP threshold of $5,000 and 5.3% at a WTP threshold of $50,000 (Fig. 3 for WTP $5,000). One-way

Table 1. Model Parameters

Variable	*Source*	*Model value (range)*
Rate of superficial SSI	Estimate	15% (1%–30%)
Cost of ciNPWT	Institutional source	$549
Cost of superficial SSI	Schweizer (2014)	$19,536.62 ($16,237.34–$22,834.48)
Odds ratio for ciNPWT	James (2024)	0.3 (0.17–0.53)
Physical component SF-36	Hart (2021)	
Infection	Hart (2021) + estimated range[a]	42.94 (40.79–45.09)
No infection	Hart (2021) + estimated range[a]	47.01 (44.66–49.36)

[a]Range estimates are ±5%.
SSI = surgical site infection; ciNPWT = closed incision negative pressure wound therapy.

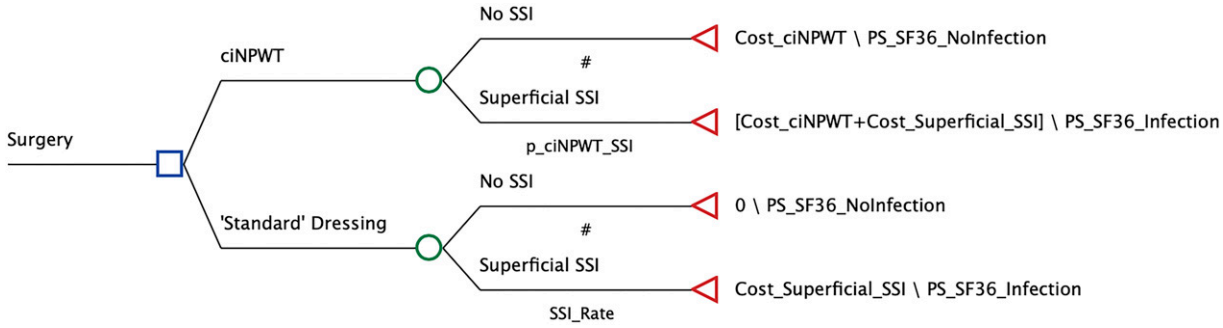

FIG. 1. Cost-effectiveness model.

sensitivity analysis of the OR for SSI with ciNPWT demonstrated that ciNPWT was the more cost-effective option below ORs of 0.89 and 0.98 at WTP thresholds of $5,000 and $50,000, respectively (Fig. 4 for WTP $5,000). One-way sensitivity analyses conducted at the $50,000 threshold are shown in Supplementary Figures S1 and Figure S2.

The interaction between SSI rate and the OR for ciNPWT is illustrated in the two-way sensitivity analyses at the WTP thresholds of $5,000 and $50,000 (Fig. 5 for WTP $5,000). In both WTP scenarios, the likelihood of ciNPWT being the optimal tactic increases as baseline infection rate increases, even as the effectiveness of ciNPWT decreases, as described by an increasing OR. The two-way sensitivity analysis conducted at the $50,000 threshold is included in Supplementary Figure S3.

Discussion

The results of this study suggest that ciNPWT is a cost-effective tactic for reducing superficial SSIs across a wide range of baseline infection rates and, therefore, a wide range of surgical populations. Surprisingly, our model was not sensitive to changes in WTP, providing similar outcomes at both the $5,000 and $50,000 thresholds. According to our model, at a WTP threshold of $5,000, ciNPWT was the preferred option when the baseline rate of superficial SSI was above 6.4% and the OR of SSI for ciNPWT was below 0.89.

The purpose of cost-effectiveness analysis is to "determine if the value of an intervention justifies its cost."[21] When an intervention both improves outcomes and results in lower overall costs than a comparator, the intervention is considered

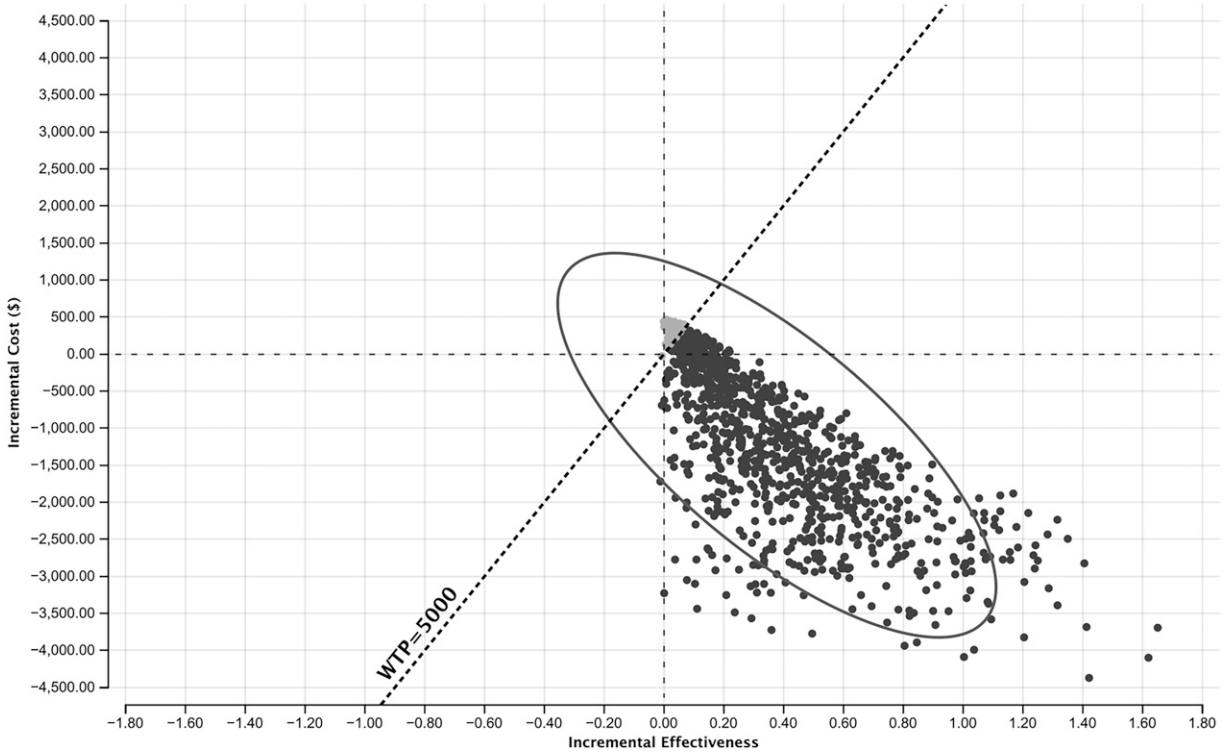

FIG. 2. Incremental cost effectiveness scatterplot for ciNPWT versus "standard" dressing at WTP = $5,000. Points on scatterplot represent results from probabilistic sensitivity analysis for ciNPWT using "standard" dressing as the baseline. The ellipse represents the 95% confidence interval for the analysis. Dark gray = ciNPWT is the optimal tactic. Light gray = ciNPWT is not the optimal tactic. ciNPWT = closed incision negative pressure wound therapy; WTP = willingness to pay.

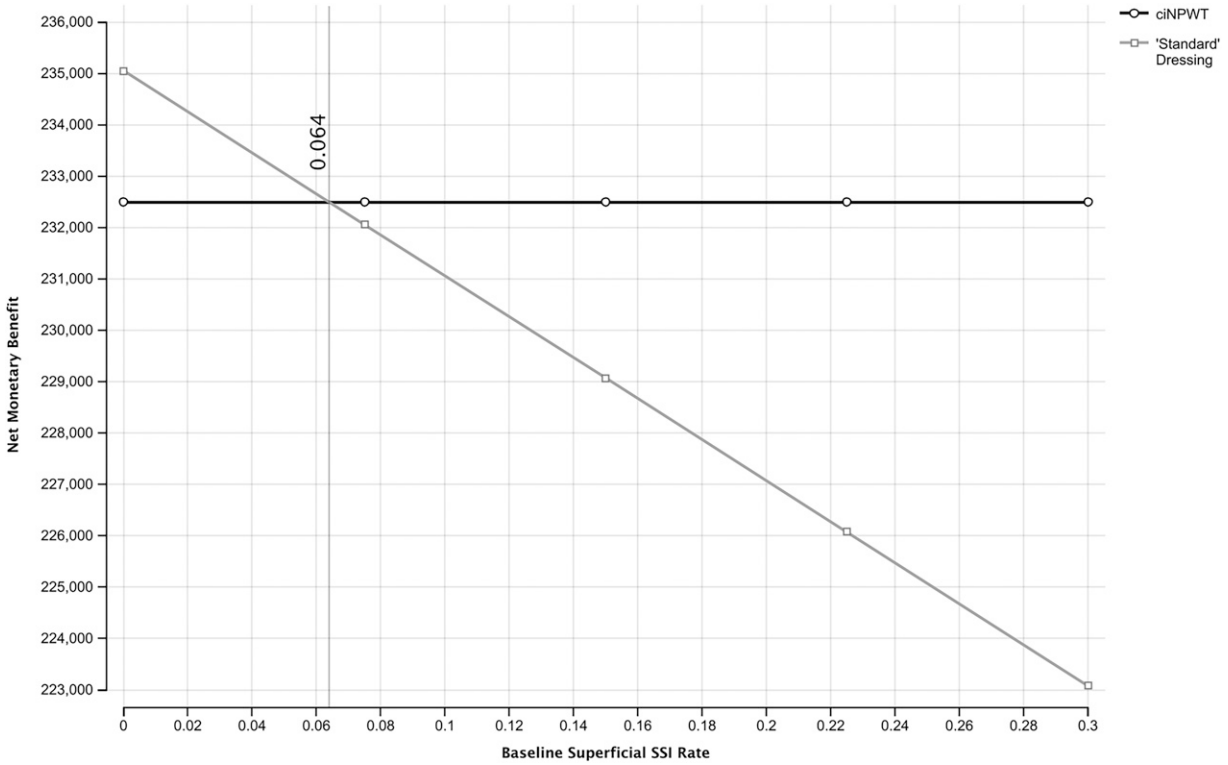

FIG. 3. One-way sensitivity analysis for superficial SSI rate at WTP = $5,000. SSI = surgical site infection; WTP = willingness to pay.

economically "dominant."[22] In our model, ciNPWT improves outcomes by lowering superficial SSI rates. Although this improvement comes at an increased initial cost for the device itself, the resulting cost savings from reduced infection rates more than make up for the device cost, resulting in ciNPWT being the "dominant" tactic.

Sensitivity analysis in these models is a valuable tool for evaluating the intervention. Model parameters can be allowed to take on a wide range of values, allowing the intervention to be evaluated under a variety of potential cases and limiting the impact of uncertainty in the parameters being evaluated. Sensitivity analysis can also help to answer practical questions about how to apply the intervention. In our study, we use sensitivity analysis to answer two simple questions as follows: (1) above what baseline infection rate is it potentially beneficial to use ciNPWT? and (2) how poorly can ciNPWT function and still be of value? We, therefore, seek to define practical constraints/limitations on the baseline infection rate and OR for superficial SSI reduction.

Our model suggests that this intervention is cost-effective above a minimum baseline risk of superficial SSI (6.4% in our study). Hyldig et al. found ciNPWT to reduce SSI rates from 9.2% to 4.2% in a population of obese patients undergoing cesarean delivery.[11] Similarly, a recent meta-analysis of vascular groin wounds (baseline SSI rate 18%–42%) found ciNPWT to be effective at reducing SSI.[23] In operative groups with low baseline SSI risk, studies have not found ciNPWT to be cost-effective. Hawkins et al. found that ciNPWT was not cost-effective at reducing the rate of superficial SSI in cardiac operation for a population with a baseline infection rate of 0.9%.[24] Png et al. similarly found ciNPWT not cost-effective in an orthopedic surgical procedure setting. In their study, approximately 5.7% of the overall population was provided antibiotic agents for presumed SSI.[25] In contrast, Nherera et al. found ciNPWT cost-effective at a baseline complication rate of 4.8%[26] in their model, including all surgical site complications. However, costs and effectiveness in their model included downstream readmissions and mortality, which may account for the favorable profile. Because of the general consistency of results in the literature, we believe that the cost-effectiveness of this intervention is unlikely to vary widely across different types of operation for reasons unrelated to baseline variability in SSI rates.[27]

Literature review of ciNPWT returns a fairly wide range of ORs for superficial SSI reduction with ciNPWT.[15] To account for this uncertainty in sensitivity analysis, we allowed our OR for superficial SSI reduction to range from 0 to 1 under an assumption that this therapy would not increase infection rates. We found that the upward constraint on the OR in our model is 0.89 at a WTP threshold of $5,000 and 0.98 at a $50,000 WTP threshold. This means that at the current acquisition cost, ciNPWT needs only slightly reduced SSI rates to still be cost-effective. These upward constraints are significantly greater than pooled estimates from the clinical literature.[15] Although exact thresholds will be expected to vary from model to model, our findings suggest that even if ciNPWT is somewhat less effective than pooled data would suggest, it is still likely to be of high economic value under typical thresholds for WTP.

The recent SUNRISE trial is a large multicenter randomized trial of ciNPWT in patients undergoing emergent laparotomies. The authors randomized 840 patients to either ciNPWT versus surgeon preference for wound dressing and

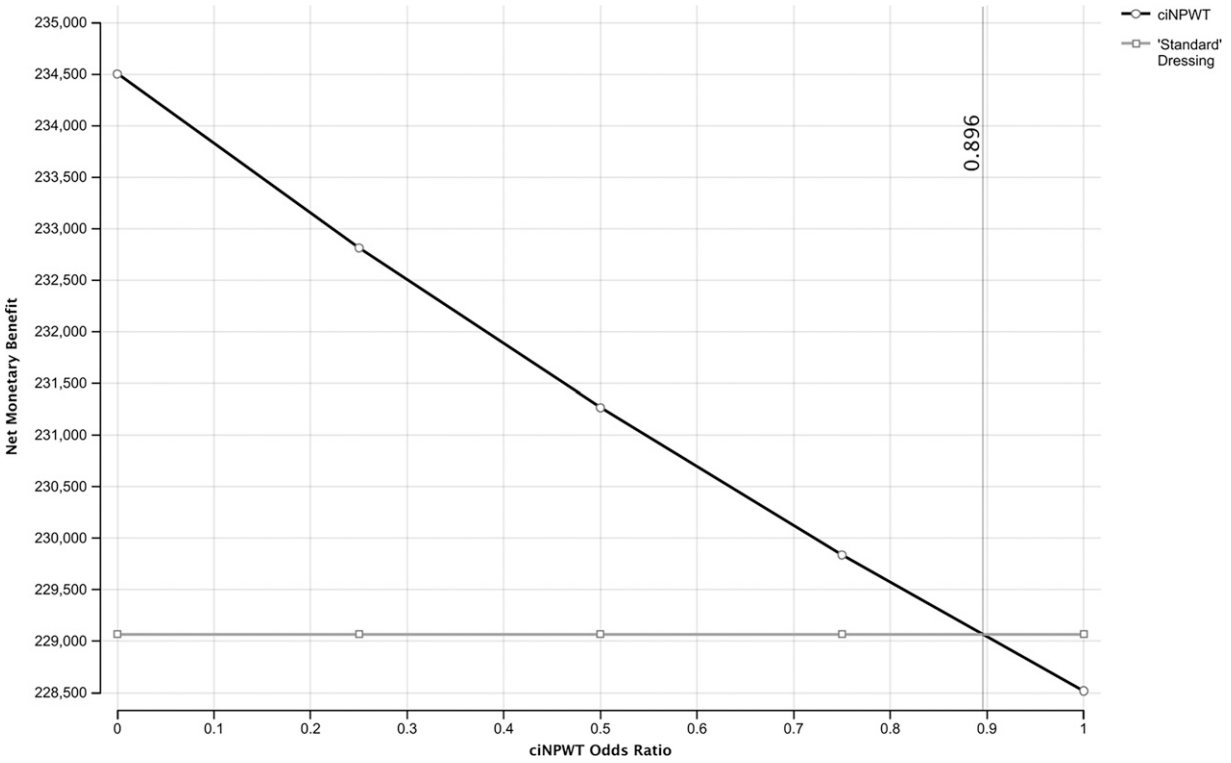

FIG. 4. One-way sensitivity analysis for ciNPWT odds ratio at WTP = $5,000. ciNPWT = closed incision negative pressure wound therapy; WTP = willingness to pay.

found no difference in superficial SSI rate.[28] Although not directly reported in the article, infection rates for each wound classification are calculable based on the data provided. These overall rates were high ranging from 21.3% overall in clean cases to 41.6% overall in dirty/infected cases.[28] Although these rates are not that dissimilar from the 28.3% (clean) and

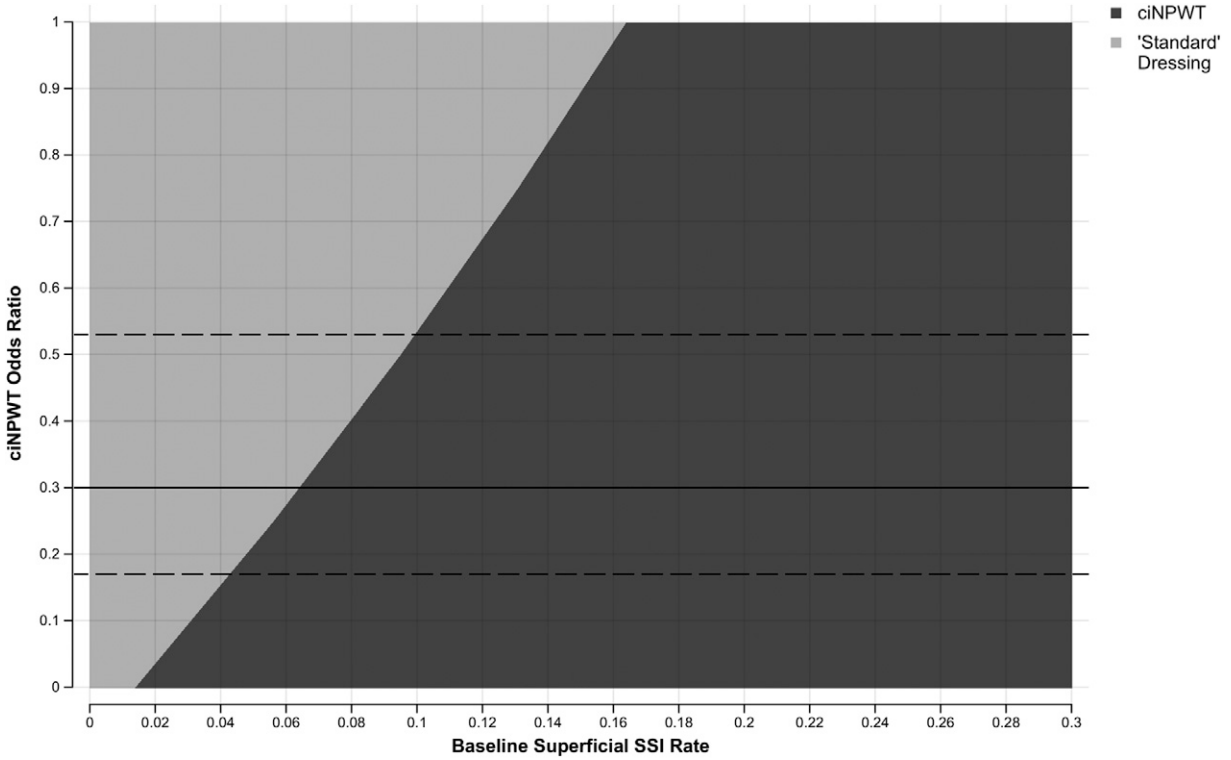

FIG. 5. Two-way sensitivity analysis for baseline SSI rate and ciNPWT odds ratio at WTP = $5,000. SSI = surgical site infection; ciNPWT = closed incision negative pressure wound therapy; WTP = willingness to pay.

35.8% (dirty) SSI rates observed in the ROSSINI trial, they are significantly greater than observed infection rates in trauma and emergency general surgical procedure.[29–31] These rates are also greater than the SSI rates observed in the STOP-IT trial, even after excluding patients who only underwent percutaneous intervention.[32] It remains to be seen if these results persist on repeat study. Including the SUNRISE trial in future meta-analyses will serve to increase the pooled OR. A benefit of our study is that the sensitivity analysis ranged up to 1 in anticipation of the true effect of ciNPWT being potentially worse than previously reported. Our study suggests that depending on the WTP, the true OR can range between 0.89 and 0.98 and still be cost-effective.

Leaving the skin open to heal by secondary intention has been a long-practiced method of minimizing infection risk for patients who are deemed to be either at high risk for infection (because of contamination, immunosuppression, or other factors) or inability to tolerate a future infection. Although the infection risk for a contaminated wound may be high, an infection does not develop in most patients.[30,31] Wound healing by secondary intention may avoid the superficial SSI, but this practice comes at the cost of increased hospital length of stay, increased number of outpatient office visits, and a substantial negative patient experience.[30,33] Recent interest in ciNPWT is one method of potentially increasing the number of patients whose skin can remain intact after operation. A recent survey of Surgical Infection Society members suggested that 30% of providers would still close the skin of a dirty/infected case with most of these surgeons choosing ciNPWT.[34] We do not suggest that all wounds should be closed. Physician judgment should continue to dictate whether it is safe to close a particular patient's wound or not. However, if the surgeon believes that it is safe to close the wound, our study suggests that ciNPWT may be a reasonably cost-effective adjunct in many cases.

This study has several limitations. Probability parameters were based on meta-analyses, which suffer from the inherent limitation of pooling data gathered from sources with varied methodology. In addition, cost estimates were taken from acquisition costs from our institution, which may not be generalizable to other settings. Because our model assumes the perspective of a healthcare administrator, it incorporates and reflects hospital costs rather than patient charges. Finally, this model did not consider the effect of ciNPWT on complications other than superficial SSI. Although some studies have shown decreased rates of dehiscence, seroma, and hematoma with ciNPWT use compared with standard dressings, incorporating these outcomes was beyond the scope of this model.[35] However, ignoring these additional possible benefits only underestimates the cost-effectiveness of ciNPWT.

Conclusions

Despite the added cost of the device, ciNPWT is likely to be cost-effective and even cost saving for superficial SSI prevention across a variety of surgical infection risk rates. Our data suggest that ciNPWT should be considered for any closed wound with a baseline infection risk of greater than approximately 6%.

Authors' Contributions

Conceptualization: C.A.G. Methodology: C.A.G., L.T.K., and K.A.V. Formal analysis: C.A.G., L.T.K., and K.A.V. Investigation: All authors. Writing: L.T.K. and C.A.G. Editing and review: All authors. Visualization: C.A.G.

Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3

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ORIGINAL CONTRIBUTION

Assessment of the Risk and Economic Burden of Surgical Site Infection Following Colorectal Surgery Using a US Longitudinal Database: Is There a Role for Innovative Antimicrobial Wound Closure Technology to Reduce the Risk of Infection?

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BACKGROUND: Colorectal surgical procedures place substantial burden on health care systems because of the high complication risk, of surgical site infections in particular. The risk of surgical site infection after colorectal surgery is one of the highest of any surgical specialty.

OBJECTIVE: The purpose of this study was to determine the incidence, cost of infections after colorectal surgery, and potential economic benefit of using antimicrobial wound closure to improve patient outcomes.

DESIGN: Retrospective observational cohort analysis and probabilistic cost analysis were performed.

SETTINGS: The analysis utilized a database for colorectal patients in the United States between 2014 and 2018.

PATIENTS: A total of 107,665 patients who underwent colorectal surgery were included in the analysis.

MAIN OUTCOME MEASURES: Rate of infection was together with identified between 3 and 180 days postoperatively, infection risk factors, infection costs over 24 months postoperatively by payer type (commercial payers and Medicare), and potential costs avoided per patient by using an evidence-based innovative wound closure technology.

RESULTS: Surgical site infections were diagnosed postoperatively in 23.9% of patients (4.0% superficial incisional and 19.9% deep incisional/organ space). Risk factors significantly increased risk of deep incisional/organ-space infection and included several patient comorbidities, age, payer type, and admission type. After 12 months, adjusted increased costs associated with infections ranged from $36,429 to $144,809 for commercial payers and $17,551 to $102,280 for Medicare, depending on surgical site infection type. Adjusted incremental costs continued to increase over a 24-month study period for both payers. Use of antimicrobial wound closure for colorectal surgery is projected to significantly reduce median payer costs by $809 to $1170 per patient compared with traditional wound closure.

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LIMITATIONS: The inherent biases associated with retrospective databases limited this study.

CONCLUSIONS: Surgical site infection cost burden was found to be higher than previously reported, with payer costs escalating over a 24-month postoperative period. Cost analysis results for adopting antimicrobial wound closure aligns with previous evidence-based studies, suggesting a fiscal benefit for its use as a component of a comprehensive evidence-based surgical care bundle for reducing the risk of infection. See **Video Abstract** at http://links.lww.com/DCR/B358.

EVALUACIÓN DEL RIESGO Y LA CARGA ECONÓMICA DE LA INFECCIÓN DEL SITIO QUIRÚRGICO DESPUÉS DE UNA CIRUGÍA COLORRECTAL UTILIZANDO UNA BASE DE DATOS LONGITUDINAL DE EE.UU.: ¿EXISTE UN PAPEL PARA LA TECNOLOGÍA INNOVADORA DE CIERRE DE HERIDAS ANTIMICROBIANAS PARA REDUCIR EL RIESGO DE INFECCIÓN?

ANTECEDENTES: Los procedimientos quirúrgicos colorrectales suponen una carga considerable para los sistemas de salud debido al alto riesgo de complicaciones, particularmente las infecciones del sitio quirúrgico. El riesgo de infección posoperatoria del sitio quirúrgico colorrectal es uno de los más altos de cualquier especialidad quirúrgica.

OBJETIVO: El propósito de este estudio fue determinar la incidencia, el costo de las infecciones después de la cirugía colorrectal y el beneficio económico potencial del uso del cierre de la herida con antimicrobianos para mejorar los resultados de los pacientes.

DISEÑO: Análisis retrospectivo de cohorte observacional y análisis de costo probabilístico.

AJUSTES: El análisis utilizó la base de datos para pacientes colorrectales en los Estados Unidos entre 2014 y 2018.

PACIENTES: Un total de 107,665 pacientes sometidos a cirugía colorrectal.

PRINCIPALES MEDIDAS DE RESULTADO: Se identificó una tasa de infección entre 3 y 180 días después de la operación, los factores de riesgo de infección, los costos de infección durante 24 meses posteriores a la operación por tipo de pagador (pagadores comerciales y Medicare), y los costos potenciales evitados por paciente utilizando una tecnología innovadora de cierre de heridas basada en evidencias.

RESULTADOS: Infecciones del sitio quirúrgico, diagnosticadas postoperatoriamente en el 23,9% de los pacientes (4,0% incisional superficial y 19,9% incisional profunda / espacio orgánico). Los factores de riesgo aumentaron significativamente el riesgo de infección profunda por incisión / espacio orgánico e incluyeron comorbilidades selectivas del paciente, edad, tipo de pagador y tipo de admisión. Después de 12 meses, el aumento de los costos asociados con las infecciones varió de $ 36,429 a $ 144,809 para los pagadores comerciales y de $ 17,551 a $ 102,280 para Medicare, según el tipo de infección del sitio quirúrgico. Los costos incrementales ajustados continuaron aumentando durante un período de estudio de 24 meses para ambos pagadores. Se prevé que el uso del cierre antimicrobiano de la herida para la cirugía colorrectal reducirá significativamente los costos medios del pagador en $ 809- $ 1,170 por paciente en comparación con el cierre tradicional de la herida.

LIMITACIONES: Los sesgos inherentes asociados a las bases de datos retrospectivas limitaron este estudio.

CONCLUSIONES: Se encontró que la carga del costo de la infección del sitio quirúrgico es mayor que la reportada previamente, y los costos del pagador aumentaron durante un período postoperatorio de 24 meses. Los resultados del análisis de costos para la adopción del cierre de heridas antimicrobianas se alinean con estudios previos basados en evidencia, lo que sugiere un beneficio fiscal para su uso como componente de un paquete integral de atención quirúrgica basada en evidencia para reducir el riesgo de infección. Consulte **Video Resumen** en http://links.lww.com/DCR/B358. *(Traducción—Dr. Gonzalo Hagerman)*

KEY WORDS: Antimicrobial sutures; Colorectal surgery; Deep incisional infection; IBM MarketScan; Organ-space infection; Superficial incisional infection; Surgical care bundles; Surgical site infection.

In the United States, elective colorectal surgery ranks in the top 10 of operating room procedures, with over 300,000 procedures reported in 2012.[1] This presents a high cost to health care systems, in part relating to increased length of hospital stay and the high risk of managing postoperative complications, including surgical site infection (SSI).[2] The rate of SSI after colorectal surgery is one of the highest of any surgical specialty, with a reported incidence ranging from 9% to 41%.[2–4] Patient comorbidities related to this group of patients further increase the risk of SSI.[5,6] In addition, SSIs are associated with prolonged hospital and intensive care unit stays, increased readmission to the hospital, and additional community care.[3,7–9] In the United States, SSIs have been reported to account for $3.2 billion in attributable cost per year to acute care hospital budgets.[10,11] More accurate understanding of the epidemiology of infection and the associated patient comorbid risk factors are important considerations in the effort to mitigate their occurrence and provide patients with appropriate interventional care.

Evidence-based surgical care bundles have been devised to reduce the incidence of SSI after selective surgical

procedures and improve patient outcomes. Components of these care bundles have included interventions such as weight-based, antibiotic prophylaxis; antiseptic skin preparation; appropriate hair removal; maintenance of normothermia; and glycemic control.[3,12] A meta-analysis of 13 studies involving 8515 patients has documented that the use of evidence-based care bundles can significantly lower SSI rates after open, elective, colorectal surgery compared with standard management: 7.0% compared with 15.1% (relative risk, 0.55; 95% CI, 0.39–0.77).[3] A subsequent analysis of 35 randomized controlled trials (RCTs) published in 2017 involving 17,557 patients documented a 40% reduction ($p < 0.001$) of SSIs following colorectal surgery when a care-bundle strategy was implemented.[12] In this meta-analysis, only 1 study included the analysis of antimicrobial suture (triclosan) wound closure used in its care bundle. Although antimicrobial wound closure is not documented in many of the systematic reviews and meta-analyses of surgical care bundles, the use of antimicrobial wound closure, using triclosan-coated or -impregnated sutures, is supported by level 1A clinical evidence to reduce the risk of SSIs following selective (clean, clean-contaminated, and contaminated) surgical procedures.[13–19]

The objective of the current study using a nationwide longitudinal database was to accurately assess the true incidence and actual costs associated with SSIs following colorectal procedures in the United States. The findings of this analysis suggest a potential economic and clinical outcome benefit for the inclusion of antimicrobial wound closure technology as a sentinel component of an evidence-based colorectal surgical care bundle.

MATERIALS AND METHODS

Database Analysis

A retrospective observational cohort analysis using the IBM MarketScan Commercial, Multi-State Medicaid and Medicare Supplemental databases was conducted to evaluate adult patients (≥18 years) undergoing colorectal surgery in the United States between 2014 and 2018. Colorectal surgery was defined as the index procedure using the *International Classification of Diseases, 9th* and *10th Revision, Clinical Modification* (ICD-9-CM and ICD-10-CM) procedure codes and *Current Procedural Terminology* codes (Supplemental Table 1 http://links.lww.com/DCR/B355). All patients were required to have continuous enrollment for ≥12 months before and 6 months after each colorectal surgical procedure. Patients were categorized by demographic and clinical comorbidities using the 31 domains of the Elixhauser Comorbidity Index.

The following outcomes were evaluated: the rate of SSI (using diagnostic codes for superficial or deep incisional infections) identified from the 3rd to the 180th postoperative day, risk factors associated with deep incisional/organ-space SSI, and costs of infection over a 24-month follow-up period by payer type (commercial payers and Medicare). Infections identified within the first 2 days after surgery were not included because they may have been present on admission. The time from index operative procedure to any identified SSI was recorded. The full list of diagnostic codes used to inform superficial and deep incisional/organ-space infections are available in Supplemental Table 2 http://links.lww.com/DCR/B356 and Supplemental Table 3 http://links.lww.com/DCR/B357.

Statistical analyses were performed fitting the data with logistic regression models to evaluate which variables were associated with a deep incisional/organ-space SSI. Generalized linear regression models with log-link and gamma distribution were used to evaluate the adjusted total payments for patients with and without SSI. The adjusted incremental cost of each infection was calculated using least-squares means over 24 months after the index procedure. To obtain the accurate costs associated with each infection type, the IBM MarketScan database was reviewed to break down deep incisional/organ-space infections. In cases where patients had multiple readmissions throughout the study period, resulting in codes for both infection types being used, the category of both combined was retained. All payments were adjusted to a 2018 consumer price index. All regression analyses were conducted using SAS 9.0.

Cost Analysis

An exploratory cost analysis utilizing data extracted from the retrospective observational cohort, in combination with publicly available literature, was created to evaluate the potential economic impact of introducing antimicrobial wound closure after colorectal surgery to commercial payers and Medicare. A decision tree was designed and run as a Monte Carlo simulation to compare colorectal procedures in a current treatment practice with where antimicrobial suture wound closure was utilized in future practice (Fig. 1).

Key variables for each of the model branches included the differential cost of antimicrobial wound closure compared with traditional suture technology, the probability of developing an SSI with antimicrobial sutures compared to traditional sutures, and the inpatient cost of SSI. The probability of SSI with traditional sutures was assumed to be equal to the rate calculated from the retrospective observational database cohort. Because antimicrobial sutures are not likely to impact organ-space infection rates, the cost analysis was performed on superficial and deep incisional SSIs only. The SSI risk reduction with antimicrobial wound closure was taken from available publications on contaminated and dirty (class 3 or class 4) wound types.[20] Costs of SSI were taken from the 12-month adjusted cost for superficial incisional and deep SSIs from

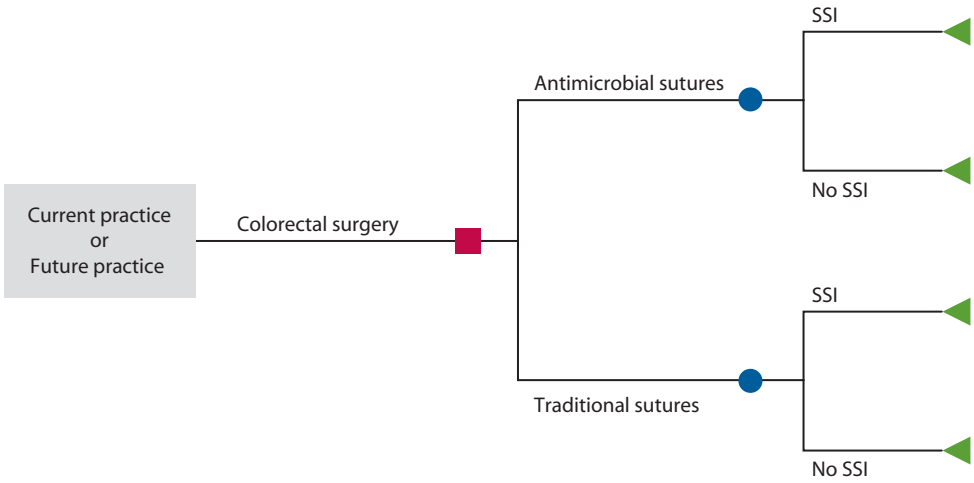

FIGURE 1. Basic structure of decision-tree cost model. The model was run for each type of payer and infection evaluated. SSI = surgical site infection.

the retrospective observational database cohort. The unit costs of traditional sutures and antimicrobial sutures were obtained from the vendor. With the probabilistic analysis, the increased incremental cost associated with antimicrobial sutures was assumed to be approximately $0.48 (USD) per suture strand, with a log-logistic distribution.

Results of the model consisted of a primary analysis that examined the incremental costs per patient over the first postoperative 12 months for superficial and deep incisional SSI. A secondary analysis, removing superficial infection rates and costs, was performed to examine the impact of deep incisional SSI only. To address uncertainty in input parameters, the results of the primary and secondary analyses were conducted probabilistically.

RESULTS

Database Analysis

A total of 107,665 patients undergoing colorectal surgery between 2014 and 2018 were included in the analysis (Fig. 2). The demographics and clinical presentation of patients at the time of their index surgery are shown in Table 1. Within 6 months of the postindex procedure, 23.9% of patients had a diagnosis of SSI after colorectal surgery. The majority of infections were classified as deep incisional/organ-space infections, accounting for 19.9% of infections; whereas the remaining 4.0% were superficial incisional infections. Differences in the risk of infection were noted for a few key populations. For example, emergency procedures had a higher risk of deep incisional/organ-space infections (29.1% vs 17.4%) and superficial incisional infections (5.2% vs 3.7%) compared with nonemergency procedures. For open versus laparoscopic procedures, deep incisional/organ-space infection rates were 25.2% and 12.7%, and superficial incisional SSI rates were 4.8% and 2.7%. For unspecified approach procedures (n = 21,015, 19.5% of total patients), the deep incisional/organ-space SSI rate was 21.1% and the superficial SSI rate was 4.4%, similar to the rates for open procedures (Table 1). Most infections, diagnosed postprocedure, occurred within 3 to 25 days (50%) and, by 2 months, 75% had been identified. A summary of patient baseline comorbidities relative to infection status at 6 months is summarized in Table 2. When analyzing the risk factors associated with deep incisional/organ-space SSIs, regression analysis found certain patient comorbidities, age, payer type, and admission type to be associated with adverse outcome (Fig. 3).

For more accurate costs associated with SSIs, deep incisional/organ-space infections were broken down into separate categories. Rates of deep incisional, organ-space, and combined deep incisional/organ-space infections were 10.6%, 4.8%, and 4.5% (Fig. 4). For the commercial payer population, after adjusting for patient demo-

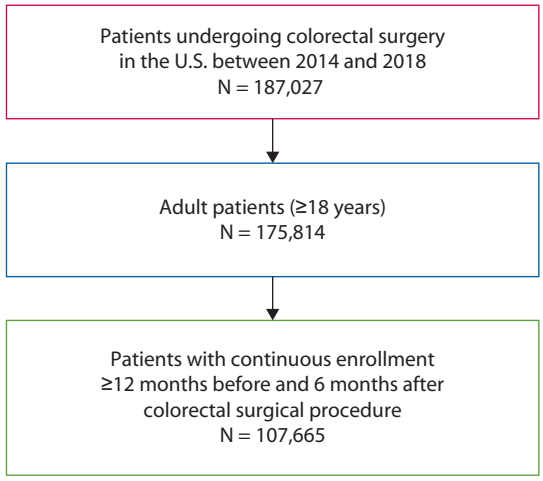

FIGURE 2. Flow diagram for included patients undergoing colorectal surgery.

TABLE 1. Demographics and clinical presentation of study patients at time of index surgery

	Overall (n = 107,665)		*Deep incisional/organ-space SSI (n = 21,441)*		*Superficial SSI (n = 4292)*		*No infection (n = 81,932)*	
Data categories	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Male sex	50,246	46.7	9919	46.3	1997	46.5	38,330	46.8
Years								
2014	27,970	26.0	5754	26.8	1268	29.5	20,948	25.6
2015	23,110	21.5	4832	22.5	921	21.5	17,357	21.2
2016	21,725	20.2	4499	21.0	801	18.7	16,425	20.1
2017	18,714	17.4	3584	16.7	691	16.1	14,439	17.6
2018	16,146	15.0	2772	12.9	611	14.2	12,763	15.6
Age category								
18–24	3290	3.1	845	3.9	102	2.4	2343	2.9
25–34	6196	5.8	1541	7.2	268	6.2	4387	5.4
35–44	12,763	11.9	2733	12.8	500	11.7	9530	11.6
45–54	26,966	25.1	5064	23.6	1054	24.6	20,848	25.5
55–64	36,257	33.7	6840	31.9	1415	33.0	28,002	34.2
65–74	10,507	9.8	2048	9.6	420	9.8	8039	9.8
75+	11,686	10.9	2370	11.1	533	12.4	8783	10.7
Site of care								
Outpatient	5076	4.7	658	3.1	153	3.6	4265	5.2
Inpatient	102,589	95.3	20,783	96.9	4139	96.4	77,667	94.8
Admission type								
Nonemergency	84,805	78.8	14,784	69.0	3109	72.4	66,912	81.7
Emergency	22,860	21.2	6657	31.1	1183	27.6	15,020	18.3
Surgical approach								
Open	48,144	44.7	12,127	56.6	2322	54.1	33,695	41.1
Laparoscopic	38,506	35.8	4889	22.8	1042	24.3	32,575	39.8
Unspecified	21,015	19.5	4425	20.6	928	21.6	15,662	19.1
Database indicator								
Commercial	70,243	65.2	12,605	58.8	2530	59.0	55,108	67.3
Medicaid	15,690	14.6	4542	21.2	827	19.3	10,321	12.6
Medicare	21,732	20.2	4294	20.0	935	21.8	16,503	20.1
Charlson Comorbidity Index								
0	39,743	36.9	7255	33.8	1348	31.4	31,140	38.0
1–2	36,333	33.8	6909	32.2	1463	34.1	27,961	34.1
3–4	16,971	15.8	3530	16.5	753	17.5	12,688	15.5
+5	14,618	13.6	3747	17.5	728	17.0	10,143	12.4
Functional Comorbidity Index								
0	20,225	18.8	3627	16.9	649	15.1	15,949	19.5
1–2	40,003	37.2	6864	32.0	1336	31.1	31,803	38.8
3–4	28,270	26.3	5693	26.6	1181	27.5	21,396	26.1
+5	19,167	17.8	5257	24.5	1126	26.2	12,784	15.6
Elixhauser Comorbidity Index								
0	17,730	16.5	3180	14.8	556	13.0	13,994	17.1
1–2	38,363	35.6	6365	29.7	1293	30.1	30,705	37.5
3–4	27,666	25.7	5294	24.7	1139	26.5	21,233	25.9
+5	23,906	22.2	6602	30.8	1304	30.4	16,000	19.5

SSI = surgical site infection.

graphic and clinical characteristics, the incremental costs of superficial incisional SSIs were $28,866 at 6 months, $36,429 at 12 months, and $44,281 at 24 months after the index surgery. The adjusted incremental costs for deep incisional, organ-space, and combined deep incisional/organ-space SSIs ranged from $43,490 to $122,177 at 6 months, $52,628 to $144,809 at 12 months, and $64,563 to $164,471 at 24 months after the index surgery. For the Medicare population, the incremental costs for superficial SSIs were $16,026 at 6 months, $17,551 at 12 months, and $20,758 at 24 months after the index surgery. The adjusted incremental costs for deep incisional, organ-space, and combined deep incisional/organ-space SSIs ranged from $25,387 to 84,067 at 6 months, $32,456 to $102,280 at 12 months, and $45,771 to $121,274 at 24 months after the index surgery. Across the study time horizon, superficial incisional SSIs were associated with the lowest cost to payers and combined deep incisional/organ-space infections were associated with the highest cost (Table 3). The longitudinal analysis found that the cost associated with all SSI types can be substantial and increase out to 24 months after surgery.

TABLE 2. Key comorbidities of patients included in the study, at study start and based on infection status at 6 months after the index surgery

	Overall (n = 107,665)		*Infection (n = 25,733)*		*No infection (n = 81,932)*	
Elixhauser comorbidity	*n*	*%*	*n*	*%*	*n*	*%*
Hypertension, uncomplicated	50,553	47.0	12,981	50.4	37,572	45.9
Solid tumor without metastasis	32,289	30.0	6934	26.9	25,355	30.9
Chronic pulmonary disease	19,544	18.2	5813	22.6	13,731	16.8
Fluid and electrolyte disorders	18,722	17.4	6456	25.1	12,266	15.0
Cardiac arrhythmias	18,710	17.4	5559	21.6	13,151	16.1
Diabetes mellitus, uncomplicated	18,253	17.0	5234	20.3	13,019	15.9
Depression	17,380	16.1	5334	20.7	12,046	14.7
Obesity	16,865	15.7	4773	18.5	12,092	14.8
Liver disease	15,363	14.3	3867	15.0	11,496	14.0
Hypothyroidism	13,678	12.7	3482	13.5	10,196	12.4
Deficiency anemia	13,520	12.6	3743	14.5	9777	11.9
Weight loss	9990	9.3	3437	13.4	6553	8.0
Peripheral vascular disorders	9446	8.8	2846	11.1	6600	8.1
Diabetes mellitus, complicated	8360	7.8	2692	10.5	5668	6.9
Valvular disease	8186	7.6	2328	9.0	5858	7.1
Metastatic cancer	7327	6.8	2024	7.9	5303	6.5
Renal failure	6811	6.3	2213	8.6	4598	5.6
Congestive heart failure	6608	6.1	2268	8.8	4340	5.3
Hypertension, complicated	6335	5.9	1977	7.7	4358	5.3
Rheumatoid arthritis/collagen vascular diseases	5343	5.0	1660	6.5	3683	4.5
Other neurological disorders	5052	4.7	1865	7.2	3187	3.9
Blood loss anemia	4820	4.5	1311	5.1	3509	4.3
Coagulopathy	3979	3.7	1308	5.1	2671	3.3
Drug abuse	3559	3.3	1362	5.3	2197	2.7
Alcohol abuse	3248	3.0	1042	4.0	2206	2.7
Pulmonary circulation disorders	2895	2.7	1041	4.0	1854	2.3
Peptic ulcer disease	2447	2.3	715	2.8	1732	2.1
Psychoses	1665	1.5	640	2.5	1025	1.3
Paralysis	1625	1.5	847	3.3	778	0.9
Lymphoma	1103	1.0	311	1.2	792	1.0
AIDS/HIV	524	0.5	127	0.5	397	0.5

Cost Analysis

Results of the primary cost analysis suggest that the use of antimicrobial wound (fascial and incisional) closure would result in a statistically significant cost avoidance for superficial and deep incisional SSIs at 12 months compared to the current practice for both Medicare and commercial payers. Median costs avoided per patient for commercial payers and Medicare were $1170 (95% CI, $146–$4884) and $1036 (95% CI, $111–$4823) (Fig. 5). In the secondary analysis of deep incisional SSIs only, incremental costs avoided per patient were similarly reduced, with commercial payers and Medicare predicting avoidance of $809 (95% CI, $26–$4481) and $870 (95% CI, $33–$4624) per patient for antimicrobial suture wound closure (Fig. 6).

DISCUSSION

The IBM MarketScan Commercial, Multi-State Medicaid and Medicare Supplemental database is a unique, observational, cohort database study that highlights the true cost and accurate economic burden of SSIs following colorectal surgery. With over 1 in 5 patients at risk to experience an SSI within 6 months after colorectal surgery, and the cost burden of each episode ranging from $16,026 to $144,809 over 6 to 12 months, the cost of SSIs to the US health care system is substantial. These results demonstrate the importance of minimizing SSI-related costs by using evidence-based care bundles.

All surgical wounds are contaminated to some degree at closure; the primary determinant of whether the contamination is implicated in establishing a surgical infection is dependent on patient comorbid risk factors, degree of wound contamination, and immune-host tissue competency at the time of closure.[21] At first incision, sebaceous glands and hair follicles are transected, allowing skin-colonizing bacteria to contaminate the surgical wound. The intrinsic virulence of the skin flora combined with the level of contaminating bioburden can be the nidus for infection in a susceptible host. Furthermore, the rate of SSI for colorectal procedures is significantly influenced by the "layering-effect" of multiple, comorbid risk factors such as obesity, diabetes mellitus, low serum albumin, alcohol consumption, cigarette smoking, extended operative times, and anesthetic time.[22]

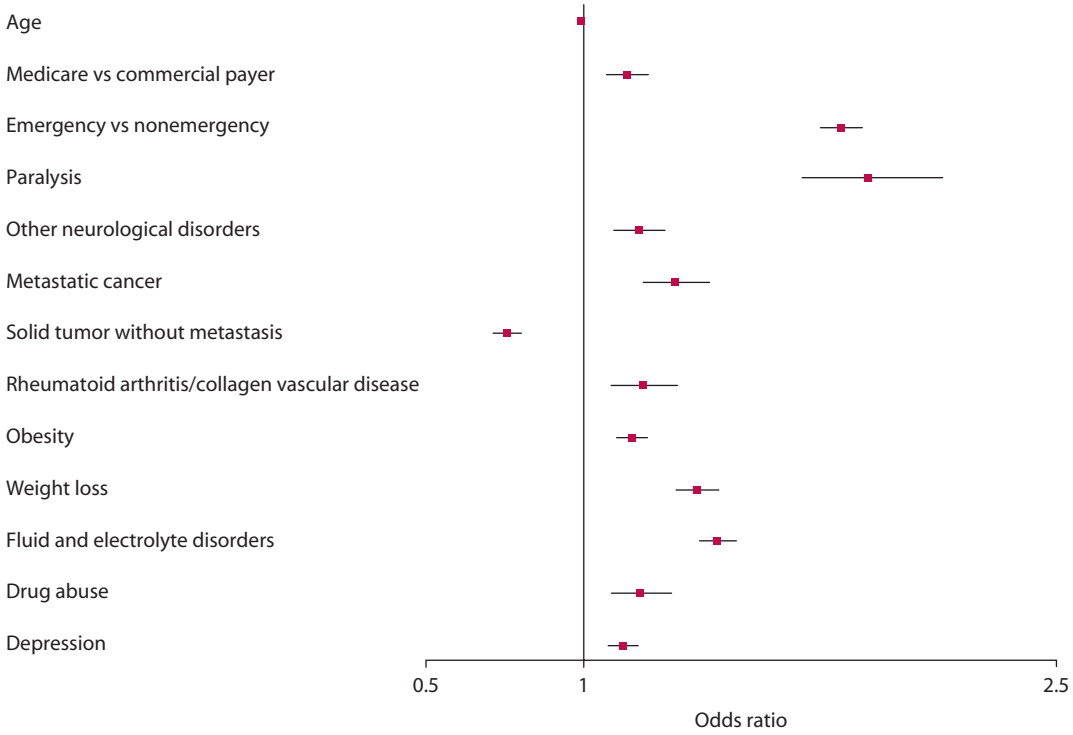

FIGURE 3. Risk factors significantly associated with deep incisional/organ-space SSI ($p < 0.001$). SSI = surgical site infection.

Several recent studies, meta-analyses, and systematic reviews have documented the beneficial role of an evidence-based surgical care bundle.[12,13,23–25] Although in most published care bundles the inclusion of antimicrobial sutures is absent from consideration, the intrinsic mechanistic benefit of antimicrobial wound closure for fascia and subcuticular closure relates to documented antimicrobial activity against both Gram-positive and Gram-negative surgical wound pathogens.[26,27]

When considering the benefits of an antimicrobial wound closure, 2 questions need answering. First, are the sutures placed in the surgical wound a potential nidus for infection? A study published in 2013 documented that traditional (nonantimicrobial) braided or monofilament sutures, excised from the infected wounds of surgical patients, demonstrated an established microbial biofilm in 100% of cases, clearly suggesting that an implanted suture, like other biomedical devices, is at high risk for early, microbial biofilm formation, and subsequent risk of SSI, when implanted within a contaminated field.[28] Second, does the level of evidence for antimicrobial sutures justify their inclusion in current, evidence-based colorectal surgical care bundles? Numerous RCTs, including multi-

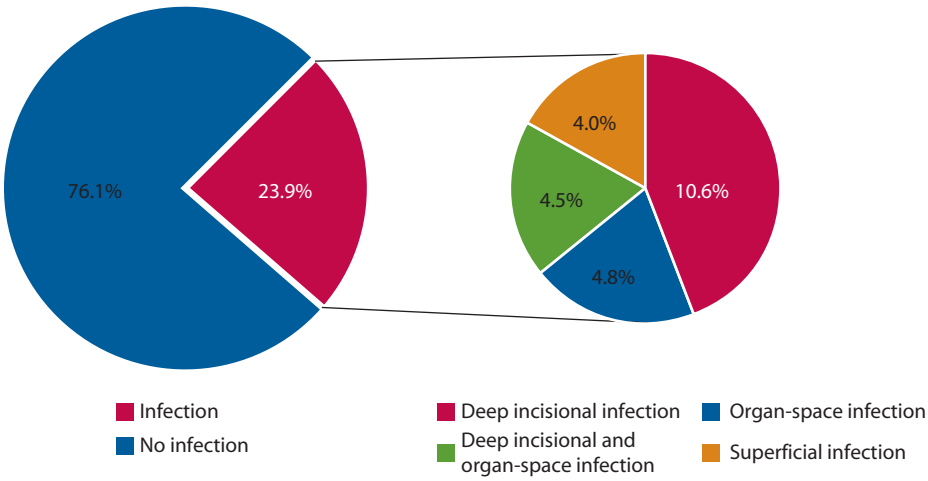

FIGURE 4. Surgical site infection rate at 6 months after the index colorectal surgery by infection type.

TABLE 3. Summary of SSI costs from the database analysis by infection type, payer, and time point

	Mean SSI cost (95% CI)			
Payers	*Deep incisional and organ-space*	*Deep incisional*	*Organ-space*	*Superficial*
Commercial payers				
6 months	$122,117 ($117,490–$127,007)	$43,490 ($42,120–$44,888)	$71,324 ($67,859–$74,904)	$28,866 ($26,690–$31,115)
12 months	$144,809 ($137,819–$152,062)	$52,628 ($50,633–$54,670)	$85,079 ($79,641–$90,747)	$36,429 ($33,085–$39,910)
24 months	$164,471 ($152,816–$176,759)	$64,563 ($61,143–$68,097)	$96,910 ($87,550–$106,844)	$44,281 ($38,538– $50,350)
Medicare				
6 months	$84,067 ($77,457–$91,069)	$25,387 ($22,884–$28,010)	$47,955 ($44,325–$51,764)	$16,026 ($12,884–$19,375)
12 months	$102,280 ($92,575–$112,670)	$32,456 ($28,832–$36,280)	$54,547 ($49,293–$60,111)	$17,551 ($13,040–$22,408)
24 months	$121,274 ($104,102–$140,169)	$45,771 ($38,679–$53,407)	$66,784 ($56,992–$77,402)	$20,758 ($12,538–$29,834)

SSI = surgical site infection.

ple systematic reviews and meta-analyses, have been conducted to compare antimicrobial sutures with traditional, nonantimicrobial sutures (braided or monofilament absorbable sutures) for closure of fascia and muscle, subcutaneous tissues, and skin. The use of antimicrobial sutures was found to be effective at significantly reducing the risk of SSI across different surgical procedures including colorectal.[19,29–34] A recent robust analysis evaluated 25 RCTs, representing 11,957 surgical patients, demonstrated that the use of antimicrobial sutures significantly reduced the risk of SSI at 30 days (relative risk, 0.73; 95% CI, 0.65–0.82). Sensitivity analysis also documented a significant SSI reduction benefit for clean, clean-contaminated, and contaminated surgical procedures.[35]

The findings of this current study are important because they not only confirm the financial burden of SSIs after colorectal procedures, which have been reported in published indirect estimates of cost, but also emphasize that the true economic burden is underrecognized. With the longitudinal nature of the database, a large cohort (n = 107,665) of "real-world" patient information was used to determine that the incidence of SSIs within 6 months of colorectal surgery was 23.9%, a finding similar to previously reported SSI rates. It is also clear that the incidence of SSI has not been underreported in the databases used in the present study, a reflection of accurate postdischarge surveillance, the accuracy of which is often marred in previous reports – a key finding that highlights the limitations of currently available literature in establishing the actual cost of SSIs after colorectal procedures over time, with the adjusted incremental cost to payers at 6 months ranging up to $122,177. In addition, the cost of SSIs to payers is not limited to the first 6 months postprocedure. Between 6 and 12 months and 12 and 24 months, costs continued to escalate for all SSI types and payers. These findings indicate that there is often a need for prolonged care for patients who experience an SSI following colorectal surgery, especially in the case of deep incisional infections or anastomotic leak (organ-space).

In this study, the costs of an SSI were found to be higher than those previously reported that have ranged from $11,778 to $42,177.[10,36] Recent National Institute of Health and Care Excellence guidelines on SSI prevention and treatment reported an average cost of managing a single patient with an SSI of £3122.86.[16] Estimated mean attributable cost of SSI treatment cited in the Centers for Disease Control and Prevention guidelines ranges from $10,443 (2005 US dollar (USD)) to $25,546 (2002 USD)

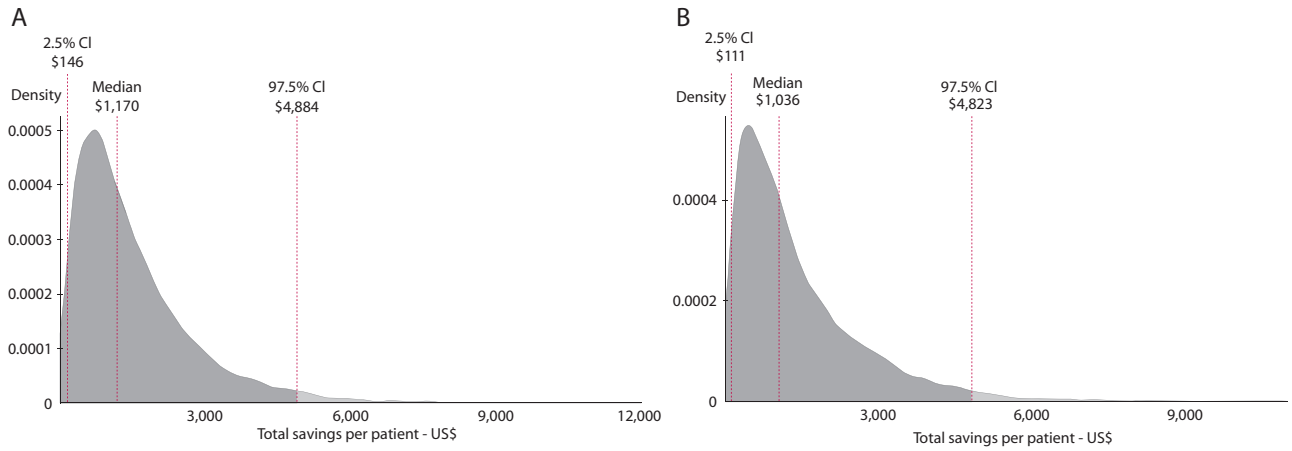

FIGURE 5. Primary cost analysis median, 95% CI, and distribution of savings per patient with antimicrobial sutures in the future practice over 12 months for deep incisional and superficial SSI: commercial payers (A) and Medicare (B). SSI = surgical site infection.

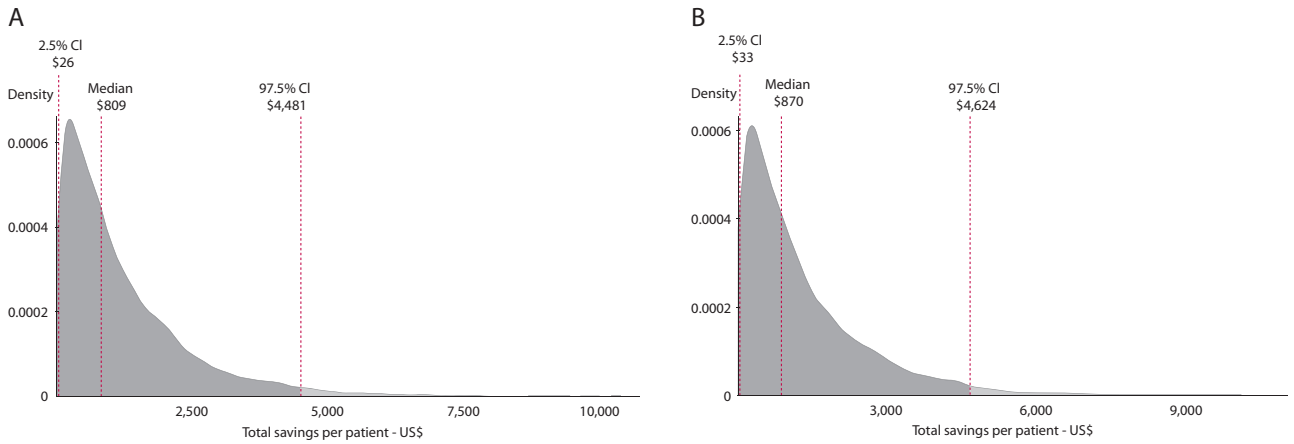

FIGURE 6. Secondary cost analysis median, 95% CI, and distribution of savings per patient with antimicrobial sutures in the future practice over 12 months for deep incisional SSI only: commercial payers (A) and Medicare (B). SSI = surgical site infection.

per SSI.[14] One reason for the disparity between these reported costs and those from this analysis, other than the extended level of postdischarge surveillance, is the increase in infection treatment costs to payers over time. Earlier reported costs were presented as 2002 to 2012 USD, whereas the costs in this study are reported in 2018 USD, although this is not likely to be the primary cause for the differences observed. In earlier publications, the most common definition for the cost of an SSI was the incremental costs to the hospital for the added inpatient stay attributable to the infection or following readmission.[36] In this analysis, costs of SSI after colorectal surgery reflect the overall cost to payers over time. These overall costs for patients provide a more accurate representation of the true cost of an SSI that has previously been underestimated by surrogate data rather than the "real world" data presented here.

Two studies involving the economic benefits associated with using an antimicrobial suture for wound closure have been recently published.[19,37] In the first study, published by Singh and colleagues,[37] the increased cost of antimicrobial sutures was minimal compared with the potential avoided costs of SSIs to third-party payers. Despite conclusions similar to the current study, there are several key differences between our analysis and those of Singh et al.[37] These differences included the population of interest (abdominal procedures), published sources for the risk and cost of infection, and the cost perspectives that were evaluated (hospital, third-party, and societal). The current analysis focuses solely on colorectal procedures using data from a large national database to inform baseline infection risk; the reduced risk of infection following the use of antimicrobial sutures, which was taken from a recent meta-analysis by Leaper and colleagues; and all the relevant costs of SSIs to different payers were captured during a 12-month period.[20] Singh et al used an overall SSI rate of 15% derived from the study of Alexander et al[38] in 2009, which evaluated morbidly obese patients. The superficial and deep incisional/organ-space SSI rates were calculated based on previously published estimates multiplied by 15%.[37] The current study utilized real-world data from over 100,000 patients to document the rates of 4.0% and 10.6% for superficial and deep incisional SSIs. Here costs avoided are presented per patient, whereas the costs from Singh et al were presented per SSI averted.[37] Compared to the recent meta-analysis and probabilistic cost analysis by Leaper et al,[20] the results presented here demonstrate that similar costs can be avoided when using antimicrobial sutures, although the magnitude of the results differ. In the United Kingdom, the costs of SSI derived from UK National Health Service sources are much lower, ranging from £3000 to £5000,[20] whereas the 12-month mean costs of an SSI used in the current study ranged from $36,429 to $52,628 for commercial payers and from $17,551 to $32,456 for Medicare for superficial and deep incisional SSIs.

The results of this study have some important limitations. As with all retrospective database observational studies, results are limited to the captured information. All information within the IBM MarketScan Commercial, Multi-State Medicaid and Medicare Supplemental databases is provided by individual health care settings and is subject to errors in incomplete hospital reporting, coding errors, or misclassification of patients; causality cannot be inferred. We were unable to control for potentially important factors including physical function, socioeconomic status, wound care, and nutritional status. The exclusion of these and other potential predictive factors could impair the accuracy of our model estimates. The occurrence of SSIs was identified based on ICD-9-CM and ICD-10-CM diagnosis codes, without the availability of laboratory confirmation, although the diagnosis of an SSI is primarily a clinical decision. Future prospective studies might be useful to supplement the results of the current analysis.

CONCLUSION

The results of this study highlight the substantial burden associated with SSI following colorectal surgery, and the potential economic benefit of including an antimicrobial suture for wound closure in an evidence-based surgical care bundle for colorectal surgery.

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Review

Surgical Antibiotic Prophylaxis: A Proposal for a Global Evidence-Based Bundle

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Abstract: In the multimodal strategy context, to implement healthcare-associated infection prevention, bundles are one of the most commonly used methods to adapt guidelines in the local context and transfer best practices into routine clinical care. One of the most important measures to prevent surgical site infections is surgical antibiotic prophylaxis (SAP). This narrative review aims to present a bundle for the correct SAP administration and evaluate the evidence supporting it. Surgical site infection (SSI) prevention guidelines published by the WHO, CDC, NICE, and SHEA/IDSA/APIC/AHA, and the clinical practice guidelines for SAP by ASHP/IDSA/SIS/SHEA, were reviewed. Subsequently, comprehensive searches were also conducted using the PubMed®/MEDLINE and Google Scholar databases, in order to identify further supporting evidence-based documentation. The bundle includes five different measures that may affect proper SAP administration. The measures included may be easily implemented in all hospitals worldwide and are based on minimal drug pharmacokinetics and pharmacodynamics knowledge, which all surgeons should know. Antibiotics for SAP should be prescribed for surgical procedures at high risk for SSIs, such as clean–contaminated and contaminated surgical procedures or for clean surgical procedures where SSIs, even if unlikely, may have devastating consequences, such as in procedures with prosthetic implants. SAP should generally be administered within 60 min before the surgical incision for most antibiotics (including cefazolin). SAP redosing is indicated for surgical procedures exceeding two antibiotic half-lives or for procedures significantly associated with blood loss. In principle, SAP should be discontinued after the surgical procedure. Hospital-based antimicrobial stewardship programmes can optimise the treatment of infections and reduce adverse events associated with antibiotics. In the context of a collaborative and interdisciplinary approach, it is essential to encourage an institutional safety culture in which surgeons are persuaded, rather than compelled, to respect antibiotic prescribing practices. In that context, the proposed bundle contains a set of evidence-based interventions for SAP administration. It is easy to apply, promotes collaboration, and includes measures that can be adequately followed and evaluated in all hospitals worldwide.

Keywords: healthcare-associated infections; surgical site infections; surgical antibiotic prophylaxis; bundle; prevention

1. Introduction

Healthcare-associated infections (HAIs) have a meaningful impact on health systems, posing a public health threat worldwide [1]. Surgical site infections (SSIs), central-line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, hospital-acquired pneumonia, and *Clostridioides difficile* infections (CDIs) account for most HAIs [2]. Some HAIs are preventable; therefore, these infections can be considered a critical quality patient-care indicator. In 2018, Schreiber et al. [3] published a meta-analysis evaluating the impact of multimodal interventions on reducing HAIs in acute or chronic care settings. They demonstrated a potential HAI rate reduction, ranging from 35% to 55%, when implementing multimodal interventions, notwithstanding the country income level. Regarding SSIs, thirty-six before-and-after studies and one randomised control trial were included in the meta-analysis. The data demonstrated a significant reduction in SSI rates in all countries independently from their economic income group, but differences between subgroups could not be explored due to high heterogeneity. The four studies reporting aggregated SSI rates demonstrated a reduction in SSI rates ranging from 31% to 84% [3]. Although additional higher-quality evidence is required to drive infection prevention efforts from a governance perspective, the results of that

meta-analysis should motivate hospitals to implement infection prevention by developing their own multifaceted strategies.

SSIs represent the most common HAIs occurring in surgical patients [4]. However, while SSI rates seem to be declining in high-income countries, this reduction is not reflected in low- and middle-income countries (LMICs) [5]. SSI rates in LMICs range from 8% to 30% [6]. In 2018, a prospective, international, multicentre cohort study about SSIs after gastrointestinal surgery in high-, middle-, and low-income countries was published. The incidence of SSIs varied significantly between countries with high, middle, and low rankings on the UN's Human Development Index [5]. Following risk factor adjustment, patients in low-income countries were those at higher risk of SSIs [5]. SSIs may have substantial morbidity, mortality, and economic impacts in these settings.

SSI prevention measures should be integrated before, during, and after surgery.

Both the World Health Organization (WHO) [7–9] and the Centers for Disease Control and Prevention (CDC) [10] have published guidelines for SSI prevention. In 2016, the American College of Surgeons and the Surgical Infection Society updated their SSI guidelines [11]. In 2019, the National Institute for Health and Care Excellence (NICE) published its new guidelines for SSI management online [12]. In 2023, a new set of joint guidelines for SSI prevention in acute-care environments was jointly published [13] by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), the Association for Professionals in Infection Control and Epidemiology (APIC), and the American Hospital Association (AHA). The evidence-based recommendations stated in these guidelines should be adopted by all healthcare providers caring for patients across the surgical pathway throughout all stages of patient surgical care.

Surgical antibiotic prophylaxis (SAP) is one of the most important measures to prevent SSIs. SAP consists of administering an antibiotic in patients without active infections before the intervention. Antibiotics for SAP have no therapeutic purposes but are only preventive, aiming to reduce the surgical field microbial burden so that the host defences are not overcome. Ideally, an antibiotic for SAP should be able to [14] achieve the following:

- Prevent SSIs;
- Reduce SSI morbidity and mortality;
- Diminish healthcare duration and cost;
- Not produce any adverse effects;
- Have no aftermath for the patient's intestinal microbial flora or the healthcare facility.

To achieve these goals, an antibiotic administered for SAP should fulfil the following:

- Active against the most likely bacteria that can contaminate the surgical field;
- Provided in an appropriate dosage and time that ensures adequate serum and tissue concentrations amid the whole operation;
- Safe;
- Administered for the shortest effective period, minimising adverse effects, opportunistic infections, antimicrobial resistance (AMR) development, and costs.

In their clinical practice, surgeons are responsible for many processes of healthcare impacting the risk of SSIs and play a key role in their prevention. However, many surgeons believe that SAP is peripheral to their clinical practice. In fact, using antibiotics properly is essential because their inappropriate use can cause serious side effects and predispose patients to opportunistic infections such as CDI and AMR development and spread.

The microbiome's indigenous bacteria have a vital host defence role because they can inhibit colonisation by potentially pathogenic bacteria. Nevertheless, opportunists can compromise the microbiota in certain circumstances, meaning it no longer protects against colonisation. Antibiotics can produce a heavy selection pressure on the human microbiome, predisposing patients to AMR, and have considerable consequences for the gut microbiota. While susceptible bacteria can be destroyed, antibiotic pressure can promote pathogenic bacterial overgrowth that may be multidrug-resistant. Moreover, antibiotics can facilitate resistance gene transmission, conferring resistance to other bacteria [14].

SAP is not necessary for all surgical procedures and must be tendered according to well-defined principles. The over-administration of SAP frequently occurs worldwide and contributes to overall antibiotic consumption in surgical units [14]. Given that approximately 15% of all antibiotics prescribed in hospital settings are allocated to SAP, it can be a crucial driver of AMR in these environments [15]. A comprehensive clinical practice guideline for SAP was published in 2015 by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) [16]. However, elevated SAP prescribing practice rates that are not compliant with guidelines are common in surgical units globally [17–22].

A quality improvement study published in 2019, analysing 9351 surgical episodes and 15,395 prescriptions, found high rates of inappropriate procedural and post-procedural antibiotic use across various Australian hospitals, patients, and surgical factors. The most common reasons for inappropriate SAP were incorrect timing (44.9%), incorrect dosing (26.1%), or an antibiotic spectrum that was too broad (15.9%). Only 65.6% of surgical episodes included a documented incision time [23].

Notably, an ethical mandate to comply with proper and adequate SAP should be considered, representing good clinical practice and correct behaviour. This ethical mandate should be grounded in ethical principles, as collated by Beauchamp and Childress [24]. Here, beneficence stands for "doing the good", non-maleficence is represented by the "*Primum non nocere*" ("Do no harm") dictum, and justice means the search for a greater good and the adequate distribution of resources.

In the multimodal strategy, to implement HAI prevention, bundles are among the most commonly used methods [25] to adapt guidelines in the local context and transfer best practices into routine clinical care. The bundle concept was developed in 2001 by the Institute for Healthcare Improvement (IHI) to support healthcare professionals in improving patient care during specific high-risk treatments. As a general principle, a care bundle should include a set of evidence-based measures that, when implemented together, can produce better outcomes and have a more meaningful impact than the implementation of isolated individual actions [25]. It should be easy to apply, simple, clear, concise, and promote multidisciplinary collaboration. It should be implemented collectively according to an "all or none" approach to accomplish the most favourable outcome and include measures appropriate to the local setting that can be adequately followed and evaluated, with compliance to the bundle assessed by healthcare workers involved in the team. Bundles used as standalone interventions or as part of multimodal strategies are associated with decreased SSI rates [26–28].

2. Methods

This narrative review proposes a bundle with evidence-based measures for SAP that is easily applicable and helpful to improve antibiotic prescribing practices among surgeons from around the world.

The best strategies for antimicrobial stewardship are not definitively established, and can vary based on local culture, routine clinical practice, and hospital resources. Therefore, it is essential to involve experts worldwide in compiling a document including measures applicable for surgeons in all regions of the world.

An international working group of 30 physicians was established by the Global Alliance for Infections in Surgery in order to define a global evidence-based bundle for appropriate SAP administration. This bundle includes five different actions that may affect adequate SAP administration. The reported measures are based on minimal knowledge of pharmacokinetics and pharmacodynamics, which should be held by all physicians regardless of discipline.

SSI prevention guidelines published by the WHO [7–9], CDC [10], NICE [12], and SHEA/IDSA/APIC/AHA [13], and the clinical practice guidelines for SAP by ASHP/IDSA/SIS/SHEA [16], were reviewed. Subsequently, comprehensive searches were also conducted

using the PubMed®/MEDLINE (National Library of Medicine, Bethesda, MD, USA) and Google Scholar (Alphabet, Inc., Mountain View, CA, USA) databases, in order to identify further supporting evidence-based documentation. The search term used was "surgical antibiotic prophylaxis". Overall, 5670 articles published in the English language between January 2012 and November 2023 were identified. Two authors selected 462 abstracts. In addition to the above-mentioned SSI prevention guidelines, 71 articles were reviewed to prepare the first draft. The resulting document was shared with all the members of the working group, thoroughly reviewed, and finally approved.

3. A Proposal for a Global Evidence-Based Bundle

The measures included in the bundle (Figure 1) may be easily implemented in all hospitals worldwide.

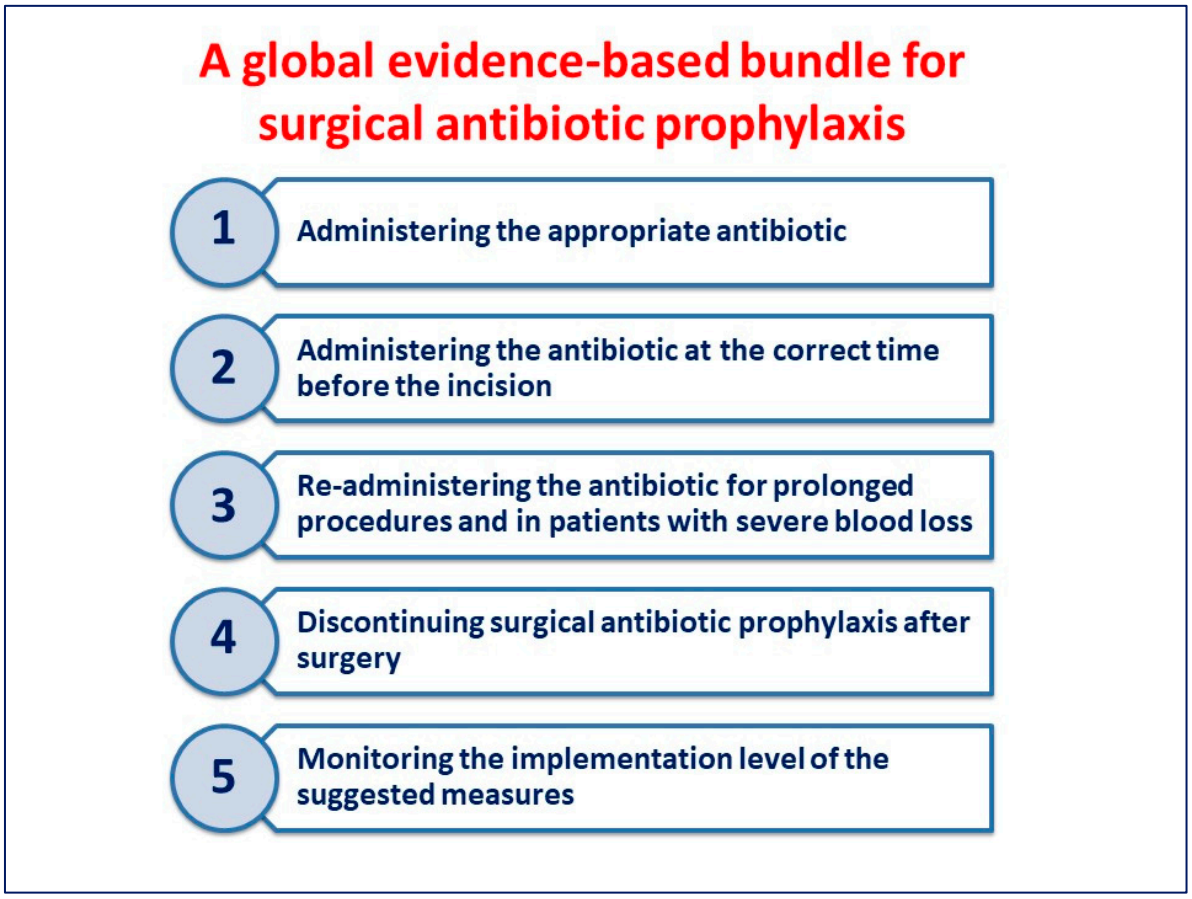

Figure 1. A global evidence-based bundle for surgical antibiotic prophylaxis.

3.1. Administering the Appropriate Antibiotic

The risk of SSIs [29] may differ depending on the site and degree of colonisation or contamination of the surgical procedure. Surgical procedures can be divided into four classes, categorised as clean (Class I), clean/contaminated (Class II), contaminated (Class III), and dirty (Class IV) [29].

SAP should be prescribed for surgical procedures at high risk OF SSIs, such as clean–contaminated and contaminated surgical procedures or for clean surgical procedures where SSIs, even if unlikely, may have devastating consequences, such as in procedures with prosthetic implants. SAP should also be prescribed in patients with medical conditions associated with a higher risk of SSI, such as immunocompromised patients [29].

The route of SAP administration may vary with the type of procedure. However, intravenous administration is ideal for most procedures because it produces rapid and pre-

dictable antibiotic tissue concentrations [16]. SAP in patients undergoing open-groin hernia surgery has been debated with conflicting results of low evidence quality [30–35]. The 2018 HerniaSurge Group International guidelines for groin hernia management recommended SAP in open-groin mesh repair in any patient in a high-risk infection environment [36]. A Cochrane systematic review of SAP for preventing SSIs in adults undergoing open elective inguinal or femoral hernia repair was published in 2020 [33]. The systematic review investigated three outcomes: superficial SSIs, deep SSIs, and all SSIs (superficial SSIs + deep SSIs). Very low-quality evidence demonstrated that it is uncertain whether SAP reduces the risk of all SSIs after hernia surgery. Moderate-quality evidence demonstrated that SAP makes little difference in reducing the risk of all SSIs after hernia surgery in a low-risk infection environment. Low-quality evidence showed that SAP in a high-risk environment may reduce the risk of all SSIs and superficial SSIs. Very low-quality evidence demonstrated that it is uncertain whether SAP can reduce deep SSIs after hernia surgery [29]. In sum, SAP should be performed in patients undergoing hernia surgery in a high-risk infection environment, but not in patients undergoing hernia surgery in a low-risk infection environment.

Another topic debated with conflicting results has been whether to prescribe SAP in patients undergoing laparoscopic cholecystectomy. Current evidence does not recommend the routine prescription of SAP for elective laparoscopic cholecystectomy for uncomplicated gallstone disease [37–40], but compliance with this evidence is generally low [41].

Antibiotics prescribed for SAP should be nontoxic, inexpensive, and have in vivo activity against the common bacteria causing SSIs. They should be effective against the most likely bacteria contaminating the surgical field. SSIs following clean interventions are usually due to Gram-positive bacteria commensal skin flora, including Staphylococcus aureus or Streptococcus species [29]. Clean–contaminated and contaminated interventions may be contaminated by various commensal flora bacteria of incised mucosae, such as Escherichia coli or other Enterobacterales and anaerobes bacteria [16]. The WHO [7–9] guidelines recommend administering SAP before the surgical incision when it is indicated. The CDC guidelines [10] recommend administering SAP only based on published clinical practice guidelines and timed in such a way as to achieve a bactericidal concentration of antibiotics in the serum and tissues when the incision is made. The SHEA guidelines [13] recommend prescribing appropriate antibiotics for SAP based on surgical procedures, the most common bacteria causing SSIs for a specific operation, and published guidelines. The NICE guidelines [12] recommend not using SAP routinely for clean, non-prosthetic, uncomplicated surgery.

The most commonly used antibiotics for SAP are first- and second-generation cephalosporins, including cefazolin, cefuroxime, cefoxitin, or the combination of cefazolin plus metronidazole, when it is necessary to cover anaerobes such as in colorectal surgery. For most surgical procedures, cefazolin is the antibiotic of choice for SAP. It has the most widely proven efficacy of a studied antibiotic. It is considered by the WHO an essential drug and as such it should be available in every hospital of the world [42].

There are few data describing the rate and quality indices of antibiotics used in hospitalised patients in LMICs especially in Africa. However, the few data show that the prevalence of antibiotic use in hospital settings in Africa is higher than the prevalence reported in hospital settings in the other continents [43]. Broad-spectrum antibiotics such as ceftriaxone and fluoroquinolones are antibiotics commonly prescribed in hospitalised patients in Africa [43]. SAP is the second most common indication for antibiotic use in African hospital settings. Therefore, SAP represents an important priority for the implementation of antimicrobial stewardship programmes (ASPs) in this continent [43].

A recent prospective trial compared piperacillin–tazobactam with cefoxitin as SAP for pancreatoduodenectomy. Among 778 patients enrolled in the study (378 in the piperacillin–tazobactam group and 400 in the cefoxitin group), the SSI rate at 30 days was lower in the piperacillin–tazobactam group compared with the cefoxitin group [44]. It is important to stress that the use of an antibiotic with such a broad spectrum may be justified for SAP only in complex operations with a very high rate of complications.

Routine use of antifungal agents should be discouraged except for very special circumstances, such as liver transplantation [45]. The routine use of glycopeptides, such as vancomycin or teicoplanin for SAP, should be discouraged. Glycopeptides can be considered for patients known to be colonised by methicillin-resistant *Staphylococcus aureus* (MRSA) or who are likely to have had recent MRSA exposure [29]. Moreover, vancomycin is less effective than cefazolin in preventing SSIs caused by *methicillin-susceptible Staphylococcus aureus* [16].

Establishing which antibiotics to use for patients known to be colonised or to have had past infection with multidrug-resistant (MDR) bacteria is complex and cannot be defined uniformly. Defining if SAP should be prescribed to provide coverage against MDR bacteria depends on many factors, such as bacteria antibiotic susceptibility, the host, and the surgical procedure. While it may be logical to prescribe SAP with an agent active against MRSA for any patient known to be colonised with MRSA who will undergo a skin incision, specific prophylaxis for resistant Gram-negative bacteria in a patient known to be colonised with such bacteria may not be necessary for a purely cutaneous procedure. Thus, patients known to be colonised or to have had past infection with MDR bacteria must be treated on a case-by-case basis, taking into account multiple considerations. Future well-designed clinical studies will assess the SAP effectiveness in patients colonised with MDR bacteria [46].

Regarding obese patients, the CDC guidelines [10] do not identify randomised controlled trials that evaluated the benefits of weight-adjusted SAP dosing and its effect on the risk of SSIs. The SHEA guidelines suggest adjusting dosing based on patient weight [13]. Regarding cefazolin, the SHEA guidelines recommend using 2 g dosing for patients weighing $\leq$ 120 kg and 3 g dosing for patients weighing > 120 kg. Data about the role of 3 g of cefazolin dosing in reducing SSIs in obese patients are conflicting. However, some (low-level) studies have shown a benefit of 3 g dosing compared to 2 g dosing in this patient population, with few adverse events [13]. On the contrary, according to other evidence, in these patients, the choice of the first dose in obese patients should be guided by the pharmacokinetics (especially tissue penetration and volume of distribution) of the individual antibiotics, depending on whether the antibiotic is hydrophilic or lipophilic. Because cefazolin is hydrophilic, penetration into tissue is not dose-dependent. Therefore, high cefazolin doses may not be necessary in obese patients [47–49]. In contrast, cefoxitin is not as hydrophilic as cefazolin and higher doses of cefoxitin may be required for obese patients.

Few data have been published regarding the SAP prescription in patients undergoing solid organ transplantation (SOT) [50,51]. SOT patients are at high risk of early postoperative infections because of the complexity of surgical procedures and therapeutic immunosuppression. SOT patients are also at increased risk of infections caused by MDR bacteria. These risks may lead to liberalised SAP in SOT patients. Perceived overuse of SAP in SOT patients has led to calls for antibiotic stewardship in the organ transplant setting [52].

Beta-lactam antibiotic allergy history should be considered when selecting SAP. Patients should be questioned carefully before the SAP administration about their antibiotic hypersensitivity background to determine whether a true allergy exists. Although up to 10% of patients will report an allergy to penicillin, the incidence of severe adverse reactions is well under 1% [16]. In addition, the patient cross-reactivity between penicillin and cephalosporin or carbapenem hypersensitivity is <5% [16]. The SHEA guidelines [13] recommend obtaining a thorough allergy history because self-reported allergy to beta-lactam antibiotics has been related to a higher risk of SSIs resulting from administering non-beta-lactam agents. Most patients with a self-reported allergy to beta-lactam antibiotics can safely receive a beta-lactam antibiotic as prophylaxis [29]. Non-beta-lactam agent alternatives include clindamycin, gentamicin, vancomycin, or fluoroquinolones. Vancomycin has a broad anti-Gram-positive activity; however, it is less effective than cefazolin at treating methicillin-susceptible *Staphylococcus aureus infections* [29]. Additionally, vancomycin and gentamicin are linked with a risk of antibiotic-associated nephrotoxicity, which has been

reported in patients receiving only a few doses of SAP [53]. Clindamycin is the most frequently prescribed antibiotic in patients with a documented beta-lactam allergy. However, clindamycin resistance to *Staphylococcus aureus* is increasing. This can decrease its efficacy against this pathogen often isolated in SSIs [53]. Clindamycin has also been reported to be associated with a nearly three-fold increased risk of CDI compared to other antibiotics [54]. Even single doses of clindamycin used for SAP have been associated with an increased risk of CDI. Consequently, appropriately evaluating allergies to beta-lactam antibiotics to limit unnecessary clindamycin exposure in surgical patients is essential to mitigate the risk of CDI [53].

Topical antibiotic prescription remains common among surgeons despite no evidence of efficacy. A systematic review and meta-analysis on the topical antibiotic prophylaxis use for SSI prevention in clean and clean–contaminated surgery was published in 2022 [54]. Thirteen randomised control trials (RCTs) comparing topical antibiotic agents with non-antibiotic agents were evaluated through the meta-analysis. As per the current evidence, administering topical antibiotic agents to surgical wounds does not diminish SSI incidence. The NICE [12], the CDC [10], and the WHO [7–9] guidelines recommend avoiding the use of topical antibiotic agents to prevent SSIs.

Oral antibiotic bowel preparation (oABP) for elective colonic surgery has been debated recently and merits particular consideration. oABP has been prescribed in addition to mechanical bowel preparation (mBP) and intravenous antibiotics [29]. Although the oABP–mBP combination has been employed widely in North America, it has been used less in Europe, perhaps because Enhanced Recovery After Surgery (ERAS®) protocols omit routine mBP in patients' preparation. The WHO guideline panel suggests that the oABP–mBP combination should be used in adult patients undergoing elective colorectal surgery to prevent SSIs. Nonetheless, the guidelines recommend the non-use of mBP alone for SSI prevention in adult patients undergoing elective colorectal surgery [7–9]. The SHEA guidelines recommend parenteral and oral combination use before elective colorectal surgery to prevent SSIs [13]. A Cochrane meta-analysis enrolling 21 RCTs with 5264 adult patients undergoing elective colorectal surgery was published in 2022 [55]. The meta-analysis compared mBP plus oABP with either mBP alone, oABP alone, or no bowel preparation. Based on moderate-certainty evidence, the meta-analysis results suggest that mBP plus oABP may be more effective than mBP alone in preventing SSIs. However, the meta-analysis was unable to clarify whether oABP alone is equivalent to MBP + oABP, because of the low to very low quality of evidence. A weighty limitation of oABP standardisation is the heterogeneity of the data about the choice of antibiotics and the duration. Antibiotics, dosages, and timing are very heterogeneous, making the results difficult to summarise. These aspects have yet to be defined by evidence [29].

3.2. Administering the Antibiotic at the Correct Time before the Incision

Adequate tissue concentrations of antibiotics should be present at the surgical site throughout the surgical procedure. The WHO global guidelines recommend administering SAP before surgical incision when indicated (depending on the type of operation). These guidelines recommend SAP administration within 120 min before the incision, based on the half-life of the prescribed antibiotic. A meta-analysis published in 2017 evaluated the proper SAP timing and compared the different administration time intervals [56]. Fourteen observational studies, including 54,552 patients, were included in this review (thirteen of these studies were included in the meta-analysis conducted by WHO experts). The study did not show a significant difference when SAP was tendered 120–60 min before surgical incision compared to when SAP was administered 60–0 min before surgical incision. However, the SSI risk doubled when antibiotics were issued after the first incision and was five-fold higher when they were furnished more than 120 min before the incision.

Weber et al. in 2017 [57] published a randomised controlled trial evaluating the optimal SAP timing consisting of a single 1.5 g dose of cefuroxime (short half-life cephalosporin) given through intravenous infusion associated with 500 mg of metronidazole in colorectal

surgery. The trial demonstrated that early antibiotic administration for SAP did not significantly reduce the SSI risk compared with late administration, not supporting any 60 min window in administering a short-half-life cephalosporin for SAP. The SHEA guidelines [13] recommend administering antibiotics within 1 h of incision to optimise the tissue concentration.

The first antibiotic dose should always be administered within 60 min, according to the prescribed antibiotic pharmacokinetics, before surgical incision for most commonly used antibiotics (including cefazolin). This can guarantee appropriate tissue concentrations during the surgical intervention. Only drugs with more extended half-lives, such as vancomycin, should be issued more than 60 min before the incision. The ideal time to administer preoperative cefazolin has been investigated recently in an interesting pharmacological study. According to the study, cefazolin reaches its peak concentration 40 min after intravenous administration, and then immediately decreases, remaining effective for 4 h [58].

3.3. Re-Administering the Antibiotic for Prolonged Procedures and in Patients with Severe Blood Loss

The NICE guidelines [12] recommend considering the antibiotic pharmacokinetics in SAP prescription. They also recommend administering a repeat SAP dose when the operation lasts longer than the administered antibiotic half-life. Although, in 2017, the CDC [10] did not identify sufficient high-quality evidence to evaluate the intraoperative redosing benefits of SAP for SSI prevention, from a pharmacokinetic standpoint, additional intraoperative doses should be issued for procedures exceeding two antibiotic half-lives or for procedures with significant associated blood loss (more than 1.5 L). This can guarantee an antibiotic concentration above the minimal inhibitory concentration at the surgical site throughout the procedure.

A meta-analysis including two randomised controlled trials and eight cohort studies [59] confirmed the importance of antibiotic redosing. Even though there was heterogeneity among the antibiotics administered, SAP intraoperative redosing reduced SSI rates compared with a single preoperative dose in any surgery. In a cefazolin case with a half-life of approximately 2 h, an additional intra-operative dose should be repeated after about 4 h. Conversely, cefoxitin has a very short half-life of 60 min, so the subsequent intra-operative dose should be repeated after roughly 2 h.

3.4. Discontinuing SAP after Surgery

SAP aims to prevent SSIs and should be administered and maintained at sufficiently high concentrations at the surgical site during the time that the incision is open. Erroneously, some surgeons believe that prolonging SAP after that the surgical incision has been closed can protect the patient from post-operative infections [29].

No evidence supports SAP use after the surgical procedure. Regardless, continuing SAP after surgery is still very common. Global Point Prevalence Survey results, including adult data from 303 hospitals in 53 countries, were published in 2015. This international point prevalence study demonstrated that SAP for more than 24 h ranged from 29.5% in Western Europe to 92.5% in Africa [60]. The WHO global guidelines [7–9] recommend not prolonging SAP administration after the operation completion to prevent SSIs. WHO experts conducting a meta-analysis [7–9] identified 69 randomised controlled trials researching the optimal antibiotic prophylaxis duration in different surgical procedures to evaluate SSI rate reduction; they found some low- to very low-quality evidence that prolonged postoperative antibiotic administration can be beneficial for reducing SSI risk in cardiac and vascular procedures. Considering the limited evidence, potentially damaging events, or AMR development associated with antibiotic prolongation, the experts advised against postoperative antibiotic administration. The CDC guidelines also recommend not administering additional SAP doses in clean and clean–contaminated procedures after the surgical incision has been closed in the operating room, even in the presence of a drain.

Also, the SHEA [13] guidelines recommend stopping antibiotics after the incisional closure in the operating room.

In 2020, a meta-analysis published by de Jonge et al. [61] evaluated the effect of continued SAP on SSI rate. They considered 83 relevant prospective randomised trials, of which 52, with 19,273 participants, were included in the primary meta-analysis. Overall, there was no conclusive evidence identifying a postoperative continuation of SAP having a benefit versus discontinuation when best infection prevention and control practices were followed. A retrospective, single-centre cohort study published in 2021 [62] compared the efficacy of single-dose antibiotic use versus 24 h SAP dosing in patients undergoing total joint arthroplasty. The study's results displayed no significant differences in patient characteristics between single-dose and 24 h dosing. Between single and 24 h dosing SAP, there were no significant differences in acute periprosthetic joint infection rates, superficial SSI, 90-day reoperation, or 90-day complications. In a multicentre, national, retrospective cohort study published in 2019 [63], increased SAP duration was associated with a higher acute renal failure risk and CDI without reducing SSIs.

3.5. Monitoring the Implementation Level of the Suggested Measures

Understanding the infection prevention and control programme effect is essential to ensure it is implemented and executed as designed. Evaluating an action plan impact through surveillance with timely feedback is crucial to infection prevention and control action. This allows hospitals and healthcare professionals to gauge the strategies' effectiveness.

The appropriateness of prevention measures may depend on healthcare workers' behaviour and the availability of appropriate environmental and structural organisation. To improve compliance with prevention measures and ensure their long-term sustainability, the frequent assessment of working practices and timely result feedback to stakeholders is crucial. A systematic review of the effective strategies for implementing care bundles was published in 2015. Forty-seven studies were included in the review, and the three most frequently used strategies when a bundle was implemented were education, reminders, and audit and feedback [64]. The SHEA guidelines [13] recommend providing ongoing SSI rate feedback to surgical and perioperative personnel and leadership. Regarding the SSI prevention setting, in 2017, the European Centre for Disease Prevention and Control (ECDC) published [65] an updated version of a technical document (HAI-Net SSI protocol, version 2.2), proposing various process indicators for SSI prevention (including SAP) based on the strength of available evidence and the feasibility of their collection.

Care bundles are sets of evidence-based recommendations that, when implemented together, can result in better outcomes than when implemented individually. In 2019, a scoping review about barriers and facilitators to successfully implementing care bundles in the hospital setting was published. Bundles with a few simple measures were described to have better compliance rates. Standardising reporting of implementation strategies may help to transfer evidence-based bundle recommendations into clinical practice [66]. To reinforce the need to monitor the implementation level, we have included this concept as the last measure of the bundle.

ASPs can optimise the treatment of infections and reduce adverse events associated with antibiotics. In the context of a collaborative and interdisciplinary approach, it is essential to encourage an institutional safety culture in which surgeons are persuaded, rather than compelled, to respect antibiotic prescribing practices.

The proposed bundle contains a set of evidence-based interventions for SAP administration. It is easy to apply, promotes collaboration, and includes measures that can be adequately followed and evaluated in all hospitals worldwide.

4. Discussion

Appropriate prescription of antibiotics should be integral to good clinical practice and standards of care. On the contrary, inappropriate antibiotic prescriptions, as well as poor

infection prevention and control practices, are contributing to the development and spread of AMR [14].

Evidence has demonstrated that hospital ASPs aimed at improviung antibiotic use can optimise the management of infections and reduce adverse events associated with antibiotic use, including the global burden of AMR [14].

Fifteen years after the joint guidelines published by SHEA/IDSA [67], the best strategies for ASPs are still not defined. Moreover, many acute care hospitals worldwide do not have any ASP. The preferred means of improving antimicrobial stewardship should include a comprehensive programme incorporating collaboration among professionals within an institution. In this context, the direct involvement of all prescribers is crucial. Surgical wards represent settings where the use of antibiotics can be optimised. ASPs should include SAP as a critical area for improvement. Standardising a shared antibiotic prophylaxis protocol should be the first step of any ASP. Compliance with this protocol should be audited regularly, and the results should be fed back to the antimicrobial prescribers and decision-makers [68,69].

The systematic review by Davey et al. [70] demonstrated strong evidence that antibiotic use interventions among inpatients were associated with increased antibiotic policy compliance and duration. Of the 159 studies with intervention outcomes, 11 (6.9%) targeted SAP. Interventions were demonstrated to successfully reduce unnecessary antibiotic use in hospitals, even though the majority did not use the most effective behaviour change techniques. Recently, a retrospective study compared the selection and duration of antibiotics for SAP over six months, both before and after a five-year intervention. The rate of appropriate prescription of antibiotics for SAP improved to 80% during the post-intervention period. The rate of correct SAP duration increased significantly, from 69.1% (n = 1598) in the pre-intervention period to 78.0% (n = 841) in the post-intervention period ($p < 0.001$). The prescriptions of third cephalosporins, such as ceftriaxone, significantly decreased, while the prescriptions of cefazolin increased by more than nine times. No increases in SSIs were detected after the intervention. The implementation of an antimicrobial stewardship programme in the surgical ward demonstrated a positive impact on SAP prescriptions [71].

Using the best evidence is a fundamental aspect of healthcare quality. Guidelines for clinical practice are essential to disseminate evidence-based practices, improving healthcare quality and safety. Several guidelines have recently been published [5–13] regarding preventing SSIs. However, guidelines are not self-implementing, and complying with measures stated in guidelines is often challenging [72]. A systematic review assessing adherence to guidelines for SAP, published in 2015, demonstrated the need for greater adherence to guidelines [73]. A prospective, multicentre cohort study in orthopaedic surgery showed that lack of compliance with SAP guidelines is significantly associated with increased SSI rate [74].

Adapting clinical SAP guidelines in the local context may improve acceptance and adherence to best practices, also considering the local microbiological epidemiology.

The evolving field of implementation research has increasingly addressed how to adapt guidelines to local contexts and translate evidence into practice. Active involvement of the guidelines users in their adaption can lead to significant changes in clinical practice. Adapting clinical guidelines in a local context, such as local protocols or bundles, while specifying responsibilities for particular actions in a hospital setting, may be helpful to engage all professionals in guideline implementation [25].

Various implementation interventions have been described and can potentially be used to promote compliance with guidelines [75]. In the setting of SSI prevention, in 2019, Ariyo et al. published a systematic review of utilised implementation strategies [76]. They categorised implementation interventions using the "four Es" approach [74]—"engage", "educate", "execute", and "evaluate"—as the core components of change behaviour.

In the context of a multimodal strategy to implement HAI prevention, bundles are one of the most commonly used methods to translate guidelines to the local setting. A systematic review of the effect of interventions on the incidence of SSIs in acute care settings was

recently published. Twenty-three studies showed that interventions effective in preventing SSIs have multiple components such as care bundles, stakeholder engagement, targeted surveillance, and education [77]. An attractive, comprehensive review of the reasons for poor compliance with guidelines was published by Leaper et al. [78], who reported recommendations to improve patient outcomes and prevent SSIs. These recommendations included the following:

- Tracking compliance with hospital care bundles and conducting qualitative research into reasons for non-compliance with bundles;
- Incorporating checklists and care bundles into the informed consent process to make them as transparent as possible;
- Developing surveillance methods with shared SSI definitions and indicators that can be reliably interpreted in clinical practice and that can promote a benchmarking analysis of anonymised individual surgeon SSI rates;
- Updating national and local guidelines as new evidence evolves;
- Recognising compliant surgery/operating theatre work teams;
- Incorporating checklists and care bundles;
- Planning effective communication strategies with healthcare providers.

In administering antibiotics for any indication, including for SAP, surgeons should always be responsible for handling antibiotics with care.

In this narrative review, an international working group of 30 physicians from many regions of the world has defined an evidence-based bundle for appropriate SAP administration. This bundle includes five actions that may affect adequate SAP administration in all surgical wards worldwide.

1. *Administering the appropriate antibiotic.* SAP should be prescribed for surgical procedures at high risk of SSIs, such as clean–contaminated and contaminated surgical procedures or for clean surgical procedures where SSIs, even if unlikely, may have devastating consequences, such as in procedures with prosthetic implants. SAP should also be prescribed in patients with medical conditions associated with a higher risk of SSI, such as immunocompromised patients. The most commonly used antibiotics for SAP are first- and second-generation cephalosporins, including cefazolin, cefuroxime, cefoxitin, or the combination of cefazolin plus metronidazole, when it is necessary to cover anaerobes such as in colorectal surgery. Patients known to be colonised or to have had past infection with MDR bacteria must be treated on a case-by-case basis, taking into account multiple considerations. Future well-designed clinical studies will assess the SAP effectiveness in patients colonised with MDR bacteria. Although topical antibiotic prescription remains common among surgeons, it should be discouraged.
2. *Administering the antibiotic at the correct time before the incision.* Adequate tissue concentrations of antibiotics should be present at the surgical site throughout the surgical procedure. The first antibiotic dose should always be administered within 60 min before surgical incision for most commonly used antibiotics (including cefazolin). This can guarantee appropriate tissue concentrations during the surgical intervention. Only drugs with more extended half-lives, such as vancomycin, should be issued more than 60 min before the incision.
3. *Re-administering the antibiotic for prolonged procedures and in patients with severe blood loss*. Intraoperative doses should be issued for procedures exceeding two antibiotic half-lives or for procedures associated with blood loss (more than 1.5 L). This can guarantee that the antibiotic concentration is maintained above the minimal inhibitory concentration at the surgical site throughout the procedure.
4. *Discontinuing SAP after surgery*. SAP aims to prevent SSIs and should be administered and maintained at sufficiently high concentrations at the surgical site during the time that the incision is open. Erroneously, some surgeons believe that prolonging SAP after that the surgical incision has been closed can protect the patient from post-

operative infections. On the contrary, SAP administration should not be prolonged after the operation completion to prevent SSIs.

5. *Monitoring the implementation level of the suggested measures.* To improve compliance with prevention measures and ensure their long-term sustainability, frequent assessment of working practices and timely result feedback to stakeholders is crucial. As a multimodal strategy to implement HAI prevention, bundles are among the most commonly used methods to adapt guidelines in the local context and transfer best practices into routine clinical care. The proposed bundle contains a set of evidence-based interventions for SAP administration. It is easy to apply, promotes collaboration, and includes measures that can be adequately followed and evaluated in all hospitals worldwide. Major efforts should be made in all hospitals around the world to verify that the proposed measures are implemented in the context of a bundle strategy.

5. Conclusions

The use of SAP contributes considerably to the total amount of antibiotics prescribed in hospitals worldwide. Its overuse can be associated with antibiotic-related adverse events, including the development of AMR and elevated healthcare costs. Approximately 15% of all antibiotics in hospitals are prescribed for SAP. Bundles are one of the most commonly used methods to adapt guidelines to the local context and implement SSI prevention.

SAP consists of administering an antibiotic without active infections before the intervention. Antibiotics have no therapeutic purposes but are only preventive, aiming to reduce the surgical field microbial burden so that the host defences are not overcome.

In this article, we have presented an evidence-based bundle for correct SAP based on a review of the best available evidence. This bundle can be easily applied everywhere and we hope that it can help improve antibiotic prescribing practices among surgeons worldwide.

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JAMA | Review

Surgical Site Infection Prevention
A Review

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IMPORTANCE Approximately 0.5% to 3% of patients undergoing surgery will experience infection at or adjacent to the surgical incision site. Compared with patients undergoing surgery who do not have a surgical site infection, those with a surgical site infection are hospitalized approximately 7 to 11 days longer.

OBSERVATIONS Most surgical site infections can be prevented if appropriate strategies are implemented. These infections are typically caused when bacteria from the patient's endogenous flora are inoculated into the surgical site at the time of surgery. Development of an infection depends on various factors such as the health of the patient's immune system, presence of foreign material, degree of bacterial wound contamination, and use of antibiotic prophylaxis. Although numerous strategies are recommended by international organizations to decrease surgical site infection, only 6 general strategies are supported by randomized trials. Interventions that are associated with lower rates of infection include avoiding razors for hair removal (4.4% with razors vs 2.5% with clippers); decolonization with intranasal antistaphylococcal agents and antistaphylococcal skin antiseptics for high-risk procedures (0.8% with decolonization vs 2% without); use of chlorhexidine gluconate and alcohol-based skin preparation (4.0% with chlorhexidine gluconate plus alcohol vs 6.5% with povidone iodine plus alcohol); maintaining normothermia with active warming such as warmed intravenous fluids, skin warming, and warm forced air to keep the body temperature warmer than 36 °C (4.7% with active warming vs 13% without); perioperative glycemic control (9.4% with glucose <150 mg/dL vs 16% with glucose >150 mg/dL); and use of negative pressure wound therapy (9.7% with vs 15% without). Guidelines recommend appropriate dosing, timing, and choice of preoperative parenteral antimicrobial prophylaxis.

CONCLUSIONS AND RELEVANCE Surgical site infections affect approximately 0.5% to 3% of patients undergoing surgery and are associated with longer hospital stays than patients with no surgical site infections. Avoiding razors for hair removal, maintaining normothermia, use of chlorhexidine gluconate plus alcohol–based skin preparation agents, decolonization with intranasal antistaphylococcal agents and antistaphylococcal skin antiseptics for high-risk procedures, controlling for perioperative glucose concentrations, and using negative pressure wound therapy can reduce the rate of surgical site infections.

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Multimedia

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A surgical site infection is defined as infection following an operation at an incision site or adjacent to the surgical incision.[1] Infections occur in approximately 0.5% to 3% of patients undergoing surgery[2-4] and are among the most prevalent health care–acquired infections.[5-7] Surgical site infections are responsible for approximately $3.5 billion to $10 billion in US health care costs annually.[8,9] Compared with patients without surgical site infections, those with them remain in the hospital approximately 7 to 11 days longer[7,10]; 1 study involving 177 706 postsurgical patients reported that 78% were readmitted as a result of the infection.[11] This review summarizes current evidence-based interventions for prevention of surgical site infection that are applicable to the majority of operations (Box).

Methods

We searched PubMed, Google Scholar, and the Cochrane database for English-language studies of pathogenesis, clinical presentation, and prevention of surgical site infections published from January 1, 2016, when guidelines were most recently published by the World Health Organization, to September 15, 2022. In addition, we manually searched the references of selected articles for additional relevant publications. We prioritized randomized trials, systematic reviews, meta-analyses, clinical practice guidelines, and articles pertinent to general medical readership. Of 94 studies identified, 69 were included, consisting of 14 randomized trials, 19

systematic reviews, 12 meta-analyses, 4 clinical practice guidelines, 17 cohort studies, and 3 cross-sectional studies.

Discussion and Observations

Pathophysiology

Surgical site infection acquisition depends on several factors, namely, exposure to bacteria and the host's ability to control the inevitable bacterial contamination of the incision. They are typically caused by bacteria inoculated into the surgical site at the time of surgery. Approximately 70% to 95% are caused by the patient's endogenous flora.[12] The most common organisms are *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and *Escherichia coli*.[13] In some patients, introduction of only 100 colony-forming units of bacteria into the surgical site can cause infection.[14] However, exogenous sources of contamination during surgery such as bacteria transmitted from surgical personnel or heater-cooler units can also lead to infections.

Pathogens that cause infection vary by surgical location. The most common pathogens are components of skin flora such as *S aureus* and *Streptococcus* species. In contrast, infections following gastrointestinal procedures are typically associated with enteric organisms such as *Enterococcus* species and *E coli*.[15] Overall, *S aureus* is the most common cause of infection; for example, *S aureus* was associated with 24% of nonsuperficial surgical site infections in a cohort study including 32 community hospitals in the southeastern US.[4] Although methicillin-resistant *S aureus* (MRSA) was previously more likely to cause surgical site infections than methicillin-sensitive *S aureus* (MSSA), the rate of MSSA-derived infections from 2013 to 2018 was higher (0.07 per 100 procedures) than the rate of MRSA infections during the same period (0.05 per 100 procedures).[4] MRSA surgical site infections lead to worse clinical outcomes than those caused by less resistant pathogens.[10] Specifically, compared with MSSA surgical site infections, those due to MRSA were independently associated with 5.5 additional hospital days (95% CI, 1.97-9.11).[10] *E coli* and *Enterococcus* species respectively cause approximately 9.5% and 5.1% of all surgical site infections.[13]

Factors Associated With Surgical Site Infection

Factors associated with surgical site infection include older age, presence of immunosuppression, obesity, diabetes, effectiveness of antimicrobial prophylaxis, surgical site tissue condition (such as the presence of foreign material), and degree of wound contamination (**Table 1** and **Table 2**). For example, a national study of more than 387 000 patients found that for most surgery types, rates of surgical site infection were increased in patients with obesity.[21] The rates of surgical site infection following mastectomy among 16 473 patients increased with body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. Those with a BMI of 20 to 25 had a surgical site infection rate of 4.66%; BMI of more than 30 to 40, 7.06%; and BMI of more than 40, 10.58%. Similarly, after 29 603 laparoscopic cholecystectomy procedures (urgency not specified), the infection rate increased with BMI: 8.57% with a BMI of 20 to 25; 10.62% with a BMI of 30 to 40; and 17.11% with a BMI of more than 40.

Box. Commonly Asked Questions

How can the generalist clinician help in preventing surgical site infections?

The the generalist can help patients improve modifiable characteristics associated with increased risk of surgical site infections. such as helping obese patients lose weight, assisting patients who have diabetes with optimal glucose control, and assisting with smoking cessation.

Is there a threshold hemoglobinA_{1C} value above which surgical site infections are more common and surgery should be delayed?

Perioperative hyperglycemia in patients with or without diabetes is associated with surgical site infections, and randomized clinical trials support perioperative glucose control as an evidence-based practice to decrease risk of surgical site infection. In contrast, there are no randomized clinical trials that have found a clear association between a specific hemoglobin A_{1c} cutoff value and surgical site infections. However, patients with higher hemoglobin A_{1c} levels will likely have higher perioperative glucose values and glucose levels that are harder to control.

What therapies can prevent a surgical site infection?

Numerous strategies are currently recommended as outlined in this review. Six are supported by randomized clinical trials: (1) do not remove hair at the surgical site unless necessary; (2) decolonization with intranasal antistaphylococcal agent and antistaphylococcal skin antiseptic prior to high-risk procedures (eg, cardiothoracic, orthopedic); (3) use a chlorhexidine gluconate-alcohol antiseptic agent for skin preparation; (4) maintain normothermia intraoperatively; (5) control perioperative glucose values between 110 and 150 mg/dL; and (6) use incisional negative pressure wound dressings.

Some of these risk factors associated with surgical site infection are modifiable, such as hyperglycemia, obesity, and tobacco use. Other factors are nonmodifiable, such as age, which must be considered when deciding on the surgical intervention for the patient.[26,49]

Clinical Presentation

The median time to diagnosis of surgical site infection varies by procedure.[50] For example, *S aureus* infection is typically diagnosed a median of 14 days after plastic surgery, 24 days after general orthopedic surgery, and 28 days after orthopedic surgery where a prosthetic device was inserted. A surgical site infection is suspected when purulent drainage is present at the incision site or when there is evidence of an abscess involving the surgical bed. Physical examination findings such as systemic signs of infection (eg, fevers, rigors), local erythema, wound dehiscence, pain, nonpurulent drainage, or induration are the most common. However, the presence or absence of these symptoms varies depending on factors such as surgical site, host, and time from surgery to presentation. For example, fevers can be present in 14% of patients with a chronic prosthetic joint infection but up to 75.5% of patients if the etiology of the prosthetic joint infection is hematogenous.[51] Articular effusion and swelling may be present in 29% to 75% of prosthetic joint infections of the knee,[52] and delayed wound healing, wound dehiscence, or wound drainage

Table 1. Modifiable and Nonmodifiable Patient-Related Factors Associated With Surgical Site Infections

Factor	Pathophysiology
Patient-related, modifiable	
Diabetes	Hyperglycemia impairs the innate immune system and promotes glycosylation of proteins, which compromises wound healing.[16] Diabetes can lead to higher perioperative glucose levels and hyperglycemia that is more difficult to treat.[17]
Immunosuppressive medications and conditions	Immunosuppressive clinical conditions or medications diminish the inflammatory phase of wound healing.[18,19]
Malnutrition	Malnutrition can decrease collagen synthesis, granulation formation in surgical wounds, and result in poor tissue healing. Hypoalbuminemia weakens innate immunity by prompting macrophage apoptosis and diminishing macrophage activation. Low albumin also accelerates the seepage of interstitial fluid into the surgical wound and promotes general tissue edema.[20]
Obesity	Adipose tissue has less blood flow, which inhibits the delivery of oxygen and antibiotics.[21-23]
Preoperative infections	Prior to elective surgery, recognize and treat all infections (even if they are distant from the surgical site).[24]
Tobacco use	Tobacco use causes vasoconstriction, which can progress to alterations in collagen metabolism, decreased inflammatory response, and relative ischemia.[25]
Patient-related, nonmodifiable	
Age	The skin's basement membrane and dermis thin with increasing age, and the skin loses its reserve of cutaneous blood vessels and nerves that diminish wound healing.[26,27]
History of prior skin and soft tissue infections	A history of skin and soft tissue infections may be indicative of issues with inherent immunity and propensity for infection.[28]
History of radiation therapy	Treatment with radiation induces underlying tissue injury and inhibits wound healing.

Table 2. Modifiable Operation–Related Factors Associated With Surgical Site Infections

Factor	Pathophysiology
Airborne contamination	Raising the amount of microorganisms in the operating room environment provides additional opportunity for surgical site infection. Most of the airborne pathogens are generated by persons in the operating room and their movements.[29,30]
Anticoagulation	Anticoagulants may generate continual oozing of the incision and slow wound healing.[31]
Blood transfusions	Blood transfusions impair macrophage activity and influence infection risk.[32]
Decreased tissue oxygenation	Diminished tissue oxygenation lends itself to decreased oxidative killing by neutrophils and impaired tissue healing from depleted epithelialization, neovascularization, and collagen formation. Low oxygen settings can curtail the efficacy of perioperative antibiotics.[33,34]
Foreign material	Foreign material stimulates inflammation at the surgical site and raises the risk of surgical site infection.[35,36]
Operation length	Longer operative time is associated with higher damage to wound cells, wound contamination, and exposure to the outside environment.[37]
Perioperative hypothermia	Perioperative hypothermia weakens immune system protection against surgical wound contamination: vasoconstriction leads to impaired tissue perfusion and less access for key immune cells, less motility of key immune cells, and decreased scar formation.[38]
Postoperative hyperglycemia	Cellular functions of bactericidal activity, leukocyte adherence chemotaxis, and phagocytosis are enhanced by insulin and glycemic control, suggesting a direct relation between elevated blood glucose and cellular function deficits.[39] This relationship is observed in patients with and without a diagnosis of diabetes.
Surgical technique	Wound healing is decreased by leaving behind devitalized tissues, inadvertent entry into hollow viscera, inadequate blood supply maintenance, rough manipulation of tissue, misplaced drains and sutures, and unsuitable postoperative wound care.[40]
Wound care	Wounds that remain uncovered following surgery can be contaminated, or uncontrolled drainage can diminish the integrity of the surrounding skin.[41,42]
Wound contamination from patient's own flora	Wound classification delineates the degree of contamination of a surgical wound at the time of the operation.[43] Skin preparation and perioperative antibiotic administration reduce but do not eliminate the introduction of microorganisms at the surgical site.[44,45] Shaving leads to microscopic cuts in the skin that can become niduses for bacteria to multiply.[40] Without appropriate drapes and barrier devices, bacteria from hair follicles and deeper skin layers can recolonize the surgical site.
Wound contamination from operating room personnel	Transition of microorganisms from the surgical personnel's shoes, mouths, or body can contaminate surgical wounds.[14] Microorganisms from the hands of health care workers in the operating room can move onto the patient and operating field if personnel do not perform appropriate handwashing or gloving.[14,46,47]
Wound contamination from surgical instruments	Sterilization eliminates all microorganisms on the surfaces of surgical instruments. Using insufficiently sterilized tools can lead to pathogen transmission.[48]

may accompany up to 44% of prosthetic joint infections.[53,54] The presence of a sinus tract or purulent drainage has a specificity of between 97% and 100% and a positive predictive value of 100%.[55] Joint stiffness has a reported sensitivity of 20.5% and specificity of 99% in patients with a hematogenous source of prosthetic joint infection.[56] Many of the aforementioned

Table 3. Surgical Site Infection Prevention Strategies From Prospective Studies

Intervention	Type of studies	Absolute or median value	RR or OR (*P* value)
Preoperative			
Do not remove hair at the surgical site unless the presence of hair will affect the procedure[a]	Meta-analysis of 19 RCTs and 6 quasi-randomized trials[59]	• Razor vs clippers: 4.4% (84 of 1889) vs 2.5% (46 of 1834) • Razor vs depilatory cream: 7.8% (68 of 868) vs 3.6% (26 of 725) • Razor vs none: 4.2% (34 of 819) vs 2.1% (19 of 887)	• RR, 1.64 (.005) • RR, 2.28 (.02) • RR, 1.82 (.03)
Decolonize surgical patients with intranasal antistaphylococcal agent and antistaphylococcal skin antiseptic for high-risk procedures (eg, cardiothoracic, orthopedic)[b]	Meta-analysis of 5 RCTs and 12 observational studies[60]	Decolonization vs none: 0.8% (52 of 19 940) vs 2.0% (253 of 12 790)	RR, 0.41 (<.001)
Antimicrobial prophylaxis within 1 h of incision with weight-based antimicrobial agents selected based on most common pathogens for specific procedure[61,62c]	Cohort[61]	• Administration within 30 min before incision vs 30-60 min before incision: 1.6% (22 of 1339) vs 2.4% (38 of 1558) • Administration within 30 min before incision vs after incision: 1.6% (22 of 1339) vs 5.2% (9 of 174)	• OR, 0.67 (.13) • OR, 3.27 (.003)
Use a checklist based on the World Health Organization 19-item surgical checklist to ensure adherence to best practices[63,64]	Multicenter, quasi-experimental study[65]	Without vs with checklist: 6.2% vs 3.4%	RR, 0.55 (<.001)
Intraoperative			
Using chlorhexidine gluconate and alcohol-containing skin preparatory agent in combination[d]	Meta-analysis of 4 RCTs[66]	Chlorhexidine gluconate + alcohol vs povidone iodine + alcohol: 4.0% (54 of 1337) vs 6.5% (86 of 1326)	RR, 0.62 (.005)
Maintain normothermia during the surgical procedure	Systematic review of 3 RCTs[67]	Hypothermia vs normothermia: 4.7% (14 of 299) vs 13% (37 of 290)	RR, 3.67 (.008)
Postoperative			
Maintain and monitor blood glucose levels regardless of diabetes status Maintain blood glucose values between 110 and 150 mg/dL	Meta-analysis of 15 RCTs[68]	Glycemic control (<150 mg/dL) vs conventional control (>150 mg/dL): 9.4% (231 of 2464) vs 16% (392 of 2488)	RR, 0.59 (<.001)
Application of incisional negative pressure wound dressings	Meta-analysis of 23 RCTs[69]	Incisional negative pressure wound therapy vs standard dressings: 9.7% (124 of 1279) vs 15% (191 of 1268)	RR, 0.67 (<.001)

Abbreviations: OR, odds ratio; RCT, randomized clinical trial; RR, relative risk.

SI conversion factor: To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

[a] If hair removal is necessary, remove outside of the operating room. For male genitalia, 1 RCT suggested that preoperative hair removal on scrotal skin using a razor as opposed to clippers resulted in less skin trauma without an increased risk in surgical site infection.[70]

[b] Antistaphylococcal skin antiseptic agents include chlorhexidine gluconate baths or wipes or dilute bleach baths.

[c] Two hours are allowed for vancomycin and fluoroquinolones; redose antimicrobials for procedures with excessive blood loss and lengthy surgeries.

[d] Alcohol containing skin preparation products are contraindicated for some procedures (eg, mucosa, cornea, or ear).

presentations may overlap with noninfectious conditions, such as a hematoma, seroma, or stitch abscess at points of suture penetration.

Classification of Surgical Site Infection

Despite variable presentations of surgical site infections, the US Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) and the National Surgical Quality Improvement Program (NSQIP) provide specific surgical site infection definitions for surveillance and epidemiological purposes.[57,58] Surveillance consists of systematic monitoring of patients following surgery to detect variance in surgical site infection rates and to develop quality improvement initiatives to lower infection rates. The goal of these definitions is to be simple and objective but flexible enough to encompass clinically relevant infections. Both NHSN and NSQIP categorize surgical site infections into 3 groups: superficial-incisional (involving the skin or subcutaneous tissue layers of the incision), deep-incisional (involving muscle or connective tissue layers of the incision), and organs/spaces deep to the incision. Surveillance for surgical site infections continues for 30 days for most procedures and 90 days for specific procedures involving implanted materials. The NHSN collects data on all NHSN-eligible procedures, and NSQIP analyzes a subsample of 20% of cases for analysis via an 8-day systematic sampling cycle.

Prevention

Preoperative Period

A recent meta-analysis including 19 randomized and 6 quasi-randomized trials involving 8919 patients evaluated various ap-

proaches to preoperative hair removal for reducing surgical site infection (**Table 3**).[59] Across 7 randomized clinical trials (RCTs), hair removal with a razor was associated with a higher rate of surgical site infection: 4.4% (84 of 1889) patients whose hair was removed with a razor experienced an infection vs 2.5% (46 of 1834) whose hair was removed with clippers experienced an infection (relative risk [RR], 1.64 [95% CI, 1.16-2.33], *P* = .005). Across 9 RCTs, hair removal with a razor was associated with a higher rate of surgical site infection: 7.8% (68 of 868) patients vs 3.6% (26 of 725) patients whose hair was removed with a depilatory cream (RR, 2.28 [95% CI, 1.12-4.65]; *P* = .02). Seven RCTs demonstrated that removing hair with a razor was associated with an increased risk of surgical site infection: 4.2% (34 of 819) patients vs 2.1% (19 of 887) patients whose hair was not removed at all (RR, 1.82 [95% CI, 1.05-3.14]; *P* = .03).[59] Three RCTs reported that hair removal with clippers did not increase the risk of surgical site infection: 5.7% (49 of 863) patients vs 6.0% (52 of 870) patients whose hair was not removed (RR, 0.95 [95% CI, 0.65-1.39]; *P* = .80). If hair removal is necessary, it should be removed in the preoperative holding area and not in the operating room.

One method used to reduce surgical site infections is decolonization, in which patients are treated with an intranasal antimicrobial, skin antiseptic agent, or both to eliminate or temporarily reduce *S aureus* colonization prior to surgery. Evidence to support this recommendation is strongest for high-risk surgical procedures such as cardiothoracic surgeries and prosthetic joint replacement. This process typically includes an intranasal treatment with an antistaphylococcal agent (eg, mupirocin ointment or povidone iodine) and/or application of an antistaphylococcal skin antiseptic agent (eg, chlorhexidine gluconate solution or wipes) for 5 days. However, the precise timing, agent, and frequency of application are unclear because trials addressing this issue have used different strategies. The decolonization strategy should be completed as close to the surgical procedure as possible. A meta-analysis that included 5 RCTs and 12 observational studies showed that nasal decolonization was associated with lower rates of surgical site infections caused by gram-positive bacteria than no decolonization: 0.8% (152 of 19 940) vs 2.0% (253 of 12 790; RR, 0.41 [95% CI, 0.30-0.55]; *P* < .001).[60]

This association persisted among the 11 studies in which patients were decolonized regardless of *S aureus* colonization status (RR, 0.40; 95% CI, 0.29-0.55) and among the 6 studies in which nasal decolonization was combined with skin antisepsis (RR, 0.29; 95% CI, 0.19-0.44, primary data not provided).[60] In contrast, other trials that included a more heterogeneous group of surgeries did not find a difference in surgical site infection incidence with decolonization.[71] For example, a prospective cohort study that included 8 surgical categories (abdominal, orthopedic, urological, neurological, cardiovascular, thoracic, and plastic surgery and solid organ transplant) found that decolonization strategies did not reduce MRSA surgical site infections.[72] The authors identified 60 MRSA infections (0.55%) among 10 910 procedures in the control group compared with 70 MRSA infections (0.65%) among 10 844 procedures during the intervention period (*P* = .29). As a result, decolonization is typically focused on orthopedic, cardiothoracic, or high-risk procedures such as spine and brain surgeries.

The intervention requires a significant amount of coordination to perform the appropriate test prior to surgery, have the result reviewed, and ensure the appropriate decolonization approach was applied. Given the number of steps required, some hospitals perform decolonization on all patients undergoing high-risk surgical procedures, an approach that may ultimately be cost-effective (estimated $153 per person) based on modeling studies.[73] In contrast, widespread use of antistaphylococcal antibiotics such as mupirocin may ultimately increase rates of resistant *S aureus* infections.[74,75]

Conducting RCTs for surgical site infection prevention is challenging given the relatively low incidence of the outcome of interest. Thus, additional prevention strategies in the preoperative setting exist, but lack high-quality evidence. As a result, these interventions are predicated on expert opinion and results from retrospective cohort studies. For example, in contrast to postoperative glucose control, no RCTs have found a clear association between a specific hemoglobin A_{1c} cutoff and surgical site infections.

The administration of antibiotic prophylaxis is recommended in all surgical site infection prevention guidelines, despite the absence of RCTs.[14,17,76,77] One multicenter cohort study involving 4186 patients found that risk of infection increased as the time from antibiotic infusion to incision increased, although the trend was not statistically significant: administration within 30 minutes prior to incision was associated with a risk of 1.6% (22 of 1339) vs 2.4% (38 of 1558) with administration of antibiotic between 31 and 60 minutes before surgery (*P* = .13).[61] In the absence of trial data, guideline consensus is that antibiotics should be given within 60 minutes of the incision to maximize tissue concentration of the antibiotic. Additional recommendations include dosing antibiotics according to the patient's weight to ensure that adequate tissue concentrations are achieved and administering subsequent doses of antibiotics for lengthy procedures if excessive bleeding occurs. For example, cefazolin, the most commonly used agent for antimicrobial prophylaxis, should be redosed every 4 hours until completion of the procedure. These recommendations are mainly based on older cohort studies and evaluation of secondary outcomes (eg, tissue concentrations of antibiotics).[62] Although the optimal duration of prophylactic antibiotics is not known, prolonged antimicrobial prophylaxis is increasingly associated with patient harm, such as acute kidney injury.[78] Authors of a systematic review of 28 randomized trials involving 9478 patients receiving either a single dose for prophylaxis or multiple doses concluded that additional doses did not reduce the risk of infection 6.2% (278 of 4499) vs 5.9% (261 of 4440; OR, 1.06 [95% CI, 0.89-1.25]).[79] Thus, guidelines recommend stopping antibiotic prophylactic antibiotics when the surgical wound is closed.

The WHO's surgical safety checklist is a 19-item list to improve adherence with best practice and decrease surgical site infection incidence. WHO developed this safety checklist to promote more consistent implementation of best practices. This 19-item checklist included surgical site infection (eg, antimicrobial prophylaxis) and non–surgical site infection components (eg, surgical time-out). A multicenter, quasi-experimental study of 8 sites and 3733 patients showed that the infection rate prior to the implementation of the checklist was 6.2% compared with 3.4% after implementation of the checklist (*P* value <.001 for the risk difference).[65] These results have been supported by subsequent multi- and single-center prospective studies.[63,64] However, the exact mechanism of improvement is unclear and most likely multifactorial.

Intraoperative

Topical alcohol is highly bactericidal but does not have persistent activity when used as monotherapy for skin antisepsis (Table 3). Multiple guidelines recommend that surgical site antisepsis should be performed with a product that contains alcohol and another antiseptic agent (eg, chlorhexidine gluconate or povidone iodine).[17,76,80] Products that combine alcohol and antiseptic agents are available in the US. Chlorhexidine gluconate plus alcohol appears to be superior to povidone iodine plus alcohol for the prevention of surgical site infections.[81] In a meta-analysis of data from 4 RCTs involving 6916 women who had cesarean deliveries, the authors concluded that surgical site preparation with chlorhexidine gluconate plus alcohol was associated with lower rates of infection than preparation with povidone iodine plus alcohol: 4.0% (54 of 1337) vs 6.5% (86 of 1326; RR, 0.62 [95% CI, 0.45-0.87]; $P = .005$).[66] Similarly, a meta-analysis of 20 RCTs and 5 prospective, 4 retrospective, and 1 ambispective studies, including more than 29 000 participants found that skin preparation with chlorhexidine gluconate was associated with fewer surgical site infections than povidone iodine: 4.8% (725 of 15 263) vs 6.7% (925 of 13 743; RR, 0.65 [95% CI, 0.55-0.77]; $P < .001$).[82]

Normothermia to keep core body temperatures from dropping during surgery is maintained by combinations of forced warm air, skin warming, and warmed intravenous fluids (Table 2). Targets for core temperatures vary: more than 35.5 °C and more than 36 °C. A systematic review of 3 RCTs examining active body surfacing warm systems for preventing complications of inadvertent perioperative hypothermia in adults found that using a forced air warming device was associated with lower rates of the risk of surgical site infection than no forced air warming: 4.7% (14 of 299) vs 13% (37 of 290; RR, 0.36 [95% CI, 0.20-0.66]; $P = .008$; Table 3).[67]

Postoperative

Although there are no RCTs that have evaluated intensive glucose control to lower the preoperative average glucose (hemoglobin A_{1c}) vs usual care before surgery, postoperative hyperglycemia was associated with an increased risk of surgical site infections in patients with and without diabetes (Table 3).[48,83,84] As a result, strategies to prevent hyperglycemia to prevent surgical site infection are recommended in all major guidelines. Most data to support this strategy are from RCTs involving patients with diabetes. In a meta-analysis of 15 RCTs comparing the use of tight glycemic control (<150 mg/dL; 8.32 mmol/L) with conventional control (>150 mg/dL), tight control was associated with lower rates of surgical site infection: 9.4% (231 of 2464) vs 16% (392 of 2488; RR, 0.59 [95% CI, 0.50-0.68]; $P < .001$).[68]

Incisional negative pressure wound therapy, defined as wound dressing systems that continuously or intermittently apply subatmospheric pressure to the system, can reduce the risk of surgical site infection by promoting reducing fluid accumulation in the wounds, thereby accelerating primary wound healing. Authors of a meta-analysis of 23 RCTs involving 2547 patients undergoing various surgical procedures (eg, abdominal, cesarean delivery, orthopedic, vascular) concluded that use of incisional negative pressure wound therapy for primary wound closure was associated with lower rates of surgical site infection than use of standard dressings: 9.7% (124 of 1279) vs 15% (191 of 1268; RR, 0.67 [95% CI, 0.53-0.85]; $P < .001$); however, the effect varied by procedure type.[69] The authors indicated that they did not find evidence for substantial differences between the different types of surgery. Similarly, authors of a recent meta-analysis of 28 RCTs concluded that incisional negative pressure wound therapy was associated with lower rates of surgical site infection than standard dressing: 8.8% (194 of 2193) vs 14% (315 of 2205; RR, 0.61 [95% CI, 0.49-0.76]; $P < .001$).[85] The authors specified that when stratified by surgical discipline, the greatest benefits for surgical site infection reduction occurred in vascular surgery (RR, 0.45; 95% CI, 0.32-0.65; $P < .001$) and cardiac surgery (RR, 0.17; 95% CI, 0.03-0.96; $P = .05$), whereas the intervention was not associated with statistically significant benefit for abdominal surgery (RR, 0.56; 95% CI, 0.30-1.03), obstetric surgery (RR, 0.73; 95% CI, 0.44-1.20), orthopedic or trauma-derived surgery (RR, 0.68; 95% CI, 0.43-1.08), and plastic surgery (RR, 0.82; 95% CI, 0.26-2.63). The broader CIs for these later 4 subgroups suggest the possibility that they were underpowered to find a significant difference.

Hospital-Wide Surveillance

As one of the original surgical site infection prevention investigations, data from the Study on the Efficacy of Nosocomial Infection Control (SENIC)[86] supported the use of routine surveillance and feedback to reduce infections. The multicenter, 1985 SENIC study, evaluated infection prevention practices and found that the use of standardized surgical site infection surveillance by trained infection prevention personnel and routine feedback to surgeons was associated with an estimated reduction in infections in US hospitals from 586 000 to 510 000 compared with when no surveillance and feedback were given. Current recommendations advise health care institutions to identify high-volume, high-risk procedures and implement a system for collecting and storing data. Periodic reports should be prepared and given to key stakeholders to provide feedback on infection rates. Surveillance and feedback, along with several other quality improvement strategies (eg, education of surgeons, surgical staff, and patients) are endorsed by all surgical site infection prevention guidelines.[14,17,77,80]

Limitations

This review has several limitations. First, this review focused on prevention of surgical site infection following general, commonly performed surgical procedures. Second, not all recommendations in previously published guidelines were summarized herein given the lack of available RCT data. Third, some interventions had been studied in only a small number of RCTs. Fourth, in some cases, the only available studies were older. Fifth, quality of included literature was not assessed. Sixth, some relevant studies may have been missed.

Conclusions

Surgical site infections affect approximately 0.5% to 3% of patients undergoing surgery and are associated with longer hospital stays than patients with no surgical site infections. Avoiding razors for hair removal, maintaining normothermia, use of chlorhexidine gluconate plus alcohol–based skin preparation agents, decolonization with intranasal antistaphylococcal agents and antistaphylococcal skin antiseptics for high-risk procedures, controlling for perioperative glucose concentrations, and using negative pressure wound therapy can reduce the rate of surgical site infections.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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