



## Practice Forum

# Considering a new domain for antimicrobial stewardship: Topical antibiotics in the open surgical wound



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The global push to combat the problem of antimicrobial resistance has led to the development of antimicrobial stewardship programs (ASPs), which were recently mandated by The Joint Commission and the Centers for Medicare and Medicaid Services. However, the use of topical antibiotics in the open surgical wound is often not monitored by these programs nor is it subject to any evidence-based standardization of care. Survey results indicate that the practice of using topical antibiotics intraoperatively, in both irrigation fluids and powders, is widespread. Given the risks inherent in their use and the lack of evidence supporting it, the practice should be monitored as a core part of ASPs, and alternative agents, such as antiseptics, should be considered.

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## THE ANTIMICROBIAL STEWARDSHIP ERA

Over the last decade, the problems of antibiotic resistance and the resultant push for antibiotic stewardship have come to the forefront of global health care issues. In a 2013 report, the World Economic Forum went so far as to say that, “arguably the greatest risk...to human health comes in the form of antibiotic-resistant bacteria.”<sup>1</sup> How this point was reached is evident from the background statistics: in 2009, >3 million and in 2010 >13 million kilograms of antibiotics were administered to humans and animals in the United States.<sup>2</sup> The Centers for Disease Control and Prevention (CDC) has estimated that of those antibiotics administered to humans, between 20% and 50% were either “unnecessary or inappropriate.”<sup>3</sup> They further estimated that >2 million people are infected with antibiotic-resistant organisms resulting in 23,000 deaths each year.<sup>3</sup> In the United Kingdom’s 2016 “Review on Antimicrobial Resistance” report, it is predicted that by 2050, 10 million

lives a year and a cumulative \$100 trillion of economic output will be lost globally because of antibiotic resistance.<sup>4</sup>

In response to this, antibiotic stewardship programs (ASPs) designed to promote the appropriate use of antibiotics have been recommended by multiple organizations, including the Society for Healthcare Epidemiology of America (SHEA), Infectious Diseases Society of America (IDSA), Surgical Infection Society (SIS), Association for Professionals in Infection Control and Epidemiology (APIC), American Hospital Association, and CDC. Subsequently, effective from January 1, 2017, The Joint Commission (TJC) and Centers for Medicare and Medicaid Services (CMS) have both mandated ASPs for accreditation and federal reimbursement of services, respectively.<sup>5,6</sup> The American Hospital Association has identified that antibiotic stewardship should be one of the top 5 areas for improvement in hospital resource utilization.

## ASPS, INFECTION PREVENTION PRACTITIONERS, AND TOPICAL ANTIBIOTICS IN THE OPEN SURGICAL WOUND: CURRENT RELATIONSHIP

A key tenet of these programs is the fact that the more often bacteria are exposed to antibiotics, particularly when evidence does

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not support their use, exposure times are insufficient, or levels are subtherapeutic, the more likely bacteria are to develop resistance. The topical administration of antibiotics in open surgical wounds for the prevention of surgical site infection (SSI) represents a prime example of this. Currently, surgical patients are exposed to topical antibiotics intraoperatively, either through the application of antibiotic powders or through antibiotic-containing irrigation fluids. The American Society of Health-System Pharmacists, SIS, IDSA, and SHEA have all stated that because of insufficient evidence, this use of topical antibiotics cannot be recommended.<sup>7</sup> The World Health Organization SSI prevention panel strongly recommended that incisional wound irrigation with antibiotic solutions before closure should not be used for the prevention of SSIs. This expert panel also felt that this practice could be associated with the risk of antibiotic resistance.<sup>8</sup> Although neither the TJC or CMS has directly addressed this use of topical antibiotics, the standard of the CMS §482.42(A)(4) has called for facilities offering surgical services to have an infection prevention program and ASP which specifically addresses these SSI issues.<sup>6</sup> Nevertheless, evidence suggests that, in the absence of specific topical antibiotic use guidelines, the practice remains widespread and may indeed jeopardize patient safety.<sup>9–11</sup>

A 2008 survey of 186 practicing academic and community orthopedic surgeons revealed that 46% reported the regular use of antibiotic irrigation in surgery,<sup>9</sup> and a 2013 survey of operating room (OR) nurses at the Association for periOperative Registered Nurses revealed that 35% reported the regular use of antibiotics in surgical irrigation.<sup>10</sup>

More recently, a 2017 survey of 164 infection prevention practitioners (IPs) across the United States was performed to determine current practice related to the use of antibiotic irrigation solutions and antibiotic powders and involvement, if any, of their ASP.<sup>11</sup> The survey was created for the authors by an independent IP and sent to 3 APIC chapter presidents, representing 1 chapter on the west coast and 2 on the east coast, who then distributed it to their members. Additionally, an infection prevention consulting firm distributed it to their database of IPs, resulting in a total of approximately 400 IPs to whom the survey was sent. All responses were collected through Survey Monkey (Survey Monkey, San Mateo, CA). Although the response rate was low at 41%, and although 35% of respondents did not complete the entire survey for reasons that are unclear, the authors feel the results still provide some valuable insight into current practice. The demographics of the respondents are important in that the lack of knowledge about irrigation practices and installation of antibiotic powders seemed to reach across the spectrum of experience, bed size, and IP responsibility. Most of the IPs had significant IP experience, with 42% having ≥11 years, 44% having 3–10 years, and only 15% had ≤2 years. Their facilities ranged in bed size with 24% having ≤100 beds, 39% having 101–350 beds, and 40% having 351 to >600 beds. Respondents indicated that 50% had responsibility for the OR, and 39% had responsibility for the labor and delivery area and C-section suite.

The survey results showed that not only are most facilities using topical antibiotics in the OR, but in most cases, this use of antibiotics was not being monitored by their ASP.<sup>11</sup> In fact, although 92% of respondents reported having ASPs in their facilities, Table 1 demonstrates that only 10% reported the use of topical antibiotic powders in open surgical wounds for infection prophylaxis were being monitored by the program, and only 17% reported antibiotic irrigation solutions were monitored.<sup>11</sup> We therefore propose that, based on existing evidence, facilities should address the topical administration of antibiotics in open surgical wounds as part of their ASP and consider alternative practices.

Table 2 demonstrates that in the same survey, 33% of IPs indicated that topical antibiotics (powders) were used during surgery in their facility, and 36% reported that they were not used. The lack of

**Table 1**

Survey results of IPs regarding ASP monitoring practices related to surgical wound irrigation and instillation of antibiotic powders (N = 106)<sup>11</sup>

ASP monitoring	Responses
Preoperative prophylaxis antibiotics	78 (83)
IV antibiotics given for treatment of infection	84 (89)
Antibiotic powders instilled directly into the surgical wound	10 (10)
Antibiotic solution uses to irrigate wounds	17 (18)

NOTE. Values are % (n).

ASP, antimicrobial stewardship program; IP, infection prevention practitioner; IV, intravenous.

**Table 2**

Survey results of knowledge of infection prevention practitioners related to surgical irrigation and topical antibiotic powder practices (N = 106)<sup>11</sup>

Surgical area	Aware of surgical irrigation practices	Use of topical antibiotic powders
OR		
Yes	81 (86)	33 (36)
No	19 (20)	36 (38)
Do not know	N/A	30 (32)
L&D/Csec		
Yes	9.5 (10)	1 (1)
No	48 (51)	60 (64)
Do not know	42 (45)	39 (41)

NOTE. Values are % (n).

L&D/Csec, labor and delivery area and C-section suite; N/A, not applicable; OR, operating room.

attention to this practice is illustrated by the fact that 30% of the IPs were unaware of whether topical antibiotics were used in their surgical suite. In the labor and delivery and C-section area, <1% used antibiotic powders as part of the operative procedure, 66% did not use them, and 39% of the responding IPs did not know what the practice was. Eighty-one percent of the survey respondents also indicated they were aware of surgical irrigation practices in their ORs, whereas 19% were not aware of irrigation practices. Additionally, 9.5% of the IPs reported the use of antibiotic irrigation fluids in the labor and delivery and C-section, and the remaining respondents did not know.

The lack of knowledge about the use of topical antibiotics in open surgical wounds, whether in irrigation fluids or in powder form, by so many IPs underscores the need to focus more attention on these practices. The fact that there are no recommended standards by TJC or CMS also probably contributes to this inattention; however, the practices have multiple inherent risks and limitations: they can result in systemic exposure to the antibiotic, use significant resources, contribute to allergic reactions, and potentially foster the development of antibiotic resistance.

It is commonly accepted that ASP activities contribute to the control and reduction of antibiotic resistance and enhance patient safety. Therefore, it is proposed that, based on existing evidence, facilities should address the topical administration of antibiotics in open surgical wounds as part of their ASP and consider alternative practices.

## TOPICAL ANTIBIOTICS IN THE OPEN SURGICAL WOUND

### Practice origins

The use of topical agents to prevent wound infection has a long history. Hippocrates described the use of wine (alcohol) to prevent infections in wounds during the 4th and 5th centuries BCE.<sup>12</sup> Subsequent reports demonstrate a wide variety of agents having been used, including egg yolk in the 1500s and carbolic acid in the early 1900s.<sup>12,13</sup>

The development of sulfonamides and penicillin heralded the era of antibiotics and has been followed by a wide variety of antimicrobials

ranging from ampicillin to vancomycin.<sup>13</sup> The use of topical antibiotics in open surgical wounds, as prophylaxis prior to wound closure, has largely involved the addition of antibiotic(s) to a saline solution that is then used to irrigate the wound; however, the **use of topical antibiotic powders and antibiotic-impregnated sponges-fleeces, beads, and cements have also been used for SSI prevention.**<sup>13–23</sup> The theory fueling this use has been that the local concentration of these agents in the open surgical wound would eliminate or prevent bacterial contamination in that targeted site because the concentrations would greatly exceed minimum inhibitory concentrations (MICs).<sup>13,24</sup>

It has long been known that the predominant factors contributing to SSI development are host defense, microbial burden in the surgical incision, and virulence of that bioburden.<sup>14</sup> Hence, the idea that this bioburden could be reduced mechanically by irrigation and biologically by the addition of antibiotics to the irrigant spawned a variety of surgical irrigation practices.<sup>13,14</sup> Many surgeons also speculated that this local concentration would avoid systemic exposure, and the potential toxicities associated with it, and thereby minimize the possibility of antibiotic resistance.<sup>13</sup> However, newer data suggest that there is a potential for toxicities and systemic exposure leading to resistance associated with these practices.<sup>8,12</sup>

### An evidence problem

It was not until the 1950s that researchers began studying the use of topical antibiotics in open surgical wounds; however, in the ensuing 60 plus years, there remains a paucity of well-designed clinical studies which have evaluated their efficacy and safety.<sup>7,8,13,14,25–27</sup> In reviewing the studies that have assessed this topic, including those identified through a PubMed search and those we knew based on our experience in the fields of surgery and infection prevention and control, it is clear that they have often **yielded conflicting results regarding the impact of topical antibiotics on SSI rates.** The large reviews and meta-analyses of these studies have concluded, relatively consistently, that there is **insufficient evidence to support intraoperative topical antibiotics for SSI prevention and that many of the studies performed to date have been flawed.**<sup>13,14,25–30</sup>

One of the first large reviews was performed by Roth et al in which all published studies evaluating the use of antibiotics in surgical irrigation between 1964 and 1984 for pelvic, abdominal, orthopedic, and vascular procedures were reviewed.<sup>31</sup> They determined that the poor quality of available studies precluded an evidence-based consensus on the practice and called for further studies before the practice could be validated.

In 2011, McHugh et al published a literature review of peer-reviewed publications studying the intraoperative application of topical antibiotics for SSI prophylaxis for the period between 1980 and 2010.<sup>26</sup> The authors reported that although there was some evidence to justify the use of topical antibiotics in selective cases, such as joint arthroplasty and cataract surgery, overall there was insufficient randomized controlled trial-based evidence to support their use.<sup>26</sup> A year later, Huiras et al published a review of 22 prospective, randomized controlled trials evaluating the impact of topical intraoperative antibiotics on SSI rates.<sup>25</sup> They evaluated the impact the practice of topical antibiotic use had on overall SSI rates and then analyzed the impact based on surgical subspecialty for dermatologic, orthopedic, abdominal, colorectal, and cardiothoracic surgery. They concluded that “overall there is a significant lack of level I evidence supporting this practice for any of the surgical genres evaluated. . .[and] recommendations supporting this practice for surgical site prophylaxis cannot be made.”<sup>25</sup>

Mueller et al published a meta-analysis of evidence for the effect of intraoperative irrigation on SSI after open abdominal surgery, which compared irrigation with saline, povidone-iodine, or antibiotics with no irrigation.<sup>32</sup> The authors found that the use of antibiotics in sur-

gical irrigation fluids had a benefit in SSI reduction; however, they qualified this with the statement, “given the many methodological flaws and large heterogeneity of the analyzed trials, the clinical relevance [of this finding] has to be balanced against the risk of impaired wound healing and the potential of antimicrobial resistance.”<sup>32</sup>

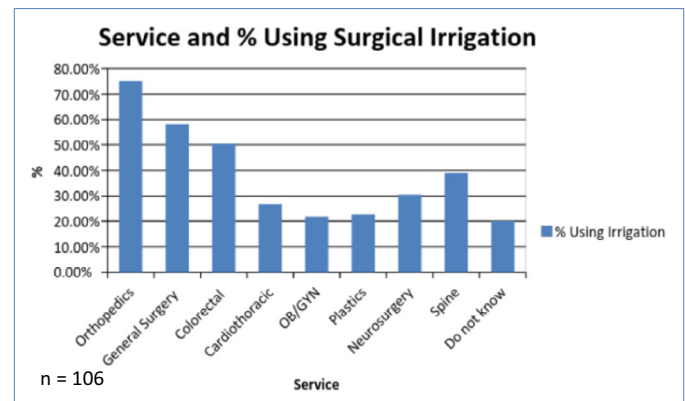
A prime example of the lack of high-quality evidence exists for the common practice of applying topical vancomycin powder in spinal surgery.<sup>27,33,34</sup> In 2015, 2 large systematic reviews were published on this practice. Bakhsheshian et al found a statistically significant benefit in SSI rates with the use of topical vancomycin but conceded that most supporting evidence was class III.<sup>34</sup> Similarly, Kang et al described a protective effect “based on the limited literature and evidence currently available” but advised that surgeons should proceed with caution in extrapolating their findings to best practice based on the “lack of significant high-quality evidence.”<sup>33</sup>

Kruckenhausner et al reviewed studies published during 2013, evaluating the use of all lavage solutions used in arthroplasties, and they concluded there is insufficient evidence-based research to establish a gold standard for irrigation solutions in those procedures.<sup>28</sup> In his 2016 review, Fry summarized the essential problems with most of the available literature on the topic by stating those studies demonstrating a benefit to topical antibiotic use often had high infection rates in the control groups and those demonstrating no benefit were often underpowered.<sup>13</sup>

It should be noted, however, that **there are published studies documenting a reduction in SSI rates associated with the use of topical antibiotics in the open surgical wound.**<sup>32,35,36</sup> In a 2016 Cochrane review of randomized and quasi-randomized trials assessing the effects of topical antibiotics in surgical wounds healing by primary intention, Heal et al concluded that “topical antibiotics. . .probably reduce the risk of SSI relative to no antibiotic,” but they were unable to draw conclusions about the effect they had on adverse outcomes, such as allergic contact dermatitis, or on antibiotic resistance.<sup>36</sup> The authors did comment that “many of the studies were small, and of low quality or at risk of bias.”<sup>36</sup>

Although the CMS standard §482.42(B) calls for the “requirement for hospitals to promote evidence-based use of antibiotics,”<sup>9</sup> surveys clearly indicate that, despite a lack of high-quality evidence, surgical irrigation with antibiotic solutions is widely practiced across a range of surgical services.<sup>9–11</sup>

Figure 1 demonstrates the breakdown of usage, by surgical specialty, in the aforementioned survey of IPs. Orthopedics, general surgery, and colorectal surgery were reported as having an irrigation utilization rate of ≥50%, followed by neurosurgery and spine (30%–39%), cardiothoracic surgery (26%), and the lowest use was identified in obstetrics-gynecology and plastics (22%–23%). Twenty



**Fig 1.** Surgical specialties using antibiotic irrigation of surgical wounds.<sup>11</sup> OB/GYN, obstetrics-gynecology.

percent of respondents did not know what specific services were doing in their facility.

#### *Topical antibiotics in the open surgical wound: Limitations and potential risks*

Opponents of topical antibiotic application in the open incision, prior to wound closure, often cite a number of problems inherent in the practice: insufficient exposure time between the bacterial target and the antimicrobial agent, toxicity or adverse reactions, and the potential for contributing to antibiotic resistance.<sup>8,13,14,18</sup>

#### *Drug-microbe exposure time: A mechanistic consideration*

The fundamental flaw associated with antibiotic irritation resides in a failure to recognize the mechanistic nature of how antibiotics work within the host. Many critics of antibiotics in irrigation solutions point out that **these solutions often end up having only a very brief dwell time (15–30 seconds) in the open incision before being suctioned out, which does not allow adequate time for the antibiotic to achieve its biologic effect.**<sup>3,37</sup> The principles of antibiotic therapy require the agent to achieve a therapeutic activity exceeding the minimum inhibitory concentration required to inhibit ninety percent of common surgical wound pathogens. In the case of peritoneal lavage with antibiotics after a colorectal procedure, aerobic and anaerobic bacterial can contaminate the peritoneal cavity by rapidly and tenaciously attaching to the serosal mesothelium.<sup>38</sup> Once adherence to the mesothelium occurs, the process is not mitigated by successive, rapid peritoneal antibiotics irrigation. Although the “solution to pollution is dilution” has been the mantra in abdominal surgery for >75 years, the addition of antibiotics to the lavage fluid offers no significant advantage over saline alone.<sup>38</sup> The use of antibiotic-impregnated collagen sponges or fleeces has been used by some surgeons as a solution to this problem, particularly in abdominal or cardiothoracic surgery.<sup>19–21</sup> Rutten and Nijhuis found a **significant reduction in SSI** rates for elective **colorectal surgeries** (n = 221) and abdominoperineal resections (n = 97) when **gentamicin-impregnated sponges were implanted.**<sup>19</sup> However, in a study of 602 patients undergoing colorectal surgery, Bennett-Guerrero et al found **a significantly increased incidence of SSI (P = .01) when gentamicin sponges were implanted.**<sup>20</sup>

Friberg et al found a significant reduction in sternal SSI rates in a randomized study of gentamicin sponges involving 2,000 cardiothoracic patients published in 2005.<sup>20</sup> A randomized controlled study of 1,500 cardiac surgery patients published 5 years later, however, identified no reduction in SSI rates with the use of gentamicin sponges.<sup>22</sup> In speculating about the discrepant outcomes, the authors of the latter study describe “important quality-control measures that were not incorporated in the previous study: onsite monitoring and source data verification, central adjudication of outcomes by an independent blinded committee, and the inclusion of a large number of hospitals (48 vs 2).”<sup>22</sup> In 2012, a large meta-analysis by Creanor et al of studies using gentamicin sponges in cardiothoracic surgery found insufficient evidence to support their use.<sup>39</sup> Formanek et al performed a meta-analysis of randomized controlled trials between 1990 and 2012 assessing the efficacy of gentamicin-collagen sponges in preventing SSIs among patients undergoing cardiac, colorectal, pilonidal sinus, hernia, and gastrointestinal procedures.<sup>35</sup> Their results were notable for demonstrating a significant protective effect among cardiac surgery patients.<sup>35</sup> The authors did note, however, that among all studies evaluated, a significant effect was more likely to be demonstrated by the low-quality and earlier studies than among the higher-quality and later studies.<sup>35</sup>

Similarly, conflicting results have been demonstrated with the use of antibiotic-impregnated cement or beads for orthopedic

procedures, with many experts citing the need for further evidence to justify the practice.<sup>23,40–44</sup>

The direct application of antibiotic powders to the open surgical wound has also been used as a potential solution to the exposure limitation associated with antibiotics in irrigation fluids,<sup>13,16,17,45</sup> but studies again report conflicting results, and there have been **numerous reported problems related to systemic absorption and adverse reactions.**<sup>13</sup>

#### *Systemic absorption*

From an antimicrobial stewardship perspective, perhaps one of the most important problems identified in some studies of topical antibiotic use during surgery is that of systemic absorption. Although it has been theorized that local (topical) application would avoid systemic exposure, a number of important cases have demonstrated significant serum antibiotic levels after topical exposure.<sup>46–52</sup> El Oakley et al found serum vancomycin levels of up to 4.4 mg/mL in cardiopulmonary bypass patients 3–4 hours after the application of 1 g of topical vancomycin powder intraoperatively.<sup>46</sup>

In a larger study of patients undergoing elective coronary artery bypass grafts, Desmond et al **measured significant levels of vancomycin in blood up to 6 hours after the topical application of either vancomycin powder or irrigation solution, and in urine up to 5 days postoperatively.**<sup>52</sup> Of particular concern was the fact that peak serum levels were 5 mg/mL, with a mean of 3 mg/mL.<sup>52</sup> The authors noted that the MIC of vancomycin for methicillin-resistant *Staphylococcus aureus* reported in some isolates from cardiac patients was 8 mg/mL, suggesting that “this [topical vancomycin] exposure is often below the dose required to inhibit *S. aureus* growth and, therefore, this bacterium may be proliferating while being exposed to vancomycin, which markedly increases the potential to develop vancomycin resistance.”<sup>52</sup>

In a study of joint **arthroplasty using gentamicin irrigation,** Ng et al found serum gentamicin levels **>2 µg/mL** in 16% of patients undergoing total joint replacement and in 30% of patients undergoing hemijoint replacement **4 hours postoperatively.**<sup>47</sup> **This was notable because serum gentamicin levels are recommended to be kept <2 µg/mL to avoid risks of oto- and nephrotoxicity.**<sup>47</sup> **In addition, the authors found no reduction in SSIs with use of the gentamicin irrigation.**<sup>47</sup>

Similar reports of significant serum concentrations have been reported after irrigation with kanamycin and amikacin solutions, even when immediate fluid aspiration was performed.<sup>48,49</sup> Ericsson et al even reported that after peritoneal lavage with a bacitracin solution, mean peak serum concentrations exceeded mean peak serum concentrations seen after intramuscular injection of the same dose of bacitracin (50,000 U).<sup>49</sup>

#### *Antibiotic resistance and selective pressure*

Antibiotic resistance is an obvious potential consequence from both insufficient drug-microbe contact times and from systemic absorption of antibiotics at subtherapeutic levels. In both cases there is inadequate time for the antibiotic to exert its biocidal effect on bacteria, leaving room for the bacteria to develop resistance. Many researchers have pointed to this potential as a reason for avoiding the use of topical antibiotics in the open surgical wound.<sup>13,14,18,24,30,52</sup> Additionally, some evidence suggests that topical application for SSI prophylaxis can also lead to selective pressure on wound flora.<sup>18</sup> In a study of 981 patients undergoing spinal surgery, in whom an average dose of 1.13 g of vancomycin powder was applied to the open surgical wound, Ghobrial et al found an increased incidence of gram-negative and polymicrobial SSIs, “lending support to [their] hypothesis that intraoperative [topical] vancomycin provides a



selective pressure resulting in increased prevalence of Gram negative and polymicrobial wound infections.”<sup>18</sup>

### Adverse reactions

Significant adverse reactions after topical administration of antibiotics, both with powders and irrigation solutions, have been documented. Multiple cases of anaphylaxis after the use of bacitracin irrigation in surgical procedures have been reported.<sup>53–56</sup> Bacitracin is not Food and Drug Administration approved for use in irrigation; however, a survey of attendees of the 2013 Association for periOperative Registered Nurses Congress indicated that, of those OR nurses reporting the use of antibiotics in irrigation, the most commonly added antibiotic was bacitracin.<sup>10,57</sup> Mariappan et al reported a case of anaphylaxis after the use of vancomycin powder in spine surgery.<sup>58</sup> In a study of rat models, Rappaport et al demonstrated a significantly increased incidence of peritoneal adhesions after irrigation with cefazolin and tetracycline compared with a control group which was irrigated with normal saline.<sup>59</sup> Nephro- and neurotoxicity have been reported after the use of neomycin irrigation solutions,<sup>60</sup> and respiratory insufficiency has been reported from the intraperitoneal administration of kanamycin.<sup>61</sup>

Another risk inherent in the practice of intraoperative topical antibiotic application, specifically antibiotic irrigation, involves the actual mixing of these irrigation solutions. Although United States Pharmacopeia Standard 797 and pharmacy protocols for safe mixing of medications recommend mixing under a laminar air flow hood to decrease risk of contamination, in many cases antibiotic irrigation solutions are mixed in the OR by OR nurses or scrub technicians, instead of the sterile compounding environment of a pharmacy. Potential exists for contamination of the solution when mixed in the OR from the airborne route just as it can occur with opened sterile instrument trays and other sterile OR equipment.<sup>62</sup> Additionally, cases of improper dosing, resulting in excessively and inappropriately high antibiotic concentrations in irrigation solutions, have been reported.<sup>63</sup> Outbreaks of toxic anterior segment syndrome in ophthalmologic patients resulting from dilutional errors in vancomycin solutions mixed for surgical irrigation have been reported.<sup>63</sup> Figure 2 shows the reported locations for antibiotic solution preparation in the survey of IPs: 32% indicated that antibiotic irrigation solutions were being mixed in the OR, whereas 37% were not aware of where they were being mixed.

Among those facilities where the solutions were mixed in the OR, most respondents were unaware of who was doing the mixing. Of those who were aware, surgical scrub technicians or OR nurses were the individuals most often reported to be doing the mixing (Fig 3).

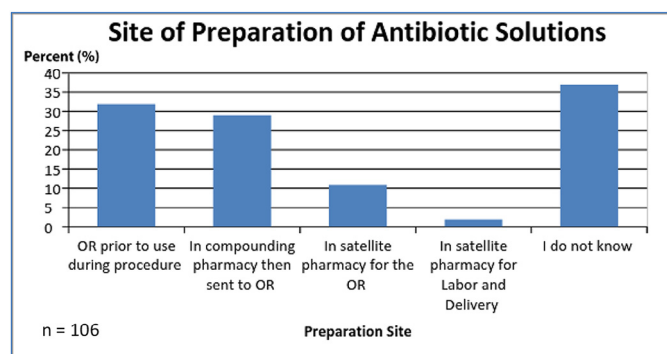


Fig 2. Survey results related to site of preparation of antibiotic irrigation solutions.<sup>11</sup> OR, operating room.

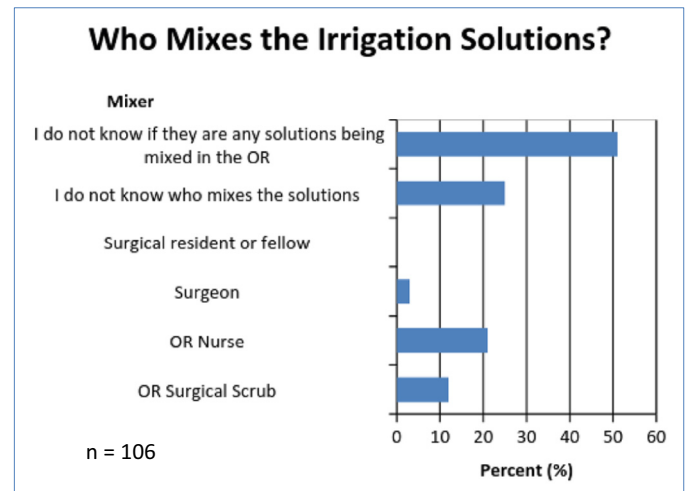


Fig 3. Survey results related to which personnel mixes antibiotic irrigation solution in the OR.<sup>11</sup> OR, operating room.

The new CMS mandate certainly identifies a role for the IP and ASP to monitor both the preparation of these solutions. Given the competing priorities and time constraints OR personnel face, it would seem appropriate to adopt an ASP-monitored policy of having all solutions premixed in the pharmacy or purchased from the manufacturer to ensure a sterile irrigation solution containing the desired concentration of antibiotic agent.

### ASPs, IPs, and topical antibiotics in the open surgical wound: Looking to the future

When TJC and CMS released their new requirements for ASPs, many facilities had to create or accelerate their existing program. To aid in this process, the CDC released a list of 7 essential elements to be used to establish an ASP in 2014.<sup>64</sup>

1. Leadership commitment: dedicate necessary human, financial, and information technology resources.
2. Accountability: appoint a single leader responsible for program outcomes who is accountable to an executive-level or patient quality-focused hospital committee. Experience with successful programs shows that a physician leader is effective.
3. Drug expertise: appoint a single pharmacist leader responsible for working to improve antibiotic use.
4. Action: implement at least 1 recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (ie, antibiotic time-out after 48 hours).
5. Tracking: monitor process measures (eg, adherence to facility-specific guidelines, time to initiation or de-escalation), impact on patients (eg, *Clostridium difficile* infections, antibiotic-related adverse effects and toxicity), antibiotic use, and resistance.
6. Reporting: report the aforementioned information regularly to doctors, nurses, and relevant staff.
7. Education: educate clinicians about disease state management, resistance, and optimal prescribing.

The obvious goal with these initiatives is to reduce unnecessary antibiotic use and mitigate antibiotic resistance. It stands to reason that all antibiotics, regardless of delivery route, should be monitored as part of these ASPs. Given the insufficient evidence supporting their use and the risks inherent in that use, topical antibiotics for open surgical wounds should certainly fall under the purview of ASPs, and in fact, the new CMS mandate clearly demands that

the IP and ASP of health care facilities be involved across the continuum of health care.

The practice of surgical wound irrigation has long been unstandardized and unmonitored.<sup>37</sup> There are no formal recommendations from any major medical organizations regarding any aspect of the practice, which perhaps explains the fact that irrigation additives, including antibiotics in particular, have largely gone unregulated.<sup>37</sup> In their 2013 “Clinical practice guidelines for antimicrobial prophylaxis in surgery,” the American Society of Health-System Pharmacists, IDSA, SIS, and SHEA issued a warning against the use of topical vancomycin in surgical incisions and followed up with the statement that “the safety and efficacy of topical antimicrobial [irrigations, pastes, and washes] have not been clearly established; therefore routine use of this route cannot be recommended in cardiac or other procedures.”<sup>7</sup> However, the survey of IPs demonstrated that most of those who responded reported no policy or association between their infection prevention program facility or ASP and the use of antibiotic powders or irrigation solutions in the OR.<sup>11</sup>

As facilities begin to create or expand their ASPs in accordance with CMS and TJC guidelines, it will probably fall to the IP to advocate for inclusion of intraoperative topical antibiotics in the program; however, collaboration between all parties (eg, surgeons, pharmacy, OR staff, IPs, hospital epidemiologists, laboratories) will be essential to developing a comprehensive policy. Engaging the identified lead pharmacist in this may aid in this effort. Changing practice will likely require education of surgical staff on the lack of existing quality evidence supporting the application of topical antibiotics in the open incision. A rigorous monitoring system that tracks all antibiotics sent from pharmacy to the OR, including those intended for topical use, should be instated, as well as comprehensive surveillance for patient outcomes for SSIs, allergic reactions, and toxicity adverse events during the transition.

Evaluation of alternative agents with bactericidal action such as certain antiseptics may be a viable alternative to consider, and ASP programs should work with surgeons and OR staff to transition to such an alternative.<sup>65</sup> By monitoring outcomes which, according to current literature, should demonstrate improved patient safety, the team can confidently move forward with this change.

Antiseptics hold great potential in aiding the effort to reduce antibiotic resistance because they have a much broader mechanism of action than that of antibiotics.<sup>24,66,67</sup> However, concerns about local tissue toxicity and a relative paucity of randomized controlled trials have hampered their widespread use.<sup>13,14,24</sup> A number of experts have pointed to the need for identifying an antiseptic concentration whose microbiocidal activity is carefully balanced with its cytotoxic effect.<sup>13,68</sup>

The only antiseptic currently cleared by the U.S. Food and Drug Administration for use in wound cleansing and debridement is 0.05% chlorhexidine gluconate, mixed with sterile water. In a 2013 article published in the *American Journal of Infection Control*, Edmiston et al demonstrated a 5-log<sub>10</sub> reduction in bacterial colony forming units of *Staphylococcus* spp and *Escherichia coli* when exposed to a 0.05% chlorhexidine solution.<sup>14</sup> They further describe the evidence demonstrating the safety of this concentration and the prolonged antiseptic effect provided by the binding of chlorhexidine to epidermal, mucous, and subcutaneous tissues after application.

Dotson et al demonstrated significant reductions ( $P = .0002$ ) in superficial incision, deep incision, and organ space SSIs along with overall SSI rates during a 7-month retrospective review when a 0.05% chlorhexidine gluconate solution was used during surgical irrigation during abdominal procedures compared with the 7 months prior.<sup>69</sup> In fact, the Wisconsin Department of Public Health recently issued SSI prevention guidelines which included the recommendation to consider the use of aqueous 0.05% chlorhexidine gluconate for intraoperative irrigation.<sup>70</sup>

It has been postulated that antiseptics have an alternative role in SSI prophylaxis during wound irrigation, and their established role in chronic wound management to reduce bioburden with subsequent uncontrolled colonization and the risk of infection. The risk of antiseptic resistance is small, but antiseptic stewardship, similar to that of antibiotics, will be needed for safe practice.<sup>71</sup>

## CONCLUSIONS

As the CMS mandate states, the obvious aim of the new ASP requirements is to improve the quality of patient care through “reducing the incidence of hospital-acquired conditions (HACs), including reduced incidence of healthcare-associated infections (HAIs); reduced inappropriate antibiotic use; and strengthened patient protections overall.”<sup>6</sup> Health care facilities, however, also stand to gain financially through reduced *C difficile* infection rates, drug cost savings, and potentially reduced multidrug-resistant organism infections.<sup>6</sup> CMS estimates that for drug cost savings alone, the figures could reach \$520 million for acute care facilities and \$37 million for critical access hospitals. They estimate \$2.5 billion in savings over 5 years could be realized by lowering *C difficile* infection hospitalization and readmission rates.<sup>6</sup>

For these benefits to be achieved, much will be demanded of IPs. Their role continues to evolve as increasing emphasis is placed on preventing health care-associated infections, decreasing risk of multidrug-resistant organisms, monitoring and reporting mandatory data, and now advancing antimicrobial stewardship. This is reflected in the deliberate expansion of the scope of the responsibilities of IPs in the new CMS mandate, specifically §482.42(C)(2).<sup>6</sup>

In the recent survey of IPs, respondents were asked if they believed the CMS or TJC ASP requirements would enhance their role in the OR. Only 43% felt that their role in the OR would be enhanced, and 30% thought it would “help a little but not enough.” Fifteen percent said it was not addressed at all in their facility.<sup>11</sup>

These responses are thought-provoking because the new CMS mandates very specifically call for IP and ASP oversight of issues related to SSIs.<sup>6</sup> The emphasis in both the CMS and TJC mandates on strong multidisciplinary collaboration must translate into a strengthened relationship between IPs, ASPs, and the OR or surgical departments. A strong and ongoing partnership between all parties will be critical to developing a robust ASP that monitors all antibiotic usage, including topical antibiotics in the OR.

Given that in some facilities this partnership between IPs, ASPs, and the OR may not currently exist and may require a significant amount of development work, it will be essential for hospital administrations, which are now accountable for the success of the IPs and ASPs, to provide the necessary support. Examples of such support could include funding a gap analysis of antibiotic use at the facility, which could help identify priority areas for improvement, including topical antibiotic use in the OR, or simply requiring surgeons to collaborate more closely with IPs. The Institute for Healthcare Improvement asserts that the overarching driver for the success of ASPs is engagement of administrative and clinical leadership as champions and promotion of the appropriate organizational culture to promote optimal antimicrobial use within the facility.<sup>72</sup>

An alternative approach would be for professional or regulatory organizations to collect data from facilities on their current topical antibiotic usage, policies and protocols, and outcomes. This pooling of data could help generate a more robust body of evidence surrounding the practice, which might ultimately lead to more effective regulation (Table 3).

These new ASP mandates are creating a sea of change in the world of infection prevention and control. Many of the issues leading to this change, including the overuse-inappropriate use of antibiotics, have not previously been formally tied to federal reimbursement,

**Table 3**

Policies for use of antibiotic irrigation fluids and education of OR staff and surgeons related to best practices for surgical irrigation (N = 106)<sup>11</sup>

Policy area	Yes	No	Do not know
Medical-surgical staff policy	14 (15)	54 (58)	31 (33)
OR policy	25 (27)	49 (52)	25 (27)
Infection prevention policy	8 (9)	86 (91)	6 (6)
Education programs	49 (52)	11 (12)	40 (42)

NOTE. Values are % (n).  
OR, operating room.

but ignoring them has almost reached a crisis point. If all forms of inappropriate antibiotic use continue to be ignored, including that of topical antibiotics in the open surgical wound, the battle may be even further from being won than was originally feared. Until robust, high-quality evidence supporting the use of topical antibiotics is available, ASPs should work to eliminate this practice.

Finally, adoption of a standardized intraoperative irrigation strategy, potentially involving use of an effective, rapidly cidal antiseptic agent in combination with other evidence-based care bundle measures, offers an inexpensive and effective strategy to reduce the risk of postoperative SSI.<sup>37,73,74</sup> A recent review of available evidence by Roberts et al concluded that antiseptics should be considered as “an integral part of antimicrobial stewardship strategies for the prevention...of surgical site...infections.”<sup>75</sup> Further study of antiseptic agents in this role, however, is needed, and it is crucial that appropriate antiseptic stewardship is engaged early to prevent any risk of theoretical widespread antiseptic resistance, and cross-resistance, becoming a reality.

## References

- Howell L, editor. Global risks 2013, eighth edition: an initiative of the Risk Response Network. Geneva (Switzerland): World Economic Forum; 2013.
- Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *New Engl J Med* 2013;368:299–302.
- Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance. 2017. Available from: <http://www.cdc.gov/drugresistance>. Accessed January 5, 2017.
- O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London (UK): Review on Antimicrobial Resistance; 2016.
- The Joint Commission. New antimicrobial stewardship standard. 2016. Available from: [https://www.jointcommission.org/assets/1/6/New\\_Antimicrobial\\_Stewardship\\_Standard.pdf](https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf). Accessed February 23, 2017.
- Centers for Medicare and Medicaid Services. Medicare and Medicaid programs; hospital and critical access hospital (CAH) changes to promote innovation, flexibility, and improvement in patient care. 2016. Available from: <https://www.federalregister.gov/documents/2016/06/16/2016-13925/medicare-and-medicaid-programs-hospital-and-critical-access-hospital-cah-changes-to-promote>. Accessed February 24, 2017.
- Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70:195–283.
- Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, de Jonge S, de Vries F, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e288–303.
- Tejwani NC, Immerman I. Myths and legends in orthopaedic practice: are we all guilty? *Clin Ortho Rel Res* 2008;466:2861–72.
- Twomey C. The surgical healthcare-associated infection: uncovering the truth about surgical irrigation. 2013. Available from: <http://www.infectioncontrolday.com/articles/2013/07/the-surgical-healthcare-associated-infection-uncovering-the-truth-about-surgical-irrigation.aspx>. Accessed September 29, 2016.
- Survey Monkey, Inc. Antibiotic stewardship survey. 2017. Available from: <https://www.surveymonkey.com/results/SM-8FST8KPF/>. Accessed February 23, 2017.
- Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. *Ann Surg* 2011;253:1082–93.
- Fry DE. Topical antimicrobials and the open surgical wound. *Surg Infect* 2016;17:520–4.
- Edmiston CE, Bruden B, Rucinski MC, Henen C, Graham MB, Lewis BL. Reducing the risk of surgical site infections: does chlorhexidine gluconate provide a risk reduction benefit? *Am J Infect Control* 2013;41(Suppl):S49–55.
- Mohammed S, Pisimisis GT, Daram SP, Bechara CF, Barshes NR, Lin PH, et al. Impact of intraoperative administration of local vancomycin on inguinal wound complications. *J Vasc Surg* 2013;57:1079–83.
- Andersen B, Bendtsen A, Holbraad L, Schantz A. Wound infections after appendectomy. I. A controlled trial on the prophylactic efficacy of topical ampicillin in non-perforated appendicitis. II. A controlled trial on the prophylactic efficacy of delayed primary suture and topical ampicillin in perforated appendicitis. *Acta Chir Scand* 1972;138:531.
- Andersen BJ, Korner B, Ostergaard AH. Topical ampicillin against wound infection after colorectal surgery. *Ann Surg* 1972;176:129.
- Ghobrial GM, Thakkar V, Andrews E, Lang M, Chitale A, Oppenlander ME, et al. Intraoperative vancomycin use in spinal surgery: single institution experience and microbial trends. *Spine* 2014;39:550–5.
- Rutten HJ, Nijhuis PH. Prevention of wound infection in elective colorectal surgery by local application of a gentamicin-containing collagen sponge. *Eur J Surg Suppl* 1996;578:31–5.
- Friberg Ö, Svedjeholm R, Söderquist B, Granfeldt H, Vikerfors T, Källman J. Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial. *Ann Thorac Surg* 2005;79:153–61.
- Bennett-Guerrero E, Pappas TN, Koltun WA, Fleshman JW, Lin M, Garg J, et al. Gentamicin–collagen sponge for infection prophylaxis in colorectal surgery. *New Engl J Med* 2010;363:1038–49.
- Bennett-Guerrero E, Ferguson TB, Lin M, Garg J, Mark DB, Scavo VA, et al. SWIPE-1 Trial Group. Effect of an implantable gentamicin–collagen sponge on sternal wound infections following cardiac surgery: a randomized trial. *JAMA* 2010;304:755–62.
- Parvizi J, Saleh KJ, Ragland PS, Pour AE, Mont MA. Efficacy of antibiotic-impregnated cement in total hip replacement. *Acta Orthop* 2008;79:335–41.
- Anglen JO. Wound irrigation in musculoskeletal injury. *J Am Acad Orthop Surg* 2001;9:219–26.
- Huiras P, Logan JK, Papadopoulos S, Whitney D. Local antimicrobial administration for prophylaxis of surgical site infections. *Pharmacotherapy* 2012;32:1006–19.
- McHugh SM, Collins CJ, Corrigan MA, Hill AD, Humphreys H. The role of topical antibiotics used as prophylaxis in surgical site infection prevention. *J Antimicrob Chemother* 2011;66:693–701.
- O'Neal PB, Itani KM. Antimicrobial formulation and delivery in the prevention of surgical site infection. *Surg Infect (Larchmt)* 2016;17:275–85.
- Kruckenhauser EM, Nogler M, Coraça-Huber D. Use of lavage fluids in arthroplasty to prevent postoperative infections. *Drug Res (Stuttg)* 2014;64:166–8.
- Anglen JO. Comparison of soap and antibiotic solutions for irrigation of lower-limb open fracture wounds. *J Bone Joint Surg Am* 2005;87:1415–22.
- Falagas ME, Vergidis PI. Irrigation with antibiotic-containing solutions for the prevention and treatment of infections. *Clin Microbiol Infect* 2005;11:862–7.
- Roth RM, Gleckman RA, Gantz NM, Kelly N. Antibiotic irrigations a plea for controlled clinical trials. *Pharmacotherapy* 1985;5:222–7.
- Mueller TC, Loos M, Haller B, Mihaljevic AL, Nitsche U, Wilhelm D, et al. Intra-operative wound irrigation to reduce surgical site infections after abdominal surgery: a systematic review and meta-analysis. *Langenbecks Arch Surg* 2015;400:167–81.
- Kang DG, Holekamp TF, Wagner SC, Lehman RA. Intraspinal vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. *Spine J* 2015;15:762–70.
- Bakhsheshian J, Dahdaleh NS, Lam SK, Savage JW, Smith ZA. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. *World Neurosurg* 2015;83:816–23.
- Formanek MB, Herwaldt LA, Perencevich EN, Schweizer ML. Gentamicin/collagen sponge use may reduce the risk of surgical site infections for patients undergoing cardiac operations: a meta-analysis. *Surg Infect* 2014;15:244–55.
- Heal CF, Banks JL, Lepper PD, Kontopantelis E, van Driel ML. Topical antibiotics for preventing surgical site infection in wounds healing by primary intention. *Cochrane Database Syst Rev* 2016;(11):CD011426.
- Barnes S, Spencer M, Graham D, Johnson HB. Surgical wound irrigation: a call for evidence-based standardization of practice. *Am J Infect Control* 2014;42:525–9.
- Edmiston CE, Goheen MP, Kornhall S, Jones FE, Condon RE. Fecal peritonitis: microbial adherence to serosa mesothelium and resistance to peritoneal lavage. *World J Surg* 1990;14:176–83.
- Creanor S, Barton A, Marchbank A. Effectiveness of a gentamicin impregnated collagen sponge on reducing sternal wound infections following cardiac surgery: a meta-analysis of randomised controlled trials. *Ann R Coll Surg Engl* 2012;94:227–31.
- Hinarejos P, Guirio P, Leal J, Montserrat F, Pelfort X, Sorli ML, et al. The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection. *J Bone Joint Surg Am* 2013;95:769–74.
- Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *Bone Joint J* 1995;77:93–7.
- Moehring HD, Gravel C, Chapman MW, Olson SA. Comparison of antibiotic beads and intravenous antibiotics in open fractures. *Clin Orthop* 2000;372:254–61.
- Ueng SW, Lin SS, Wang IC, Yang CY, Cheng RC, Liu SJ, et al. Efficacy of vancomycin-releasing biodegradable poly (lactide-co-glycolide) antibiotics beads

- for treatment of experimental bone infection due to *Staphylococcus aureus*. *J Orthop Surg Res* 2016;11:52.
44. Hauser CJ, Adams CA Jr, Eachempati SR. Prophylactic antibiotic use in open fractures: an evidence-based guideline. *Surg Infect* 2006;7:379–405.
  45. Raahave D, Hesselfeldt P, Pedersen T, Zachariassen A, Kann D, Hansen OH. No effect of topical ampicillin prophylaxis in elective operations of the colon or rectum. *Surg Gynecol Obstet* 1989;168:112–4.
  46. El Oakley R, Al Nimer K, Bukhari E. Is the use of topical vancomycin to prevent mediastinitis after cardiac surgery justified? *J Thorac Cardiovasc Surg* 2000;119:190–1.
  47. Ng AB, Lee KH, To BS. Systemic absorption of gentamicin irrigation in joint replacement surgery: a cause of concern. *Orthop Proc* 2010;92(SIII):400.
  48. Van Way CW, Hasse GE. Amikacin concentrations in serum following intraoperative irrigation of the pleura and peritoneum. *Ann Surg* 1985;201:333.
  49. Ericsson CD, Duke JH, Pickering LK, Qadri SM. Systemic absorption of bacitracin after peritoneal lavage. *Am J Surg* 1979;137:65–7.
  50. Kopel ME, Riemersma L, Finlayson DC, Tobia V, Jones EL, Hall RI, et al. Gentamicin solution for mediastinal irrigation: systemic absorption, bactericidal activity, and toxicity. *Ann Thorac Surg* 1989;48:228–31.
  51. Ericsson CD, Duke JH Jr, Pickering LK. Clinical pharmacology of intravenous and intraperitoneal aminoglycoside antibiotics in the prevention of wound infections. *Ann Surg* 1978;188:66.
  52. Desmond J, Lovering A, Harle C, Djorevic T, Millner R. Topical vancomycin applied on closure of the sternotomy wound does not prevent high levels of systemic vancomycin. *Eur J Cardiothorac Surg* 2003;23:765–70.
  53. Blas M, Briesacher KS, Lobato EB. Bacitracin irrigation: a cause of anaphylaxis in the operating room. *Anesth Analg* 2000;91:1027–8.
  54. Sprung J, Schedewie HK, Kampine JP. Intraoperative anaphylactic shock after bacitracin irrigation. *Anesth Analg* 1990;71:430–3.
  55. Netland PA, Baumgartner JE, Andrews BT. Intraoperative anaphylaxis after irrigation with bacitracin: case report. *Neurosurg* 1987;21:927–8.
  56. Damm S. Intraoperative anaphylaxis associated with bacitracin irrigation. *Am J Health Syst Pharm* 2011;68.
  57. U.S. National Library of Medicine. Daily med: bacitracin. 2017. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3d2f60c-d3e8-4ce8-92eb-d3044783e5dd>. Accessed February 23, 2017.
  58. Mariappan R, Manninen P, Massicotte EM, Bhatia A. Circulatory collapse after topical application of vancomycin powder during spine surgery: case report. *J Neurosurg Spine* 2013;19:381–3.
  59. Rappaport WD, Holcomb M, Valente J, Chvapil M. Antibiotic irrigation and the formation of intraabdominal adhesions. *Am J Surg* 1989;158:435–7.
  60. Davia JE, Siemsen AW, Anderson RW. Uremia, deafness, and paralysis due to irrigating antibiotic solutions. *Arch Int Med* 1970;125:135–9.
  61. Noble RC. Respiratory insufficiency after intraperitoneal administration of Kanamycin: failure of calcium gluconate to reverse toxic effects. *South Med J* 1976;69:1218–9.
  62. Dalstrom DJ, Venkatarayappa I, Manternach AL, Palcic MS, Heyse BA, Prayson MJ. Time-dependent contamination of opened sterile operating-room trays. *J Bone Joint Surg Am* 2008;90:1022–5.
  63. Hayden F. Using antibiotics in irrigation solutions. 2010. Available from: <https://www.eyeworld.org/article-using-antibiotics-in-irrigation>. Accessed September 29, 2016.
  64. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. 2014. Available from: <https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html>. Accessed February 24 2017.
  65. Edmiston CE, McBain AJ, Kiernan M, Leaper DJ. A narrative review of microbial biofilm in postoperative surgical site infections: clinical presentation and treatment. *J Wound Care* 2016;25:693–702.
  66. Edmiston CE, Seabrook GR, Johnson CP, Paulson DS, Beausoleil CM. Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery. *Am J Infect Control* 2007;35:89–96.
  67. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J* 2012;9(Suppl):1–9.
  68. Leaper D, McBain AJ, Kramer A, Assadian O, Sanchez JL, Lumio J, et al. Healthcare associated infection: novel strategies and antimicrobial implants to prevent surgical site infection. *Ann R Coll Surg Engl* 2010;92:453–8.
  69. Dotson N, Rasheid SH, Marcet JE, Sanchez JE. Irrigation of incisions with chlorhexidine 0.05% reduces surgical site infections in colorectal surgery. Poster presented at: Annual Scientific Meeting of the American Society of Colon and Rectal Surgeons; May 30–June 3, 2015; Boston, MA.
  70. Wisconsin Division of Public Health. Supplemental guidance for the prevention of surgical site infections: an evidence based perspective. 2017. Available from: <https://www.dhs.wisconsin.gov/publications/p01715.pdf>. Accessed January 25, 2017.
  71. Roberts C, Assadian O, Leaper D. The role of topical antiseptic agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. *Adv Wound Care (New Rochelle)* 2017;6:63–71.
  72. Institute for Healthcare Improvement. Antibiotic stewardship driver diagram and change package. 2012. Available from: [https://www.cdc.gov/getsmart/healthcare/pdfs/Antibiotic\\_Stewardship\\_Change\\_Package\\_10\\_30\\_12.pdf](https://www.cdc.gov/getsmart/healthcare/pdfs/Antibiotic_Stewardship_Change_Package_10_30_12.pdf). Accessed February 23, 2017.
  73. Edmiston CE, Leaper DJ. Intraoperative surgical irrigation of the surgical wound: what does the future hold—saline, antibiotic agents or antiseptic agents. *Surg Infect* 2016;17:656–64.
  74. Tanner J, Assadian O, Kiernan M, Edmiston CE, Leaper D. Do surgical care bundles reduce the risk of surgical site infections in patients undergoing colorectal surgery? *Surgery* 2015;158:66–77.
  75. Roberts CD, Leaper DJ, Assadian O. The role of topical antiseptic agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. *Adv Wound Care (New Rochelle)* 2017;6:63–71.