Making a Difference in Perioperative Infection

Steven L. Shafer, MD

Last month I asserted that "anesthesiologists make a difference" was not a marketing slogan but a statement of fact.[1] Some colleagues may think that our job is putting patients to sleep and waking them up. Only anesthesiologists who give lectures put people to sleep. We anesthetize patients, render them vulnerable, keep them alive during the surgical transgression, and subsequently awaken them from the anesthetized state. This daily miracle of anesthesia is only a small fraction of the difference we make in patient care. This issue of *Anesthesia & Analgesia* features a collection of papers that will make a difference in the rate of hospital-acquired infection.

Anesthesiologists are well positioned to make a difference in perioperative infection. We administer perioperative antibiotics. Our workplace is clean (we think) but outside of the sterile field. We have frequent contact with the patient's skin and oral-nasal mucosa. Dr. Randy Loftus and his colleagues at the Geisel School of Medicine, Dartmouth-Hitchcock Medical Center, have conducted seminal investigations in the operating room biome. Four of these papers appear in this issue of *Anesthesia & Analgesia.*

Loftus and colleagues[2] examined the transmission of *Staphylococcal aureus*. They identified 2 *S aureus* phenotypes, 1 associated with transmission among patients or contaminated surfaces and 1 associated with transmission from provider hands. The patient phenotype of *S aureus* was more virulent, with a faster doubling time and increased antibiotic resistance. This isolate was associated with inpatient hospitalization before surgery. *S aureus* isolates from provider hands were substantially less virulent although still cause for concern. Although we need to wash our hands, the findings show that we also need to better clean the operating room to reduce infection risk. Loftus and colleagues[3] have similar findings for the mode of transmission of Gram-negative organisms: most transmission occurs from contact with infected surfaces, not provider hands.

Loftus and colleagues[4] performed a similar analysis for *Enterococcus*, an organism that has undergone iatrogenic evolution from a ubiquitous and generally harmless commensal gut bacterium to the second most frequent cause of hospital-acquired infection.[5] Along the way, *Enterococci* have developed and widely shared multiple drug-resistant adaptations. Loftus and colleagues found that unlike *S aureus*, most transmission of *Enterococcus* to surgical patients appears to be from our hands. This is within our power to fix.

When it comes to hand washing, we may make a difference we don't want to make. Loftus and colleagues surveyed anesthesiologists and found that we fail to recognize the need to wash our hands after contact with contaminated patients and environmental reservoirs.[6] These findings need to be incorporated in the design of educational programs that teach the fundamentals of infection control.

Recognizing that we make a difference in perioperative infection, Hopf editorializes that "each anesthesia provider {should} take stock of her/his own intraoperative practices and commit to reducing within-patient and between-patient pathogen transmission through decontamination of patient bacterial reservoirs and reducing cross-contamination of provider hands, the anesthetic workspace, and IV access ports."[7] In their colorfully entitled "Fecal Patina in the Anesthesia Work Area" Munoz-Price and Weinstein discuss the spread of vancomycin-resistant enterococci and Gram-negative bacilli.[8] The authors editorialize that we should "increase compliance with environmental disinfection of the operating room (between cases and terminal cleaning)" in addition to improved hand washing.

Dr. David Birnbach is another anesthesiologist interested in infection control and the perioperative biome. In this issue of *Anesthesia & Analgesia*, Birnbach and his colleagues[9] from the University of Miami School of Medicine evaluate a novel fluorescent technology to identify contamination of the anesthesia workplace. In a high-fidelity human simulator, they searched the anesthesia workplace for traces of a fluorescent dye placed in the mouth and on the lips of a mannequin. After just a 6-minute simulation focused on intubation, the authors found dye contamination on 100% of the IV hubs, 60% of the door handles, and even on the "unused" computer keyboard. In a second study, Birnbach and colleagues[10] used the same simulator to investigate whether the simple act of double gloving would reduce workplace contamination. It did. Double gloving reduced the number of contaminated workplace sites from 20 to 5.

In their accompanying editorial, Drs. Richard Prielipp and Sorin Brull note that double gloving before intubation, and removing the outer glove immediately following intubation, is analogous to surgeons changing their outer glove after draping the patient, a practice shown to reduce the incidence

From the Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, California.

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Address correspondence to Steven L. Shafer, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, 300 Pasteur Dr., MC-5640, Stanford, CA 94305. Address e-mail to steven.shafer@stanford.edu.

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of surgical site infections.[11] Accompanied by a sobering and vaguely disgusting table of oral flora (e.g., *Propionibacter* is associated with acne and is also used in cheese making), the editorial emphasizes changing our workplace routines to decrease contamination and improve patient safety.

Loftus, Koff, and Birnbach[12] reviewed these and other papers on bacterial transmission in the anesthesia work area. They note that "bacterial transmission in the anesthesia work area of the operating room environment is a root cause of 30-day postoperative infections affecting as many as 16% of patients undergoing surgery." In their view, the "evidence suggests that a multimodal approach targeting improvements in intraoperative hand hygiene, patient screening and decolonization, environmental decontamination, and improvements in intravascular handling and design may reduce the risk of postoperative infections."

Dr. Nikolaus L. Gravenstein and his colleagues at the University of Florida College of Medicine are also working to understand our role in perioperative infection.[13] Propofol supports bacterial growth.[14,15] Gravenstein and colleagues collected stopcocks and extension tubing from 300 postoperative patients, half of whom received propofol as part of their anesthesia. They found similar rates of contamination 6 hours after surgery between the propofol and non–propofol-containing stopcocks. By 24 hours, the stopcocks from patients who had received propofol had >10 times the colony-forming units. By 48 hours, the stopcocks with propofol had >100 times the number of colony-forming units. As the authors note, this mandates a change in our standard of care. If propofol is used and the IV line is to remain in place, then we need to change the infusion sets, or at least the stopcocks, before patients leave the postanesthesia care unit.

Our making a difference extends beyond the operating room and postanesthesia care unit. Walz and colleagues[16] from the Departments of Anesthesiology, Surgery, Infection Control, and Critical Care at the University of Massachusetts Medical School and UMass Memorial Medical Center looked at the efficacy of a "bundled approach" to central line placement in intensive care units. Their bundle included "hand hygiene, education of providers, chlorhexidine skin preparation, use of maximal barrier precautions, a dedicated line cart, checklist, avoidance of the femoral vein for catheter insertion, chlorhexidine-impregnated dressings, use of antiinfective catheters, and daily consideration of the need for the catheter." They found an astonishing 92% reduction in central line–associated bloodstream infections with the use of this bundled approach.

With so much focus on environmental reservoirs for contamination, hand washing, and the use of double gloves, one might briefly forget our responsibility for timely and appropriate administration of perioperative antibiotics. Fortunately, Ronald Gordon of the U.S. Naval Hospital in San Diego provides a thorough review of the topic.[17] Dr. Gordon assessed the clinical pharmacology, including basic pharmacokinetics and pharmacodynamics, that guide perioperative antibiotic delivery. He places our responsibility for antibiotics into the context of our overall responsibility for long-term patient outcome. In their accompanying editorial, Gravenstein and colleagues[18] acknowledge the need for scientifically based antibiotic dosing. The authors call for anesthesiologists to investigate and implement novel approaches to improve perioperative antibiotic administration, including the use of continuous antibiotic infusions to maintain tissue antibiotic concentration throughout surgery.

The content of this issue of *Anesthesia & Analgesia* relates directly to the daily clinical practice of anesthesiologists. Hand washing, double gloving, and keeping a clean workplace are easy. Why wait? After reading this editorial, and the accompanying papers in this issue of *Anesthesia & Analgesia*, why not change your routine practice starting with your next patient? Quoting actor John Belushi (in a different context): "it don't cost nothin."[a]

Anesthesiologists can make a difference reducing hospital-acquired infection. We make a difference as investigators seeking to understand hospital-acquired infections. We make a difference as clinicians implementing best practices to reduce hospital-acquired infections. As emphasized previously,[1] highlighting our role in making a difference in no way minimizes the contributions of our colleagues. Nearly all of these papers involve interdisciplinary research teams consisting of anesthesiologists, surgeons, hospitalists, nurses, and other health care professionals. We are all in this together, working to make a difference to our patients.

Anesthetizing patients and awakening them after surgery safely makes a difference. So does reducing hospital-acquired infections. That's what we do. ■

[a]John Belushi, Animal House, 1978, directed by John Landis, released by Universal Pictures. Available at: https://www.youtube.com/watch?v=Zf16YtSOaUQ. Accessed January 5, 2015.

RECUSE NOTE

Dr. Steven L. Shafer is the Editor-in-Chief for *Anesthesia & Analgesia*. This manuscript was handled by Dr. James G. Bovill, Guest Editor-in-Chief, and Dr. Shafer was not involved in any way with the editorial process or decision.

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Bacterial Reservoirs in the Operating Room

Harriet W. Hopf, MD

Anesthesiologists have long been patient safety advocates. Thus, it is not surprising that anesthesia providers in the 21st century have taken on increasing responsibility for preventing health care-associated infections (HAI) including surgical site infections (SSI). The Surgical Care Improvement Project (SCIP) was developed in 2006 to reduce surgical complication rates,[1] including SSI, by improving adherence to best practice process measures. Recent large database studies have demonstrated that SCIP compliance is not associated with a significant reduction in SSI.[1] This is not terribly surprising, given that previous compliance was already quite good and that specific interventions only benefit a subset of patients. For example, many or most patients who don't get prophylactic antibiotics don't develop SSI, and some patients who get prophylactic antibiotics still develop SSI. Given that the current process measures don't prevent all SSI, what potential new measures are we missing? Loftus et al.,[2,3] in 2 articles in this issue of the journal, begin to define the role of patient, environmental, and anesthesia provider bacterial reservoirs in transmission of bacteria within and between patients. Their results suggest 2 previously recognized but inadequately implemented interventions: preoperative patient skin and other bacterial reservoir decontamination and hand hygiene by anesthesia providers. Anesthesia providers practice in a nonsterile environment within the operating room and frequently contact areas of the patient known to have a high rate of contamination, such as the axilla, nares, and pharynx. Therefore, it is not surprising that the study identifies these as important areas for intervention.

Seminal studies by Loftus et al.[4] and Koff et al.[5] at Dartmouth Hitchcock Medical Center demonstrated that anesthesia providers directly impact bacterial transmission and infection rates. Specifically, (1) anesthesiologists rapidly and widely contaminate their work environment in the operating room[4]; (2) greater contamination of the work environment is associated with more frequent contamination of IV distribution access ports[4]; (3) without intervention, anesthesiologists commonly perform hand hygiene less than once per hour during a case[5]; (4) reminders increase the rate of hand hygiene[5]; (5) this increase in the rate of hand hygiene is associated with a reduction in work area contamination and a reduction in IV access port contamination from 32% to 8%[5]; and (6) this reduction in work area and IV port contamination is associated with a significant reduction in HAI.[5]

More recently, in collaboration with 2 other major academic health centers, the group performed a prospective, randomized, observational trial to study the frequency of bacterial transmission to IV ports within and between 274 patient pairs for first and second cases in the operating room.[6] Stopcock contamination occurred in 23% of cases, with 14 between-case and 30 within-case transmission events. The 2 current studies provide secondary analysis of the transmission of the predominant pathogens in the multicenter study, *Staphylococcus aureus*[2] and *Enterococcus*,[3] that clinically cause most SSI and HAI. Transmission events were defined as a phenotype that was cultured at 2 or more reservoir sites (including patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) across a case pair. The most proximal reservoir was assumed to be the source of transmission. The results are sobering. From a total of 2170 environmental culture sites, 2640 hand cultures, and 1087 patient skin cultures, >6000 potential and 2184 true pathogens were isolated.

For *S aureus*,[2] 2 phenotypes accounted for 65% of the 170 isolates and most transmission events. One (labeled the P phenotype) was predominantly cultured from patient sites and the other (labeled the H phenotype) from provider hands. The P phenotype was more likely to demonstrate methicillin resistance and more often cultured in 30-day postoperative cultures, indicating that the patient skin reservoir is a more common source of pathologic transmission events. This does not exclude a role for transmission to provider hands as an intermediate step in the case-pair transmission.

For *Enterococcus*, 80% (39 of 49) of confirmed transmission events were explained by 2 phenotypes. For both phenotypes, provider hands were the common reservoir of origin for 86% of the transmission events. Despite the high rate of transmission events within and between case-pairs, *Enterococci* were cultured in only 6 of 548 patients in the 30-day postoperative period.

Given that the vast majority of SSI are caused by *S aureus*, these results suggest that transmission of specific *Staphylococcal* phenotypes within and between patients is a

From the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah.

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Address correspondence to Harriet W. Hopf, MD, Department of Anesthesiology, University of Utah School of Medicine, 3C444, 30 N 1900 E, Salt Lake City, UT 84132. Address e-mail to harriet.hopf@hsc.utah.edu.

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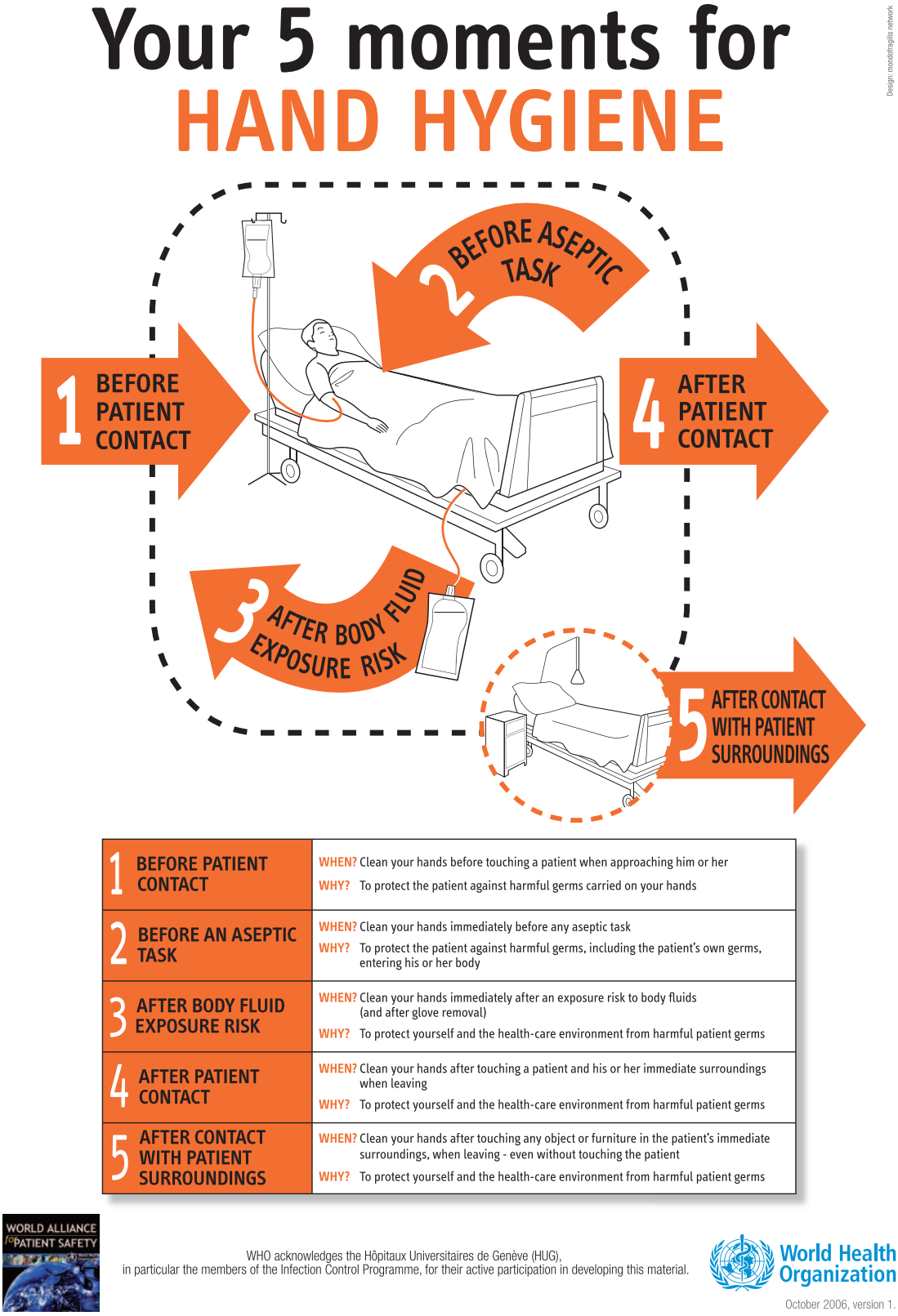

Figure 1. The WHO 5 Moments of Hand Hygiene. http://www.who.int/gpsc/tools/Five_moments/en/.

major contributor to SSI and HAI. The role of anesthesia provider hand contamination in transmission of *Enterococcus* to the workspace and patient biome is concerning, even though it was not associated with actual infection, because of rising rates of antibiotic-resistant organisms and the observation that *Enterococcus* is becoming a more prevalent pathogen. The current studies suggest 2 approaches are indicated: improved methods of patient reservoir decontamination

and more effective and frequent decontamination of provider hands. Previous preoperative patient decolonization efforts have shown mixed results, but the most effective approach focused on skin decontamination along with nasal decontamination in high-risk patients.[7] The current results may help better target patient reservoir decontamination to render it more effective.

The current studies also highlight a well-known and effective solution to the problem of bacterial transmission within and across patients: hand hygiene. It is somewhat discouraging that Ignaz Semmelweis demonstrated the almost magical value of hand washing in 1847, and yet health care providers have yet to embrace hand hygiene over 150 years later. Barriers to adequate hand hygiene include inconvenient access in the operating room, concern with dry skin, and outmoded education. Gel and foam hand sanitizers can be made available on the anesthesia cart for easy access. A variety of skin protectants and barrier creams are routinely available in hospitals to prevent skin irritation from frequent hand washing or hand hygiene. Previous World Health Organization (WHO) recommendations focused on performing hand hygiene only before entering and after leaving a patient room, and this may partly explain the low rate of hand hygiene by anesthesiologists (less than once per hour) seen in the Koff et al. study.[5] Compliance with the current "5 moments" WHO guidelines (Fig. 1) could make a major inroad into provider hand and workspace contamination; the challenge is encouraging and auditing compliance.

Could preoperative decolonization or hand hygiene be the next SCIP process measure? Not yet. The evidence supporting decolonization is not sufficiently developed to merit a process measure, although it appears that we are getting closer to defining which patients will benefit and which interventions are required. The evidence supporting hand hygiene is much stronger, but the challenging logistics of implementing a process measure related to hand hygiene make it even less likely. Anesthesia providers don't document hand hygiene on the anesthesia record, except perhaps for procedure notes for central lines and other invasive procedures. Creating a mechanism for documenting hand hygiene would be burdensome and distracting. Although the Dartmouth group's 2009 study[5] demonstrated a benefit of more frequent hand hygiene, there was no attempt to match the timing of hand hygiene with distinct opportunities for hand hygiene as defined by the WHO 5 moments. Studies of intensive care unit nurses suggest a target rate of 7 to 20 times an hour, but the timing of hand hygiene may be important. The first few minutes in the operating room are associated with the highest rate of contamination,[4] which is not surprising given that anesthesia induction requires frequent contact with the patient for application of monitors, intubation, placement of lines, and positioning of the patient.[8] The current studies, however, should cause each anesthesia provider to take stock of her/his own intraoperative practices and commit to reducing within and between patient pathogen transmission through decontamination of patient bacterial reservoirs and reducing cross-contamination of provider hands, the anesthetic workspace, and IV access ports.

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Fecal Patina in the Anesthesia Work Area

L. Silvia Munoz-Price, MD, PhD,* and Robert A. Weinstein, MD†

Since the 1970s, we have gained increasing knowledge about the transmission of multidrug-resistant pathogens in hospitals and about the spread of bacteria from patients to health care workers' hands and to the hospital environment (Fig. 1). This understanding has driven many interventions that have reduced patients' risk of acquiring antibiotic-resistant organisms and of developing health care-associated infections.[1–3]

Studies on vancomycin-resistant enterococci (VRE) established the importance of a domino effect of contamination: spread of VRE that colonize patients' gastrointestinal tracts ("rectal carriage"), to patients' skin, to the hospital environment, to hands of health care workers, and then to other patients. Among patients with VRE bacteremia, Beezhold et al.[4] showed that all these subjects had VRE in their stool. In addition, 86% and 57% of these patients had concomitant colonization of the skin in their inguinal areas and antecubital fossae (i.e., even at skin sites remote from the rectum), respectively. There was a higher proportion of VRE-contaminated environmental sites around patients who had diarrhea or who had received broad-spectrum antibiotics.

The skin contamination of patients with enteric organisms inspired the rather graphic description, the patient's "fecal patina."[5] Also referred to as a "stool veneer," this coating with enteric organisms is not only limited to patients' skin but also extends to surfaces in the surrounding environment that are touched, and thereby contaminated, by patients and by health care workers (Figs. 1 and 2). The environmental contamination spreads out from the patient in a target-like concentric pattern, with densest contamination closest to the rectum of patients who have rectal carriage of the problem bacteria.[6] This interplay among organisms on patients' body surfaces, hospital environment, and health care workers' hands constitutes the foundation for the development of infection control interventions in the field

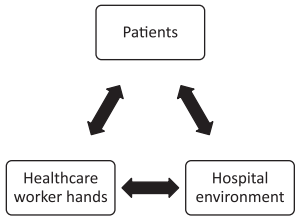

Figure 1. Epidemiological links for transmission of multidrug-resistant organisms.

of hospital epidemiology (Fig. 1). Bonten et al.[7] described a direct association between the degree of environmental contamination with VRE and the number of VRE colonized body surfaces. In addition, VRE contamination of health care workers' hands occurred after contact with either patients' skin or their surrounding inanimate environment, and importantly, either type of contact resulted in the successful transfer of VRE within the patients' hospital rooms.[8]

The key role of the hospital environment as a reservoir of some multidrug-resistant bacteria[1] is supported by the decrease in VRE patient-to-patient transmission after improved environmental disinfection.[9,10] Studies on methicillin-resistant *Staphylococcus aureus* (MRSA) have demonstrated the relation of spread of MRSA to environmental contamination: colonization of patient skin is present,[11] the hospital environment becomes

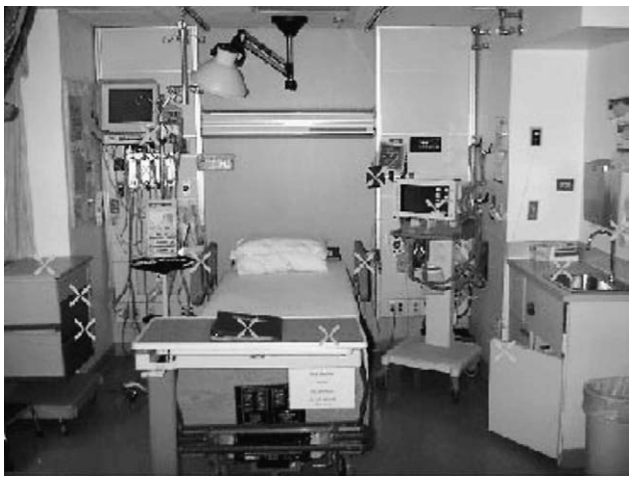

Figure 2. Environmental site contamination with vancomycin-resistant enterococci (VRE) in rooms of patients colonized with VRE. This figure graphically depicts the concept of fecal patina. Objects ("X") that grew VRE in a room that was previously occupied by a patient colonized with VRE in the rectum. Cultures were obtained after the room was terminally cleaned by environmental providers. Reproduced with permission from Elsevier.[6]

From the *Institute for Health and Society and Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; and †Departments of Medicine, Rush University Medical Center and the Cook County Health and Hospitals System, Chicago, Illinois.

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Address correspondence to L. Silvia Munoz-Price, MD, PhD, Medical College of Wisconsin, Institute of Health and Society, Health Research Center, Suite 2100, 8701 Watertown Plank Rd., P.O. Box 26509, Milwaukee, WI 53226. Address e-mail to smunozprice@mcw.edu.

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contaminated with patient strains,[12] health care workers contaminate their hands after contact with the environment or patient skin,[13] and enhanced environmental disinfection decreases transmission within the hospital.[14] Furthermore, patients admitted to rooms previously occupied by either MRSA- or VRE-positive patients have higher risks of acquisition of these organisms than do patients admitted to other rooms.[15,16]

Some Gram-negative bacilli have transmission pathways similar to those of VRE,[3] including the establishment of fecal patinas. Doi et al.[17] showed the presence of *Acinetobacter baumannii* on the skin of patients who had positive clinical cultures. Sites tested included forehead, nostrils, buccal mucosa, axilla, antecubital fossa, groin, and toe webs; arms, legs, and buccal mucosa had the highest sensitivity for the detection of *A baumannii*.[17] Frequently touched environmental sites in patient rooms had higher likelihood of being contaminated with *A baumannii* when occupants were colonized.[18] Patients admitted to a hospital room with unrecognized contamination with *A baumannii* (as determined by weekly environmental cultures) had significantly higher probability of acquiring this organism during their hospitalization.[19] Furthermore, as with VRE and MRSA, contamination of health care workers' hands, gloves, and gowns occurred after entry to a room that housed a patient colonized with *A baumannii*.[13]

In this issue of *Anesthesia & Analgesia*, Loftus et al.[20] describe the transmission of Gram-negative bacilli within the anesthesia work area while anesthesia staff were providing care in the operating room. Until recently, the infection control community largely overlooked this hospital setting as a potential risk for health care-associated infection.[21] However, in part because of the work of the authors, we have gained a better understanding of the relevance of this environmental site.[22–25] Concern about Gram-negative bacilli is currently heightened because of multidrug-resistant strains and the lack of available effective antibiotics.[26] This situation prompted the Centers for Disease Control and Prevention to name carbapenem-resistant Gram-negatives, including *A baumannii*, as serious public health threats for the American population.[27] Given the lack of novel antibiotic options in the development pipeline, there is increased interest for determining ways to decrease the transmission of these bacteria among our patients.

The study by Loftus et al.[23] evaluated randomly selected first and second surgical cases throughout the span of 12 consecutive months at 3 academic institutions. A total of 274 case pairs were tested to determine the transmission of pathogens during the procedure and between cases. This was accomplished by culturing: hands of anesthesia providers before and after each surgical case; patient body sites (nasopharynx and axillae) after anesthesia induction; and environmental surfaces (anesthesia equipment such as adjustable pressure-limiting valve and agent dial, and IV tubing), at the beginning of the first case, between cases, and at the end of the second case. Cultures were performed, using sterile swabs and nonselective blood agar media, to determine bacterial contamination. The study classified patients as carriers of Gram-negative organisms based on the axillary and throat culture results. Because many potentially pathogenic Gram-negative bacilli colonize the lower gastrointestinal tract, the omission of rectal cultures means that patients who were rectal carriers but negative at the other 2 body sites could have been misclassified as noncarriers. Such misclassification would make it impossible to determine whether the presence of these organisms in the operating room environment was caused by contamination from patients with unrecognized rectal carriage (patient contaminating environment) or whether the patients became colonized and subsequently infected as a result of the contaminated environment (environment contaminating patient) (Fig. 3). In fact, endogenous Gram-negative bacteria have been demonstrated to be an overlooked cause of postoperative clinical infections.[28] Although Loftus et al. used pulsed field gel electrophoresis to demonstrate the relationship of pairs of environmental and clinical bacterial isolates, this technique would not detect the direction of spread of the bacteria.

Despite the potential misclassification drawback, we believe that the study by Loftus et al. highlights the risk of transmission of Gram-negative bacilli within the anesthesia work area and demonstrates that the spread follows an epidemiologic pattern similar to that seen in intensive care units and inpatient wards: from patient, to environment and health care workers' hands, and to other patients (Fig. 1). These findings have clinical implications for the risk of colonization and subsequent health care-associated infections, for example, surgical site infections. Thus, the work of Loftus et al. calls attention to the need to develop realistic hand hygiene guidelines for personnel who are giving anesthesia care, to monitor and ensure adherence to such guidelines, to assess the clinical impact of improved hand hygiene, to increase compliance with environmental disinfection of the operating room (between cases and terminal cleaning), and to study further the directions of the spread of pathogens in the operating room and anesthesia work areas.

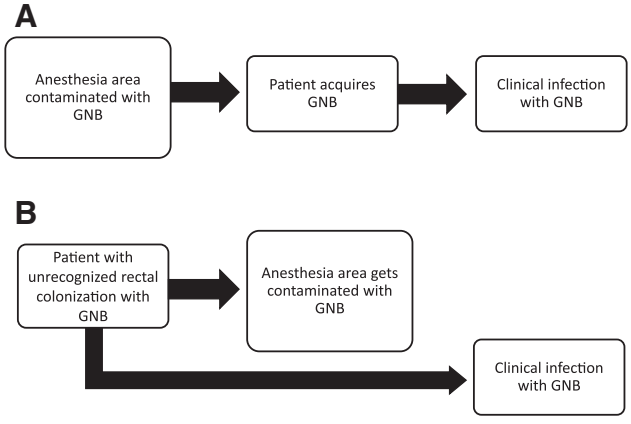

Figure 3. Possible explanations of subsequent clinical infections caused by the same organism cultured in the anesthesia work area. A, Contaminated environment exposes patient to Gram-negative bacilli (GNB) with the subsequent development of a clinical infection. B, Patient with unrecognized rectal colonization undergoes surgery, contaminates the anesthesia area with his/her endogenous GNB, and later develops a clinical infection with the same organism.

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Contribution: This author helped write the manuscript.
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Name: Robert A. Weinstein, MD.
Contribution: This author helped write the manuscript.
Attestation: Robert A. Weinstein approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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If One Is Good, Are Two Always Better?

Richard C. Prielipp, MD, MBA, FCCM,* and Sorin J. Brull, MD, FCARCSI (Hon)†

Health care-associated infections are common and costly complications in hospitalized patients, especially the critically ill. The major nosocomial infections include surgical site infections (SSI), central line-associated bloodstream infections, ventilator-associated pneumonia, catheter-associated urinary tract infections, and *Clostridium difficile*-associated disease. Each infection accrues significant direct (e.g., additional medications and increased hospital length of stay), indirect (e.g., short- and long-term morbidity, lost income to the patient and family members), and intangible (e.g., pain and suffering, patient stress) costs. In addition to the increased risk of mortality, health care-associated infections increase attributable hospital costs by $10,000 to $40,000 per patient episode.[1,2] A central question important to the pathogenesis and prevention of perioperative infections is how microorganisms are spread in the environment. The elegant investigation of Birnbach et al.[3] reported in this issue of the journal provides important insight into this question by demonstrating that "we have met the enemy, and he is us" (Pogo).

Of course, the "pathogens" in this simulated study are nonexistent, but real patients are heavily populated with numerous microorganisms making up the oral flora[4] and skin microbiome.[5] Common oral microorganisms have been implicated in diseases such as bacterial endocarditis, aspiration pneumonia, necrotizing fasciitis, brain abscesses, osteomyelitis, cardiovascular disease, meningitis, and have been associated with preterm low birth weight babies.[4] Moreover, of the 700 oral bacterial species (phylotypes), >60% have not yet been cultivated or fully identified.[4] We do know, however, that the predominance of one bacterial species or another varies throughout individual sites inside the mouth; for instance, the dorsum of the tongue is populated differently than the lateral aspects of the tongue. The various microenvironments of the buccal epithelium, the hard and soft palate, the tonsils, and even tooth plaque all favor one bacterium over another. Overall, a total of 141 different bacterial taxa were cultivated from the oral cavity of 5 healthy volunteers, including species of *Gemella, Granulicatella, Streptococcus, Veillonella, Actinomyces, Atopobium, Rothia, Neisseria, Eikenella, Campylobacter, Porphyromonas, Prevotella, Capnocytophaga, Fusobacterium* and *Leptotrichia*.[4] Organisms of the oral flora can be associated with specific diseases (Table 1). In the intensive care units or the institutionalized patient population, the aerobic and anaerobic Gram-negative bacilli often become transient and dominant opportunists, creating additional risk of secondary disease.[6]

During surgery, glove failure (e.g., perforation) defeats the protection of the surgeon from the patients' blood-borne pathogens and exposes the surgical wound to microorganisms found on the surgeon's hands. Since the incidence of inadvertent glove puncture is over 60%, double gloving or the use of gloves with puncture-indication systems that show a visible green color when damaged have been recommended.[7] The use of double gloves also has been purported as an effective method of reducing surgical cross-infection and resulting in fewer SSI. In fact, double gloving (or even triple gloving, or the use of glove liners) results in significant reduction in perforations to the inner glove, but they do not appear to reduce the incidence of SSI.[8] The practice that appears to decrease microbial contamination during orthopedic surgery is simply changing the outer glove after draping.[9] Thus, in surgery, the use of double gloves has no defined benefit on SSI, but changing the outer glove after draping decreases bacterial cross-contamination.

For the anesthesiologist, then, the obvious questions are: how will the surgical lessons of double gloving be applied so that we (and our patients) might derive maximum benefit? What is the anesthesia practice equivalent of double gloving for surgical procedures? And, more importantly, what is the anesthesia practice equivalent of changing surgical gloves after patient draping, and when is our patient at greatest risk of contamination? Birnbach et al.[3] give us a simple answer: 1 time of major contamination occurs immediately after airway management. Although this may seem intuitive, the study is brilliant not only in the fact that it addresses an important patient safety issue, but because it suggests some reasonable solutions that are readily and easily achievable.

There is ample precedent for implementation of new paradigms to reduce the risk of hospital-acquired infections. Education programs focusing on teaching doctors and nurses better sterile technique for the insertion and maintenance of catheters have been shown to significantly reduce the risk of catheter-related bloodstream infections.[10] In particular, it has been possible to show that such programs

From the *Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota; and †Department of Anesthesiology, Mayo Clinic College of Medicine, Jacksonville, Florida.

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Address correspondence to Sorin J. Brull, MD, FCARCSI (Hon), Department of Anesthesiology, Mayo Clinic College of Medicine, 4500 San Pablo Rd., Jacksonville, FL 32224. Address e-mail to sjbrull@me.com.

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Table 1. Organisms Found as Part of Human Mouth Flora

Healthy patients' mouth flora[a]	Hospitalized patients' mouth flora[6, 12]	Gram stain (GS)	Possible illness or disease[d]
Streptococcus mitis[b]	All the normal flora may coexist or be displaced by transient, opportunistic organisms like Gram-negative pathogens such as *Pseudomonas aeruginosa, Acinetobacter, Pseudomonas, Stenotrophomonas, or Burkholderia*[c] and Gram-positives such as methicillin-resistant *Staphylococcus aureus* (MRSA)	GS-positive coccus	Prosthetic valve endocarditis, necrotizing fasciitis, systemic infection in transplant, or immunocompromised patients
Gemella species		GS-positive coccus; thrives at high Pco_2 pressures	Blood sepsis, brain abscess, lung abscess, cystic fibrosis, prosthetic joint infections
Actinomyces		GS-positive rods, forms fungal-like hyphae	Mouth and tooth abscess; lung abscess; endocarditis
Neisseria meningitide [e]		GS-negative diplococcus	Meningitis and sepsis
Prevotella sp		GS-negative, nonmotile rods	Anaerobic infections of respiratory tract; empyema
Propionibacter		GS-positive rods	Acne; also used in cheese making
Eubacterium		GS-negative anaerobic rods	Periodontal disease and skin ulcers; possible association with ulcerative colitis
Lactobacillus		GS-positive rods	Dental caries (cavities)
		GS-negative rods and GS-positive cocci, MRSA	Pneumonia; urinary tract infections; bacteremia; septicemia

[a]More than 700 bacterial species have been detected in the oral cavity of humans.
[b]Able to survive long periods under harsh conditions even on inanimate objects.
[c]Aerobic and facultative anaerobic Gram-negative bacilli.
[d]Disease severity worsened by recent emergence of multidrug and pandrug resistant organisms in the hospital setting.
[e]More commonly located in the nasopharynx.

can increase compliance with the use of maximum sterile barriers under "real world clinical conditions."[10] Thus, we believe anesthesiology teaching programs would do well to embed the simple step of double gloving for airway interventions into the first week of residency orientation.

One must be careful with some of the extrapolations of the findings made by Birnbach et al.,[3] since several questions remain. Do the conditions and findings in the simulation laboratory room translate to the clinical operating room (OR)? Can anesthesia professionals be convinced to adhere to a "simple" change in practice like double gloving, or will providers stubbornly maintain old habits? For instance, we have ample evidence that hospital programs to implement universal hand-washing protocols may achieve compliance rates of only 26% despite a plethora of science, safety, and quality motivators.[11] In addition, airway management at the start of the anesthetic is not the only time when the provider's hands could become contaminated with oral microflora; similar contamination of the OR environment likely occurs after insertion of nasogastric tubes (which is unfortunately "routine" practice after tracheal intubation in some institutions), placement of oral airways, use of Yankauer and other oral or tracheal suction catheters, introduction and manipulation of esophageal bougies during surgical procedures such as Nissen fundoplication, and placement of bite-blocks to prevent bite injuries in neurosurgical cases requiring transcranial motor-evoked potential monitoring. More work is needed in these settings to better delineate the potential for bacterial contamination of the OR environment by the providers' hands. Nevertheless, the study by Birnbach et al.[3] should serve as the quintessential model for further investigations in this area.

The future will likely see the development of better educational tools, standardized protocols, and technological interventions to assist in our battle against nosocomial infections. One intervention might be introduction of standardized anesthesia protocols for reducing infection risk. We already have protocols for hand-washing and central line insertion. We envision the use of double gloves as part of standardized anesthesia infection reduction protocols. Such protocols might also include placing hand-washing gels on the anesthesia workstation, providing clearly demarcated areas for clean and contaminated items, defining work areas for "next case" preparation to minimize comingling current and future case supplies on the anesthesia machine, addressing the problem of keyboard/knob/drawer contamination, and defining policies on when unused items should be returned to storage even though they have been lying exposed on the anesthesia workstation for many hours. The work of Birnbach et al.[3] improves our understanding of the invisible contamination occurring daily during the first 6 minutes of our routine work process. It also emphasizes the need to create "best practices" infection reduction protocols that codify and facilitate interventions to minimize the risk of health care-acquired infections to our surgical patients.

RECUSE NOTE

Dr. Sorin J. Brull is the Section Editor for Patient Safety for the Journal. This manuscript was handled by Dr. Steven L. Shafer, Editor-in-Chief, and Dr. Brull was not involved in any way with the editorial process or decision.

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Name: Sorin J. Brull, MD, FCARCSI (Hon).
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
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Section Editor: **Sorin J. Brull**

The Epidemiology of *Staphylococcus aureus* Transmission in the Anesthesia Work Area

Randy W. Loftus, MD,* Matthew D. Koff, MS, MD,* Jeremiah R. Brown, MS, PhD,† Hetal M. Patel, BS,* Jens T. Jensen, MS,* Sundara Reddy, MD,‡ Kathryn L. Ruoff, PhD,§ Stephen O. Heard, MD,‖ Mark P. Yeager, MD,* and Thomas M. Dodds, MD*

BACKGROUND: Little is known regarding the epidemiology of intraoperative *Staphylococcus aureus* transmission. The primary aim of this study was to examine the mode of transmission, reservoir of origin, transmission locations, and antibiotic susceptibility for frequently encountered *S aureus* strains (phenotypes) in the anesthesia work area. Our secondary aims were to examine phenotypic associations with 30-day postoperative patient cultures, phenotypic growth rates, and risk factors for phenotypic isolation.

METHODS: *S aureus* isolates previously identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and analytical profile indexing were subjected to antibiotic disk diffusion sensitivity. The combination of these techniques was then used to confirm *S aureus* transmission events and to classify them as occurring within or between operative cases (mode). The origin of *S aureus* transmission events was determined via use of a previously validated experimental model and links to 30-day postoperative patient cultures confirmed via pulsed-field gel electrophoresis. Growth rates were assessed via time-to-positivity analysis, and risk factors for isolation were characterized via logistic regression.

RESULTS: One hundred seventy *S aureus* isolates previously implicated as possible intraoperative transmission events were further subdivided by analytical profile indexing phenotype. Two phenotypes, phenotype P (patients) and phenotype H (hands), accounted for 65% of isolates. Phenotype P and phenotype H contributed to at least 1 confirmed transmission event in 39% and 28% of cases, respectively. Patient skin surfaces (odds ratio [OR], 8.40; 95% confidence interval [CI], 2.30–30.73) and environmental (OR, 10.89; 95% CI, 1.29–92.13) samples were more likely than provider hands (referent) to have phenotype P positivity. Phenotype P was more likely than phenotype H to be resistant to methicillin (OR, 4.38; 95% CI, 1.59–12.06; $P = 0.004$) and to be linked to 30-day postoperative patient cultures (risk ratio, 36.63 [risk difference, 0.174; 95% CI, 0.019–0.328]; $P < 0.001$). Phenotype P exhibited a faster growth rate for methicillin resistant and for methicillin susceptible than phenotype H (phenotype P: median, 10.32H; interquartile range, 10.08–10.56; phenotype H: median, 10.56H; interquartile range, 10.32–10.8; $P = 0.012$). Risk factors for isolation of phenotype P included age (OR, 14.11; 95% CI, 3.12–63.5; $P = 0.001$) and patient exposure to the hospital ward (OR, 41.11; 95% CI, 5.30–318.78; $P < 0.001$).

CONCLUSIONS: Two *S aureus* phenotypes are frequently transmitted in the anesthesia work area. A patient and environmentally derived phenotype is associated with increased risk of antibiotic resistance and links to 30-day postoperative patient cultures as compared with a provider hand-derived phenotype. Future work should be directed toward improved screening and decolonization of patients entering the perioperative arena and improved intraoperative environmental cleaning to attenuate postoperative health care–associated infections. (Anesth Analg 2015;120:807–18)

Health care–associated infections (HCAIs) are a tremendous health care problem, associated with increased patient morbidity and mortality and an economic burden amounting to approximately 4.5 billion dollars annually.[1–5] This problem certainly applies to the perioperative arena, where 8% to 16% of patients suffer from ≥1 HCAIs, including surgical site infections (SSIs), the number one surgical complication today.[6–10] Surprisingly, little is known regarding the perioperative epidemiology of *Staphylococcus aureus* transmission, the number one bacterial pathogen known to cause SSIs. This lack of knowledge may partially explain the equivocal evidence surrounding the efficacy of preoperative patient decolonization strategies,[11–13] the subsequent lack of compliance with preoperative preventive measures,[9] and ultimately, the prevalence of HCAIs.[1–5] The primary aims of this study were to characterize the mode of transmission (between and/or within case), reservoir of origin, transmission locations, and antibiotic susceptibility for *S aureus* strains and/or strain characteristics (phenotypes) commonly encountered in the intraoperative anesthesia work area. Our secondary aims were to

From the *Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; †The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire; ‡Department of Anesthesiology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa; §Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; and ‖Departments of Anesthesiology and Surgery, University of Massachusetts Medical School and UMass Memorial Medical Center, Worcester, Massachusetts.

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Address correspondence to Randy W. Loftus, MD, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756. Address e-mail to randy.w.loftus@hitchcock.org.

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examine phenotypic associations with 30-day postoperative patient cultures, phenotypic growth rates, and risk factors for isolation of a more virulent phenotype.

METHODS

General Approach

We previously conducted a prospective, randomized, observational study at 3 major academic medical centers, Dartmouth-Hitchcock Medical Center in New Hampshire, the University of Iowa Hospitals and Clinics in Iowa, and the UMass Memorial Medical Center in Massachusetts to characterize the frequency and implications of bacterial transmission events to intravascular devices in the intraoperative arena.[9] The study took place over 12 consecutive months (from March 2009 to February 2010). Approval was obtained at each study site from the respective IRB for the protection of human subjects, with a waiver for informed patient consent. For the current study, additional approval was obtained from the Committee for Protection of Human Subjects at Dartmouth-Hitchcock Medical Center.

Reservoir Sampling

Sampling procedures were standardized at all 3 study sites with quality assurance monitoring of sampling techniques performed on 2 separate occasions.[9]

Hand Sampling: Using a previously validated, modified glove juice technique, provider hands were sampled before, during, and after patient care.

Patient Sampling: The patient's nasopharynx was sampled to assess the patient reservoir because nasopharyngeal pathogens have been strongly associated with postoperative SSIs. The patient's axilla was also sampled because the axilla harbors up to 30% of pathogens colonizing patient skin.

Environmental Sampling: Two sites on the anesthesia machine, the adjustable pressure-limiting valve and the agent dial, are proven representatives of the anesthesia environment and have been associated with an increase in the probability of bacterial contamination of the IV stopcock set. These sites were sampled at baseline (after active decontamination at case start for case 1 and routine decontamination at case start for case 2) and at end of the case via a standardized method. Active decontamination involved targeted cleaning of the study sites by the study investigators using a quaternary ammonium compound (Dimension III; Butcher's, Sturtevant, WI) strictly according to the manufacturer's protocol, while routine decontamination was performed by the usual operating room personnel according to their standard procedure applied to the environment between operative cases. Routine decontamination also involved use of the same quaternary ammonium compound, but personnel were not asked to specifically target the adjustable pressure-limiting and agent dial.

Sampling of Peripheral IV Tubing 3-Way Stopcocks: Bacterial cultures obtained from stopcock sets immediately on removal from the packaging (at case start) were shown to be invariably negative. A positive stopcock set at case end was defined as ≥1 colony forming unit (CFU) per culture plate, consistent with prior study protocols.

Bacterial Isolates Previously Obtained and Archived

Using the sampling methodology described above, we previously examined 2170 environmental bacterial culture sites, 2640 health care provider hand cultures, and 1087 patient skin cultures in 274 case-pairs representing 548 operating rooms across the 3 major academic medical centers. From these reservoirs, >6000 potential and 2184 true bacterial pathogens were isolated and archived for later analysis. Each pathogen received a unique identification number linked to a specific date, operating room, reservoir, patient, and provider.[9]

Reservoir Contribution to Intraoperative Transmission Events and Infection

We used a validated model for study of intraoperative bacterial cross-contamination (Fig. 1) in this prior study to prospectively evaluate the relative contribution of known intraoperative bacterial reservoirs to intraoperative bacterial transmission events to high-risk intravascular devices (stopcocks). These transmission events were identified via use of the experimental model (Fig. 1) and compared with the causative organism of 30-day postoperative infections via pulsed-field gel electrophoresis (PFGE) analysis. The potential association of each archived bacterial pathogen isolate with patient, provider and environmental characteristics and patient bacterial cultures, in those patients with 30-day postoperative infections, was assessed. Basic patient, procedural, and provider information was collected and linked to each frozen pathogen. This demographic information included the hospital site, age, sex, case 1 or case 2, ASA physical status classification, Study on the Efficacy of Nosocomial Infection Control (SENIC)[14] score (an index predicting the probability of postoperative HCAI development for a given patient), case duration, patient comorbidities, patient origin, patient discharge location, and procedure type. We also assessed the intraoperative fraction of inspired oxygen concentration (F_{IO_2}) and temperature. Case duration of >2 hours was also assessed given the prior association with increased risk of postoperative HCAIs.[9]

Prior Study Focus

Our focus in the initial study was on bacterial organisms transmitted to intravascular devices, and we used the combination of class of organism, phenotype defined by a series of biochemical reactions (analytical profile index [API]), temporal association given the timed sequence of bacterial culture acquisition during the process of patient care in each operating room (Fig. 1), and, in some cases, PFGE to examine the origin of device-related transmission events. Thus, our initial approach was not focused on 1 particular class of organisms, but on all transmission events.[9]

Current Study Focus

Our current interest was in characterizing the epidemiology of all bacterial transmission events in the anesthesia work area involving major bacterial pathogens known to cause SSIs, including *S aureus* (methicillin-sensitive *S aureus* [MSSA] and methicillin-resistant *S aureus* [MRSA]), Enterococcus (vancomycin resistant and vancomycin sensitive), and a variety of Gram-negative pathogens. By examining the mode of transmission (between and/or within case), reservoir of origin,

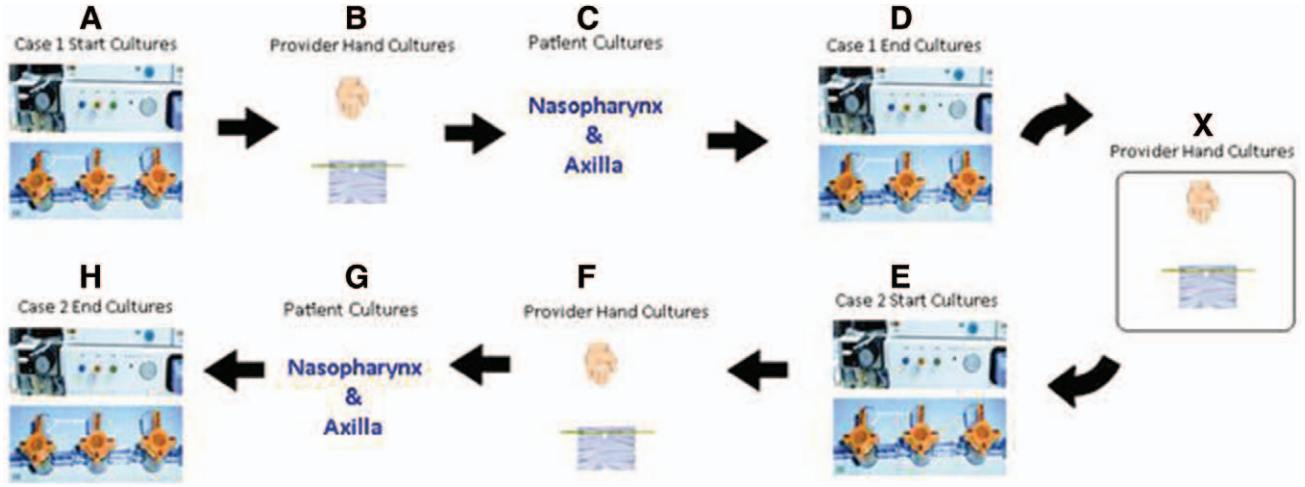

Figure 1. Schematic of culture sampling sequence. Culture samples were collected sequentially (A → H) from the operative environment (adjustable pressure-limiting valve and agent dial), patient IV tubing, provider hands, and the patient nasopharynx/axilla. Provider hands were also intermittently cultured throughout the case and on provider return to the operating room after an absence during the case (X).

and antibiotic susceptibility, an approach consistent with the Centers for Disease Control investigations of outbreaks,[15] we hypothesized that improvements in intraoperative infection control can be generated. As such, we have conducted a systematic analysis of frequently encountered strains and/or strain characteristics (phenotypes) of these pathogens in the anesthesia work area with focused analysis of more virulent phenotypes. We considered more virulent phenotypes as those more transmissible within and/or between operative cases, more often resistant to commonly used prophylactic antibiotics, and/or more often linked by PFGE to postoperative patient cultures in patients diagnosed with infection. We also sought to examine growth rates and risk factors for isolation of more common and more virulent strains, respectively.

Systematic Epidemiological Approach

The sequence of this systematic analysis focused on *S aureus* is shown in Figure 2. As the first step in this analysis, we classified all previously archived major bacterial pathogens according to colony morphology, Gram stain, and simple rapid tests. Next, we reviewed 274 case-pairs (548 cases) for evidence of possible *S aureus* transmission defined by the presence of an *S aureus* isolate in ≥2 reservoir sites across the case-pair. We then used a commercially available bioMerieux API identification system (Marcy l'Etoile, France) to identify phenotype. The API system generates a 7-digit profile number based on positive or negative reactions in a minimum of 20 phenotypic tests. The profile number can be used for isolate identification by comparing it with profiles of known strains in API's database, and profile numbers can also be used to compare the phenotypes of different strains.

Each API-derived phenotype represents observable characteristics of bacterial organisms in terms of uptake and utilization of elemental nutrients required for cell survival. Use of these elements is intimately related to the bacterial genome and allows differentiation between species.[16] With identification of the class of organism and API phenotype, we then used temporal association (the same class of pathogen isolated in >1 site surveyed in the same operating room on the same day at the same time with the same API phenotype, Fig. 1) to identify possible transmission events occurring within and between operative cases. We identified 170 *S aureus* isolates that were involved in possible transmission events across the 274 case-pairs (548 operating rooms). We then used disk diffusion antibiotic susceptibility testing analysis (antibiotic susceptibility profiling same response to methicillin and 15 commonly used prophylactic antibiotics, Appendix) to confirm and to determine the origin (provider, environment, or patient) of *S aureus* transmission events. Bacterial sensitivity was recorded and subsequently analyzed as sensitive or resistant (intermediate resistance was considered resistant due to clinical relevance) except for vancomycin where the zone in millimeters of growth inhibition was recorded and analyzed.[16] As susceptibility to antibiotics is another observable characteristic intimately related to the bacterial genome, a similar API phenotype combined with diffusion antibiotic susceptibility analysis (across 16 antibiotics) and an appropriate temporal exposure allowed us to identify with reasonable certainty intraoperative bacterial transmission events involving *S aureus* between and within operative cases, and to examine the origin of these events. Confirmed transmission events (identical *S aureus* isolates from ≥2 intraoperative locations) were defined as the isolation of ≥1 *S aureus* isolates with the same API phenotype, antibiotic susceptibility profile, and appropriate reservoir exposure (Fig. 1) from a patient, provider, or environmental site during or after patient care that was not present at case start.

Provider origin of contamination was assumed if the transmitted isolate was identical to an isolate from the hands of ≥1 anesthesia providers but not found in the patient or environmental reservoirs earlier in the sampling sequence. Environmental origin of contamination was assumed if the transmitted isolate was identical to an isolate from the environment sampled at baseline or at case end but not isolated either from the hands of providers or from the patient reservoirs earlier in the sampling sequence. The hands of all providers who would potentially interact with the anesthesia environment were sampled at baseline (Fig. 1). Patient origin of contamination

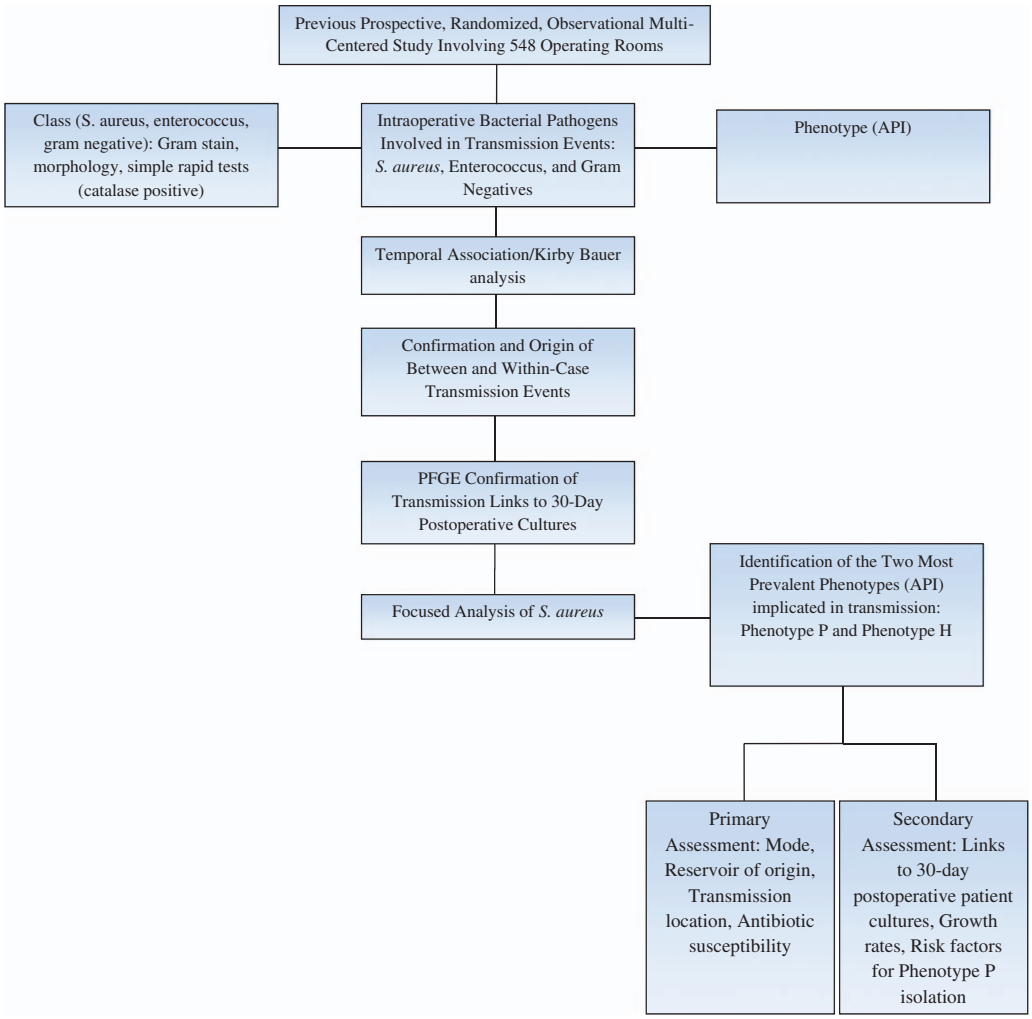

Figure 2. Systematic analysis of intraoperative *Staphylococcus aureus* transmission and subsequent infection development. API = analytical profile index; PFGE = pulsed-field gel electrophoresis; phenotype P = patients; phenotype H = hands.

was assumed if the transmitted isolate was identical to an isolate from the patient sampled at case start but was not isolated from provider hand or environmental reservoirs earlier in the sampling sequence.

Transmission events were then compared, by temporal association, biotype, and disk diffusion antibiotic susceptibility testing analysis, to all patient cultures obtained in the 30-day postoperative period. Probable patient bacterial culture links, defined by the same class of pathogen, the same biotype, the same response to 15 commonly used prophylactic antibiotics and methicillin, and an appropriate temporal exposure, were then confirmed with PFGE.[17] We used PFGE to further verify links between intraoperative transmission events and patient cultures due to the loss of temporal resolution in the 30-day postoperative period. Probable patient bacterial culture links, defined by phenotypic similarities (the same class of pathogen, API phenotype, and an appropriate temporal exposure) were examined for genotypic similarities with PFGE. While a PFGE match to an intraoperative pathogen rules in a link, it does not exclude potential links defined by phenotype, temporal exposure, and antibiotic susceptibility. In a single *S aureus* cell, as many as 300 mutations could theoretically occur in a 2.8 million nucleotide base pair genome in 30 hours.[18] These mutations could lead to genomic changes conferring differences in restriction endonuclease cutting sites, resulting in a different PFGE banding pattern and ultimately obscuring the relationship to the initial transmission event. However, our intent was to identify intraoperative *S aureus* transmission events and infection development with certainty.

As the primary assessment, this systematic analysis was used to characterize intraoperative *S aureus* isolates according to the frequency, mode, origin, and antibiotic susceptibility of intraoperative transmission events. As a secondary assessment, we analyzed links to 30-day postoperative patient cultures and growth rates for the 2 most prevalent *S aureus* phenotypes encountered in the intraoperative arena and risk factors for isolation of a high-risk *S aureus* phenotype.

Phenotypic Growth Rate Analysis

The 2 most prevalent *S aureus* phenotypes encountered in the intraoperative arena were phenotype P (patients) and phenotype H (hands). Phenotype P and phenotype H were so called to signify the most common source of

the phenotype. Each API-derived phenotype represented observable characteristics of bacterial organisms according to response to uptake and utilization of basic elemental nutrients, a process intimately related to the bacterial genome, and therefore is a differentiating factor between species and bacterial strains. Growth rate (incubation period) is another way to assess phenotype.[19] Differences in API or growth rate phenotypes could manifest as a result of genomic differences that could, in theory, confer other survival advantages (evasion of current environmental cleaning practices, prolonged survival in the intraoperative environment) and virulence, such as predisposition for bacterial transmission and subsequent infection development.[20]

To examine growth rates for the 2 most prevalent phenotypes identified by API, 5 MRSA and 5 MSSA bacterial isolates were randomly selected from the available pool of *S aureus* isolates across the 3 major academic medical centers for each phenotype (10 organisms per phenotype with 5 MRSA and 5 MSSA). Thus, each experimental phenotype group comprised 10 samples for a total of 20 samples per experiment (this experiment was duplicated for validity, see below). Selected organisms were grown on blood agar plates for 24 hours at 36.5°C. A 0.5 McFarland standard dilution was then prepared for each organism and serially diluted to a final concentration of 50,000 CFU/mL. A BacT/Alert bottle containing aerobic culture media (BacT/Alert, bioMerieux Inc., Durham, NC) was then disinfected with an alcohol prep and 30 seconds allowed for air drying. One milliliter of the 50,000 CFU/1.0 mL test concentration for each sample was then drawn up using aseptic technique and injected into the aerobic culture media contained within the BacT/Alert bottle. A negative control was prepared for each study unit via injection of 1 mL sterile saline in place of the bacterial sample. All inoculated bottles were then placed into the BacT/Alert machine and incubated at 36.5°C for 5 days or until positive. The BacT/Alert incubator identified a positive bottle based on colorimetry; a color change in the media secondary to CO_2 production from the growing bacteria was detected via spectroscopy occurring every 10 minutes. If the color change did not occur for 5 days, the bottle was determined to be negative. For positive samples, the time to positivity was recorded. For negative samples, the BacT/Alert bottle was removed from the incubator and sterility confirmed by aspirating 1 mL of the fluid using standard, aseptic technique, spreading the solution onto standard blood agar plates, and incubating for 72 hours at 36.5°C. The experiment was duplicated with a total sample size of 40 experimental units and 8 negative controls. Time to positivity in hours was then compared for each phenotype and antibiotic susceptibility (MRSA and MSSA).

Statistical Analysis

The primary aims of this study were to examine the mode (within and/or between case transmission), reservoir of origin, transmission location, and antibiotic resistance patterns of *S aureus* stains/strain characteristics (phenotypes) frequently transmitted in the anesthesia work area of the operating room environment. Our secondary aims were to examine the phenotypic contributions to 30-day postoperative patient cultures, growth rates (incubation periods) for these same phenotypes, and risk factors for transmission of a more virulent phenotype.

Primary Aims

The frequency of transmission between and within cases (mode) and the relative contributions of the patient, environmental, and provider hand bacterial reservoirs (reservoir of origin) to *S aureus* transmission events from the anesthesia work area were compared using the χ^2 or Fisher exact test where appropriate for the 2 most prevalent *S aureus* phenotypes. Differences in antibiotic resistance profiles for *S aureus* phenotypes were also compared using the χ^2 or Fisher exact test for categorical data and 2-tailed Student *t* test for comparison of continuous data (zone of inhibition in millimeters); for continuous variables, both Student *t* and Wilcoxon rank sum tests were conducted and confirmed the results (e.g., if the *P* value was <0.01 for the *t* test, the rank sum test was also <0.01 and vice versa).

Secondary Aims

The relative contributions of *S aureus* phenotypes to 30-day postoperative PFGE links to patient cultures were compared using Fisher exact test. As phenotype H was not associated with a single PFGE link to subsequent bacterial cultures, the risk ratio for PFGE links was hand calculated, and substituted 0.5 for 0 in the case of phenotype H. An α level of $P < 0.05$ was defined as statistically significant.

Growth Rate Analysis: Kaplan–Meier time to event analysis was conducted to evaluate the difference between phenotypes in time to critical growth threshold (that required for detection) after injection. We used the log rank test for equality of time to critical threshold of contamination differences across the 2 phenotypes.

Risk Factors for Phenotypic Isolation: We used univariate logistic regression to compare x, y, z on the likelihood of phenotype P positivity. An α level of $P < 0.05$ was defined as statistically significant. Predictors for phenotype P were also assessed in a multivariable model including surgical procedure, case duration, F_{IO_2}, temperature, administered prophylactic antibiotics, age, ASA physical status, sex, SENIC score, urgency, and preoperative origin using forward and backward stepwise logistic regression analysis. Important factors identified by backward stepwise logistic regression analysis were included in the final model as shown in Table 1. We assessed and excluded all 1-way interactions ($P < 0.05$). An α level of $P < 0.05$ was defined as statistically significant.

Power Analysis

This study was previously powered to detect a rate of between case stopcock bacterial transmission events of 5% with an alternative rate of 1%. Approximately 400 patients (200 pairs) were needed to be powered at 0.9 with a type 1 error rate of 0.05.[9] No additional power analyses were conducted for analysis of *S aureus* transmission events, as all *S aureus* isolates were assessed for possible transmission

events. Only those organisms implicated in transmission events were subjected to further analysis.

RESULTS

The 170 *S aureus* isolates previously implicated in potential intraoperative transmission events were stratified by API phenotype. Two phenotypes, phenotype P and phenotype H, explained 65% (phenotype P = 13% [23/170] and phenotype H = 51% [87/170]) of all potentially transmissible isolates.

Table 2 details the mode of transmission, reservoir of origin, transmission locations, and antibiotic susceptibility profiles for *S aureus* phenotype P as compared with phenotype H. Phenotype H and phenotype P were implicated in a confirmed transmission event in 28% and 39% of cases, respectively. Both phenotypes were involved in similar rates of within and between-case transmissions (Table 2). The primary route of between-case transmission for phenotype P was environmental (66%), whereas the primary route for phenotype H between-case transmission was provider hands (80%). Patient skin surfaces (odds ratio [OR], 8.40; 95% confidence interval [CI], 2.30–30.73) and environmental (OR, 10.89; 95% CI, 1.29–92.13) samples were more likely than provider hands (referent) to have phenotype P positivity. Phenotype P was more likely to be resistant to methicillin (OR, 4.38; 95% CI, 1.59–12.06; $P = 0.004$) than phenotype H (OR, 0.208; 95% CI, 0.075–0.579; $P = 0.003$).

Table 1. Multivariable Analysis of Risk Factors for Isolation of Phenotype P (Patient)

Covariate	OR	95% CI	*P* value
Age, yr	14.11	3.12–63.5	0.001
SENIC score			
1	4.43	1.28–15.3	0.019
2	0.329	0.029–3.69	0.328
ICU	8.68	0.952–78.75	0.055
Hospital ward	41.11	5.30–318.78	<0.001

OR = odds ratio; CI = confidence interval; SENIC = Study on the Efficacy of Nosocomial Infection Control; ICU = intensive care unit.

Table 2. The Mode, Reservoir of Origin, Transmission Location, and Antibiotic Susceptibility for Frequently Transmitted *Staphylococcus aureus* Phenotypes

	S aureus phenotype P (*N* = 23)	*S aureus* phenotype H (*N* = 87)			
Outcome	Percent mean (*n*) or (SD)	Percent mean (*n*) or (SD)	OR/RR	95% CI	*P* value
S aureus isolate origin					
Patient sample	78.26 (18)	40.23 (35)	5.35	1.12–15.74	0.002
Provider hand sample	13.04 (3)	55.17 (48)	0.122	0.034–0.441	0.001
Environmental sample[a]	8.7 (2)	3.45 (3)	2.76	0.43–17.59	0.581
Transmission events					
Vertical[b] transmission source	13.04 (3)	5.75 (5)			0.231
Vertical transmission event	13.04 (3)	13.79 (12)			0.926
Vertical transmission destination					
Patient	0 (0)	23.08 (3)			0.238
Provider	100 (3)	46.15 (6)			
Environment[a]	0 (0)	30.77 (3)			
Horizontal[c] transmission source	8.7 (2)	4.6 (4)			0.442
Horizontal transmission event	13.04 (3)	5.75 (5)			0.231
Horizontal transmission destination					
Patient	33.33 (1)	20 (1)			0.053
Provider	0 (0)	80 (4)			
Environment	66.67 (2)	0 (0)			
Any 1 transmission event	39.13 (9)	28.7 (25)			0.199
Antibiotic resistance					
Methicillin	43.48 (10)	14.94 (13)	4.38	1.59–12.06	0.004
Ampicillin	86.96 (22)	86.21 (76)			0.926
Cefazolin	26.09 (8)	13.79 (12)			26.09
Cefepime	30.43 (9)	16.09 (14)			0.12
Ceftazidime	95.65 (25)	88.51 (78)			0.31
Cefuroxime	30.43 (9)	13.79 (12)	2.73	0.931–8.02	0.067
Ciprofloxacin	43.48 (12)	36.78 (32)			0.557
Clindamycin	30.43 (8)	56.32 (50)	0.339	0.126–0.908	0.031
Gentamicin	4.35 (1)	2.3 (2)			0.592
Meropenem	17.39 (5)	14.94 (13)			0.773
Penicillin	86.96 (22)	85.06 (72)			0.818
Pipericillin-Tazobactam	30.43 (9)	27.59 (24)			0.787
Sulfamethoxazole/trimethoprim	4.35 (1)	1.15 (1)			0.307
Linezolid	0 (3)	3.45 (0)			0.367
Tetracycline	4.35 (1)	5.75 (5)			0.793
Vancomycin zone (mm)	15.17391 (±0.9840627)	14.96552 (±0.5380472)			0.177

Difference between *S aureus* phenotype H (*N* = 87) and *S Aureus* phenotype P (*N* = 23).
Phenotype P = patients; phenotype H = hands; OR = odds ratio; RR = risk ratio; CI = confidence interval.
[a]Adjustable pressure-limiting valve and agent dial.
[b]Within-case.
[c]Between-case.

Phenotype P was more likely than phenotype H to be linked to 30-day postoperative patient cultures (risk ratio, 36.63 [risk difference, 0.173; 95% CI, 0.019–0.329]). As compared with phenotype H, phenotype P was more frequently isolated from abdominal (43.5% vs 27.6%), orthopedic (30.4% vs 19.5%), and plastic surgical cases (17.4% vs 2.3%), with a statistical difference in surgical type at $P = 0.01$, as well as from patients arriving from the hospital ward (26.1% vs 3.45%, $P = 0.001$) and/or intensive care unit (8.7% vs 2.3%, $P = 0.001$), and from patients undergoing urgent (17.4% vs 6.98%, $P = 0.006$) or emergent (8.7% vs 2.3%, $P = 0.006$) surgery. There was no statistically significant difference between phenotypes in terms of administered prophylactic antibiotics, inadequate antibiotic coverage, case duration, SENIC score, intraoperative temperature or FIO_2, postoperative glucose (milligrams per deciliter), or ASA status (Table 3).

In multivariable logistic regression analysis, older patients (OR, 14.1; 95% CI, 3.12–63.5; $P = 0.001$) and patients with preoperative hospital ward exposure (OR, 41.11; 95% CI, 5.30–318.78; $P < 0.001$) were more likely to have phenotype P positivity (Table 1).

As shown in Figures 3 and 4, phenotype P exhibited a faster growth rate for MRSA and for MSSA as compared with phenotype H (phenotype P: median, 10.32H; interquartile range [IQR], 10.08–10.56; phenotype H: median, 10.56H; IQR, 10.32–10.8; $P = 0.012$). The greatest difference in growth rate, however, was seen for MRSA (P: median, 10.08H; IQR, 9.84–10.32; H: median, 10.8H; IQR, 10.8–11.4; $P < 0.001$), where phenotype P had a 43-minute growth advantage over phenotype H (Fig. 5).

DISCUSSION

We examined the epidemiology of perioperative *S aureus* by systematically evaluating intraoperative bacterial transmission events in 3 different medical centers. Using a previously validated experimental model for study of intraoperative bacterial cross-contamination, we identified *S aureus* isolates frequently implicated in intraoperative bacterial transmission events and stratified them according to phenotype. We identified the 2 most prevalent *S aureus* phenotypes that are encountered within the anesthesia work area and have further characterized these organisms by examining their mode of transmission, most probable reservoir of origin, transmission locations, and antibiotic susceptibility. In addition, we examined phenotypic differences in contributions to 30-day postoperative patient cultures, growth rates, and risk factors for isolation. The findings of this study are important because they confirm the importance of addressing the patient reservoir while at the same time highlighting the importance of hand hygiene and environmental decontamination for *S aureus* control, and they provide information that might serve to guide targeted interventions in the complex perioperative arena.

Our prior studies led us to study 3 different potential reservoirs of bacterial pathogens (patients, anesthesia provider hands, and the surrounding environment) and downstream catheter care of high-risk intravascular devices.[6–9,21] An important outcome of our research is the finding that patients frequently arrive to the intraoperative environment with skin surfaces colonized with major bacterial pathogens and <20% of patients are effectively decolonized preoperatively.[9] Our data have led to the hypothesis that colonized patient skin surfaces serve as a major bacterial reservoir in the operative environment, one that often participates in vertical bacterial transmission leading to infection in the patient. Surprisingly, we have strong evidence suggesting that patient-derived strains were transmitted to subsequent patients who had procedures on the same day, again leading to HCAI development. Our most striking evidence supporting the role of the patient in bacterial transmission in operating rooms came from our multicenter study in which we systematically characterized the relative importance of intraoperative bacterial reservoirs in intraoperative bacterial transmission and 30-day postoperative infection development.[9] This work clearly demonstrated that patient skin colonization is a major factor impacting other patients undergoing care in the same arena (i.e., between operative cases), is the main source of *S aureus* origin and transmission, and is the main source of 30-day postoperative infections (both between and within operative cases) from *S aureus*. While patient colonization contributed partially to bacterial transmission within the environment, it also significantly contributed to endogenous infection (in 83% of cases).

We have extended these findings in the current study by demonstrating that not only are patients most likely to harbor *S aureus*, but also they are more likely to harbor one of the more transmissible and more virulent *S aureus* phenotypes encountered in the intraoperative setting. Thus, taken together, these findings should help guide improvements in patient decolonization strategies.

Our work has led us to hypothesize that specific strains and/or strain characteristics of pathogenic organisms make them more likely to resist decontamination procedures or eradication by antibiotics that are administered during the perioperative period and thus are likely to be more transmissible to patients undergoing care in the same arena, and as a result, are more likely to lead to HCAIs, hospital readmission, and increases in the cost of patient care. If we can identify strains that are more likely to be transmitted and/or to cause infection, we can better identify patient carriers in the preoperative setting, identify environmental components that lead to transmission events during patient care, including health care provider characteristics, and identify factors that lead to transformation of less virulent to more virulent organisms. Such knowledge could lead to the development and implementation of new, patient-centered, and cost-effective screening strategies for patient decolonization or novel drug therapy. Thus, our focus is on understanding the biology of bacterial transmission in the operating room.

We have shown that there are 2 *S aureus* phenotypes frequently encountered in the anesthesia work area environment. Although these phenotypes are transmitted at similarly high rates between and within cases, they differ greatly in terms of their most probable reservoir of origin, transmission routes, and overall virulence. Phenotype P is patient and environmentally derived, transmits more frequently through the environment, and

Table 3. Links to 30-Day Postoperative Patient Cultures, Inadequate Antibiotic Coverage, and Univariate Analysis for Isolation of Phenotype P

	Staphylococcus aureus phenotype P (*N* = 23)	*S aureus* phenotype H (*N* = 87)	Difference			
	Percent mean (*n*) or (SD)	Percent mean (*n*) or (SD)	OR/RR	Risk difference	95% CI	*P* value
Link to patient culture (PFGE)	5	0.5		0.174	0.019–0.328	<0.001
Inadequate antibiotic coverage[a]	26.09 (6)	34.48 (30)				0.445
Univariate analysis for isolation phenotype P						
Surgical procedure						0.011
General abdominal	43.48 (11)	27.59 (24)				
Orthopedic	30.43 (8)	19.54 (17)				
Ear, nose, throat	0 (0)	11.49 (10)				
Gynecological	0 (0)	12.64 (11)				
Neurosurgical	0 (0)	2.3 (2)				
Plastics	17.39 (4)	2.3 (2)				
Thoracic	0 (0)	5.75 (5)				
Breast	0 (0)	10.34 (9)				
Case duration (h)	2.662319 (±1.312452)	2.255747 (±1.067396)				0.125
Intraoperative characteristics						
Fio_2	71.58095 (±15.57394)	69.37792 (±14.75067)				0.55
Temperature	36.1 (±0.5422177)	36.01061 (±0.5697851)				0.528
Prophylactic antibiotics						0.354
Ampicillin-sulbactam	0 (0)	3.45 (3)				
Cefazolin	39.13 (6)	44.83 (15)				
Cefazolin/metronidazole	0 (0)	3.45 (3)				
Cefotetan	13.04 (3)	4.6 (4)				
Cefuroxime/vancomycin	0 (0)	1.15 (1)				
Clindamycin	17.39 (1)	5.75 (1)				
None	13.04 (1)	21.84 (6)				
Vancomycin	8.7 (2)	6.9 (2)				
Ampicillin	0 (0)	2.3 (2)				
Cefotetan and ampicillin	0 (0)	2.3 (2)				
Ciprofloxacin	0 (0)	1.15 (1)				
Clindamycin and cefazol	8.7 (3)	1.15 (1)				
Gentamicin and clindamycin	0 (0)	1.15 (1)				
Age	55.82609 (±16.40303)	49.08046 (±13.92607)	1.03		0.999–1.07	0.053
ASA physical status[b]						0.148
I	0 (0)	13.79 (12)				
II	69.57 (18)	63.22 (55)				
III	21.74 (5)	20.69 (19)				
IV	8.7 (3)	2.3 (2)				
Sex (female)	26.09	51.72	0.329		0.118–0.915	0.033
SENIC score[a]						0.131
0	26.09	47.13				
1	65.22	37.93				
2	8.7	13.79				
3	0	0				
4	0	1.15				
Preoperative patient origin						0.001
Same day	65.22	90.8				
Floor	26.09	3.45				
Intensive care unit	8.7	2.3				
Other	0	3.45				
Postoperative discharge location						0.042
Same day	21.74	54.02				
Hospital ward	60.87	32.18				
Intensive care unit	8.7	5.75				
Other	8.7	8.05				
Urgency						0.006
Elective	73.91	93.02				
Urgent	17.39	6.98				
Emergent	8.7	0				

Phenotype P = patients; phenotype H = hands; Fio_2 = fraction of intraoperative inspired oxygen concentration; PFGE = pulsed-field gel electrophoresis.
[a]Study on the Efficacy of Nosocomial Infection Control (SENIC).
[b]ASA physical status classification system (I-IV).

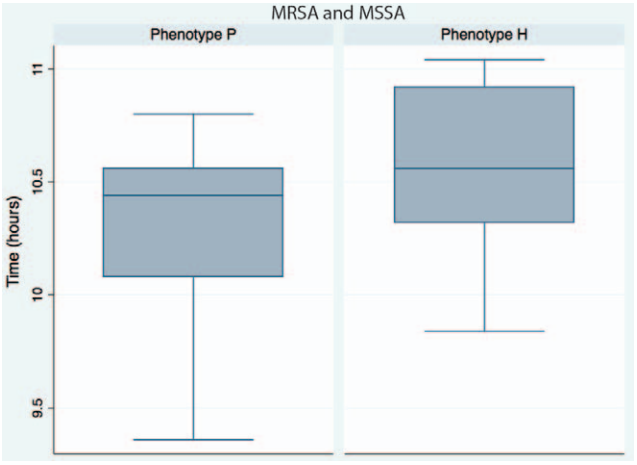

Figure 3. Growth rate (h) for phenotype H (hands) as compared with phenotype P (patients) for methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA).

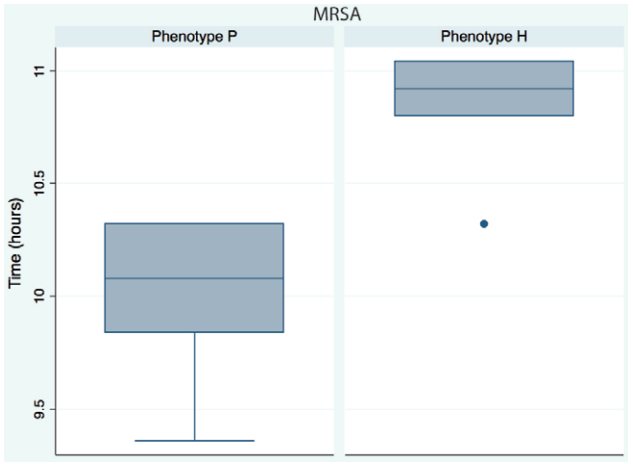

Figure 4. Growth rate (h) for phenotype H (hands) as compared with phenotype P (patients) for methicillin-resistant *Staphylococcus aureus* (MRSA).

is more virulent (increased antibiotic resistance and linkage to 30-day postoperative cultures) than the provider-derived phenotype H. These findings are important, as they confirm the need for a multimodal program in handling *S aureus*, but also serve as a foundation for future development of improved patient screening and decolonization efforts.

Our findings also provide some insight into potential reasons for previously reported variability in efficacy of patient decolonization efforts. Previous work has suggested that patient nasopharyngeal colonization with *S aureus* is a strong risk factor for SSI development,[12] and some evidence suggests that preoperative patient decolonization with nasal mupirocin and/or chlorhexidine is an effective SSI prevention strategy.[13,22] However, the overall body of evidence pertaining to preoperative patient decolonization is equivocal.[9,11] As a result, perioperative compliance with patient screening and decolonization efforts is suboptimal, and SSIs continue to affect 3% to 5% of surgical patients.[1,4,5] We previously hypothesized

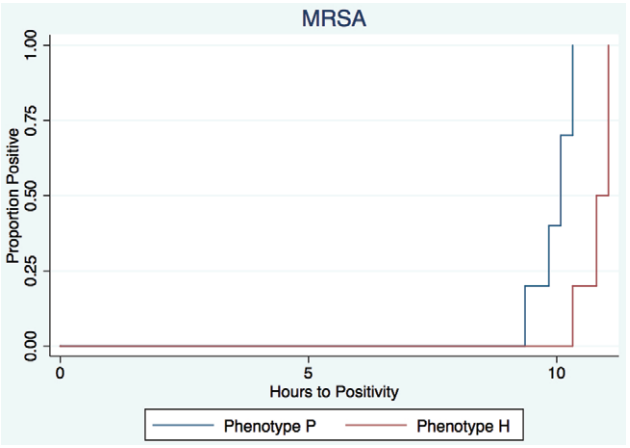

Figure 5. Kaplan–Meier time to event analysis to evaluate the difference between phenotypes P (patients) and H (hands) in time to critical growth threshold (that required for detection) following injection. We used the log rank test for equality of time to critical threshold of contamination differences across the 2 phenotypes. MRSA = methicillin-resistant *Staphylococcus aureus.*

that a better understanding of the contribution of patient skin colonization to intraoperative bacterial transmission events and subsequent infection development would provide the impetus for improvements in patient decolonization efforts.

The observation that the more virulent of these 2 highly transmissible *S aureus* phenotypes was often isolated from hospitalized patients may explain the success of Bode et al.[13] in demonstrating efficacy for patient decolonization in SSI reduction. Bode et al.[13] enrolled a particularly high-risk subgroup of patients that had been previously exposed to the surgical and/or medical wards before a subsequent surgical exposure. Given this increased risk, Bode et al.[13] may have required a smaller sample size to demonstrate a statistically significant effect as compared with the work by Konvalinka et al.,[11] in which patients undergoing elective cardiothoracic surgery, potentially of lower risk for *S aureus* SSIs, were enrolled and no effect was demonstrated.

Thus, as we have identified patients who are exposed to the hospital ward and/or the intensive care unit before surgery as a particularly high-risk subgroup for colonization with the more virulent *S aureus* phenotype, this may be an appropriate target for future improvements in patient decolonization strategies. These results also provide some insight as to whether antibiotic resistance impacts patterns of transmission. Here, we show that a particular phenotype, phenotype P, is more likely to be resistant to methicillin and is transmitted differently than a separate phenotype, phenotype H, which is more likely to be sensitive to this antibiotic. As opposed to using contaminated hands as a transmission vehicle between cases, it appears that this more virulent phenotype is able to transmit via residual contamination of the environment or nonanesthesiologist hands. The reasons for this finding are unclear and require further follow-up, but the implications are that operating rooms exposed to patients who are colonized with MRSA may need to be targeted with enhanced cleaning strategies. These results further support the argument

for a multimodal approach to intraoperative infection control. While hand hygiene is important,[23,24] it is a single pronged intervention targeting 1 pathway for transmission, and as we show here, a specific subset of dangerous bacterial pathogens.

The patient reservoir and environmental cleaning must also be addressed. For phenotype P, improvements to perioperative infection control practices might include preoperative bathing of hospitalized patients, better methods of confirming adequate cleaning of the operating room (e.g., adenosine triphosphate analysis), and abstaining from preparing for the next case while still caring for a patient in the operating room given the highly transmissible nature from patient to patient. While preoperative bathing/showering of outpatients does not appear to be effective,[25] bathing in hospitalized patients does appear to be effective.[26] Again, the results of this study may partially explain the difference in efficacy of these various approaches. For phenotype H, as we know that anesthesia provider hand hygiene is abysmal, efforts to improve intraoperative hand hygiene must be made. There is reasonable evidence for an improved intraoperative approach to hand hygiene.[8]

Our findings pertaining to phenotypic differences in *S aureus* growth rate are particularly important because these results suggest that there are important differences in behavior within MRSA and MSSA isolates. In this case, the phenotype P represents strain characteristics associated with enhanced doubling time. This may be very important in the operating room, as a 43-minute advantage for MRSA may be enough to establish growth and generate quorum sensing (a protective mechanism used by bacterial organisms that involves formation of a biofilm once a critical number of cells has been reached).[27] A potential implication therefore is that biofilm formation may begin before the concentration of prophylactic antibiotics administered immediately before incision reaches an effective tissue concentration for bactericidal or static inhibition. Thus, we may need to refine preoperative screening strategies beyond MRSA versus MSSA alone to the type of MRSA or MSSA that is colonizing the surgical patient. This could lead to improvements in preoperative therapeutic interventions, such as timing of antibiotic administration.

It is important to note that phenotypic differences in virulence as demonstrated in this study cannot be explained by differences in prophylactic antibiotic exposure, inappropriate antibiotic coverage, intraoperative temperature or F_{IO_2}, or patient severity of illness as reflected by ASA status. The lack of difference in antibiotic exposure or inappropriate administration of antibiotics is important in that it suggests that there is more to intraoperative infection prevention than simple administration of antibiotics. As discussed above, timing may be an important feature and should be further refined, perhaps, but in addition, the type of organism may have developed virulence factors that facilitate evasion of the administered agent. In other words, the phenotypic differences in outcomes that we show in this study are organism specific; there is something unique about the bacterial organism that facilitates transmission, antibiotic resistance, and infection development. The data do not suggest that these differences can be simply explained by a lack of appropriate prophylactic antibiotic exposure or predisposition to infection.

Phenotypic differences are, however, independently associated with increasing age and preoperative exposure to the hospital ward, as these associations remain intact despite adjustment for potentially confounding variables in stepwise logistic regression analysis. These findings, in combination, highlight the importance of phenotype P virulence and may highlight the importance of potential host–pathogen relationships. In addition, preoperative exposure to the hospital ward appears to be a very important factor in isolation of phenotype P. As these were secondary outcomes, these results should be interpreted with caution.

The overall strength of this study resides in the fact that it involves an extensive investigation of *S aureus* transmission across 3 major academic medical centers, thus making the results rather generalizable.[9] However, this study is limited by a lack of a genotypic explanation for phenotypic differences. Future work should address this deficit. Furthermore, although enhanced growth rates may be associated with increased virulence, we recognize that this relationship is not always true and that in this study, growth rates were analyzed under optimal in vitro conditions that may not reflect the in vivo state.

In conclusion, the results of this study provide important insight into the epidemiology of intraoperative *S aureus* transmission in the anesthesia work area environment. A prevalent, highly transmissible, virulent *S aureus* phenotype is more likely to be isolated from patient skin and environmental surfaces as compared with provider hands. Patients exposed to the hospital ward and/or the intensive care units are at particularly high risk for carriage of this important pathogen. Improvements in preoperative patient decolonization efforts, especially those targeting patients arriving to the operating room from high-risk environments, and improved environmental cleaning strategies are indicated as part of a multimodal strategy to reduce 30-day postoperative HCAIs.

APPENDIX. Antibiotics Tested in Kirby-Bauer Analysis

Ampicillin
Cefazolin
Cefepime
Ceftazidime
Cefuroxime
Ciprofloxacin
Clindamycin
Gentamicin
Meropenem
Piperacillin/tazobactam
Sulfamethoxazole/trimethoprim
Linezolid
Tetracycline
Vancomycin
Methicillin
Penicillin

DISCLOSURES

Name: Randy W. Loftus, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Randy W. Loftus has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Matthew D. Koff, MS, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Matthew D. Koff has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Matthew D. Koff received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Jeremiah R. Brown, MS, PhD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jeremiah R. Brown has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Hetal M. Patel, BS.
Contribution: This author helped conduct the study.
Attestation: Hetal M. Patel has seen the original study data and approved the final manuscript.
Conflicts of Interest: Hetal M. Patel received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Jens T. Jensen, MS.
Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
Attestation: Jens T. Jensen has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Jens T. Jensen received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Sundara Reddy, MD.
Contribution: This author helped design and conduct the study, and write the manuscript.
Attestation: Sundara Reddy has seen the original study data and approved the final manuscript.
Conflicts of Interest: Sundara Reddy received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Kathryn L. Ruoff, PhD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Kathryn L. Ruoff has seen the original study data and approved the final manuscript.
Conflicts of Interest: Kathryn L. Ruoff received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Stephen O. Heard, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Stephen O. Heard has seen the original study data and approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Mark P. Yeager, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Mark P. Yeager has seen the original study data and approved the final manuscript.
Conflicts of Interest: Mark P. Yeager received research funding from B. Braun Medical Inc. for a portion of the study.
Name: Thomas M. Dodds, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Thomas M. Dodds has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Conflicts of Interest: Thomas M. Dodds received research funding from B. Braun Medical Inc. for a portion of the study.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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The Use of a Novel Technology to Study Dynamics of Pathogen Transmission in the Operating Room

David J. Birnbach, MD, MPH,*|| Lisa F. Rosen, MA,† Maureen Fitzpatrick, MSN, ARNP-BC,† Philip Carling, MD, MPH,‡ and L. Silvia Munoz-Price, MD, PhD§||¶

Pathogenic organisms have been found in the intraoperative environment, potentially posing a risk of infection that could cause morbidity and mortality. In an effort to understand how a patient's bacteria can be spread throughout the operating room with the anesthesia provider as a vector, we conducted a study using recently developed experimental technology in a simulated operating room environment with a high-fidelity human patient simulator. (Anesth Analg 2015;120:844–7)

The operating room (OR), while considered to be the hallmark of cleanliness, is not a sterile environment.[1,2] Studies have shown that ORs are adequately cleaned during a 24-hour period in <50% of instances.[2] Known pathogens such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Clostridium difficile*, and multidrug-resistant Gram-negative bacilli have been found on many OR surfaces.[2–4] Models of bacterial transmission in the OR have definitively shown that anesthesia providers play an important role,[5] and it has been suggested that anesthesiologists may be a key vector for the spread of bacteria through their contaminated hands or gloves.[6,7] This occurs by transferring organisms from the patient to the immediate environment (including the anesthesia machine) and then from the contaminated environment back to the patient. Therefore, a better understanding of how organisms are spread in ORs may help to provide the basis for developing evidence-based preventive measures in the future.[1,8,9] We used an experimental technology in a simulated environment to show patterns of transmission and evaluated the efficacy of this technology for studying dynamics of pathogenic contamination in an OR.

Using a previously validated experimental technology[2] in a simulated OR with anesthesia residents providing the anesthetic, we aimed to: (1) evaluate the use of a new technology to study the transmission of bacteria and blood in an OR; (2) show how a contaminated patient (mannequin) can lead to pathogen spread in the OR environment with the anesthesia provider acting as a vector; and (3) characterize and quantify the number of objects contaminated by the anesthesia provider after the intubation.

From the *Department of Anesthesiology, and †UM-JMH Center for Patient Safety, University of Miami Miller School of Medicine, Miami, Florida; ‡Department of Medicine Infectious Diseases, Boston Medical Center, Boston, Massachusetts; and Departments of §Medicine, ||Public Health Sciences, and ¶Anesthesiology, University of Miami Miller School of Medicine, Miami, Florida.

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Address correspondence to David J. Birnbach, MD, MPH, UM-JMH Center for Patient Safety, University of Miami Miller School of Medicine, 1611 NW 12 Ave., Room C-300, Miami, FL 33136. Address e-mail to dbirnbach@miami.edu.

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METHODS

IRB exemption for this study was obtained. Ten anesthesiology residents (PGY 2–3) were enrolled in individual training sessions conducted in a simulated OR. On entry to the simulation session, each resident was asked to perform an anesthetic induction and intubation on a human patient simulator. These exercises were realistic; however, the residents were told that they did not need to record the anesthetic or use the computer keyboard. These simulations were designed to last 6 minutes and were part of an educational program that did not relate to glove use. Before the start of the scenario, the lips and inside of the mouth of the human patient simulator (CAE, Quebec, Canada) were coated with 0.5 mL fluorescent marker (DAZO, Ecolab, St. Paul, MN).[2] As part of the orientation, all residents were instructed to don gloves before the start of the scenario, but no further instructions regarding glove use were provided. If gloves were not removed when the simulation was terminated, the resident was asked by the nurse who was present during the scenario to remove them before leaving the OR.

The OR was cleaned between cases with both alcohol-based hand rub as well as soap and water to remove all previously placed fluorescent marker. To verify that the OR was adequately cleaned before each simulation, an observer examined the entire OR using a handheld ultraviolet light to determine the presence of any residue of fluorescent marker. If residual marker was found, it was removed. Disposable materials that could not be easily cleaned were replaced (reservoir bag, IV tubing, and syringes). After the resident had left the OR, an observer used an ultraviolet marker to determine the objects positive for fluorescence. The residents did not know that DAZO had been applied and did not alter standard practice.

The proportion of objects with fluorescent markers after the encounters was analyzed based on the resident's level of training using χ^2 or Fisher exact tests as needed. $P < 0.05$ was considered statistically significant. SAS 9.2 (SAS Institute, Inc., Cary, NC) was used for all analyses.

RESULTS

Forty potential sites within the resident's working environment were examined for the presence of fluorescent markers (Table 1). The mean number of objects stained with fluorescent marker per session was 31 (range 27–35). Thirteen sites, including the IV hub, were contaminated in 100% of the sessions (Table 2). Fluorescence demonstrating contamination

Table 1. Operating Room Areas Observed for Presence or Absence of Fluorescence After Each Simulation

1. Eyes	21. Miller blade
2. Nose	22. O2 valve
3. Forehead	23. Suction canister
4. Chest	24. Suction tubing
5. Ears	25. Suction gauge
6. Neck	26. Anesthesia cart
7. Shoulders	27. Box of nonsterile gloves
8. Upper arm	28. Anesthesia monitors
9. Head of bed	29. IV bag
10. Ether screen	30. IV tubing
11. Oxygen mask	31. IV hub
12. Anesthesia circuit	32. Antecubital fossa at IV location
13. Endotracheal tube	33. IV pole
14. Reservoir bag	34. Computer keyboard
15. Anesthesia machine surface towel	35. Door handle in OR
16. Laryngeal mask airway on anesthesia machine surface	36. Door
17. Medication syringes on anesthesia machine surface	37. OR light controls
18. Laryngoscope handle	38. Overhead room light switch
19. Laryngoscope blade (Mac)	39. Volatile agent control knob
20. Extra laryngoscope handle	40. Stethoscope

Table 2. Locations Which Were Contaminated in 100% of Scenarios

- Laryngoscope handle and blade
- Head of bed
- Eyes
- Nose
- Forehead
- Oxygen mask
- Reservoir bag
- Anesthesia machine surface
- Oxygen valve
- Anesthesia circuit
- Anesthesia cart
- IV hub
- Drape/ether screen

of IV hub is illustrated in Figure 1. Numerous areas of the mannequin's face (nose, eyes, and forehead) were found to be contaminated, as shown in Figure 2. Table 3 identifies those areas that were contaminated only occasionally. Of note, the OR door handle was contaminated in 60% of cases despite the fact that no one left the OR with gloves on, suggesting that residents were contaminating their hands at some point before contact with the door handle. In 100% of the cases, when the laryngoscope was placed on the anesthesia machine surface immediately after use, the adjacent surface and syringes were contaminated. Of interest, even unused equipment (including the computer keyboard) was contaminated in most cases. Contamination of the keyboard is shown in Figure 3. There was no difference between levels of years of residency training in number of areas contaminated (PGY 2 = 31.2, PGY 3 = 31.4, $P = 0.12$).

DISCUSSION

This study demonstrates the use of a novel technology for studying the spread of pathogenic material (e.g., blood or

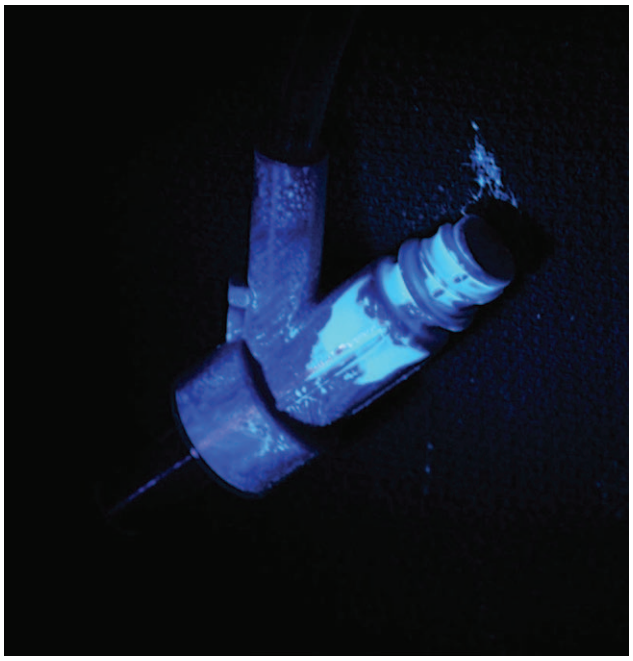

Figure 1. Contamination of IV hub.

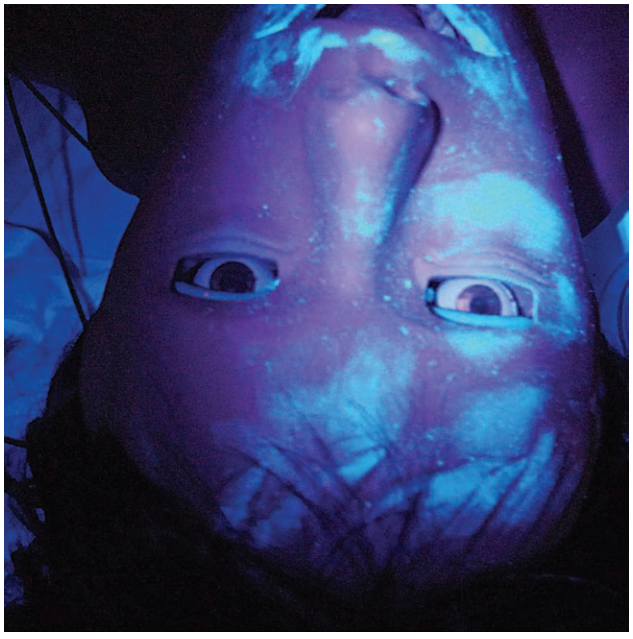

Figure 2. Fluorescence on mannequin's face after scenario.

Table 3. Other Contaminated Areas and Percentages

Volatile agent control knob	90%
Stethoscope	90%
Medication syringes	90%
Suction tubing	90%
IV bag	90%
Box of nonsterile gloves	80%
Computer keyboard	80%
Extra laryngoscope handle	60%
Door handle in operating room	60%

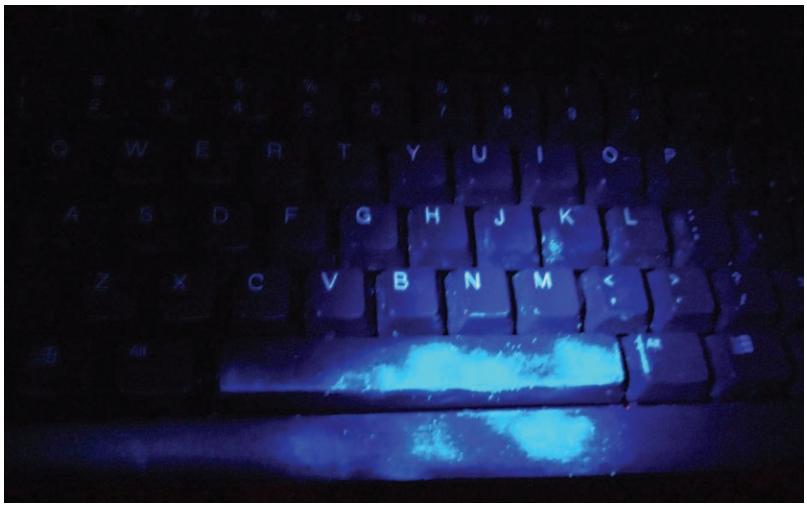

Figure 3. Computer keyboard.

bacteria) in a simulated OR. We found a high degree of spread of fluorescent marker placed at the mannequin's mouth to the OR environment. These data suggest that this technology will be useful as a tool to evaluate methods to decrease OR contamination. In addition, the findings support previous reports that anesthesiologists may be a vector for spread of pathogens from the patient to the intraoperative environment.[5] In addition to providers' hands, the IV hubs, laryngoscopes, and OR door handles appear to be surfaces that might increase the possibility for horizontal transmission of organisms among patients sharing the OR throughout the day. Moreover, the placement of a laryngoscope immediately after use on the surface of the anesthesia machine adjacent to clean syringes may create unnecessary risk of contamination of other objects with bodily fluids. Some of the areas stained by fluorescent markers in this study (including the box of nonsterile gloves) are not routinely cleaned between cases, if at all. Even if the anesthesiologist were to continually perform hand hygiene during surgery, if initial contamination from the patient to the environment occurs, there is a large risk of recontamination during the recurrent handling of the head of bed, anesthesia machine, syringes, or stethoscope.

This study has several limitations. First, it was conducted in a simulated OR using a surrogate marker for blood and oral pathogens. Behaviors in an actual OR might be different. Second, the scenario was limited to 6 minutes for performance of the induction and intubation. An actual case takes longer and may potentially lead to additional contaminated sites. Third, the examination of all mechanisms of transmission was beyond the scope of the study because it involved a small cohort of residents. Last, possible contamination was limited by the study design because other areas in the OR and areas outside the OR were not investigated for spread of fluorescence. In addition, this study was not randomized to evaluate the differences between those who removed their gloves immediately after intubation and those who did not. Although the American Society of Anesthesiologists recommendations state that gloves should be removed before touching equipment,[9] this is not routinely done.[10] This lack of compliance was evident in this study, where none of the residents removed their gloves before contaminating the OR environment.

Despite these limitations, our findings strongly suggest that anesthesiologists need to be conscious of the role they may play in pathogen transmission in the OR. Future studies with more robust approaches should compare the spread of fluorescent marking gel when gloves are removed immediately after intubation versus leaving them on for a sustained period as well as the potential benefit of wearing 2 sets of gloves. The use of this technology can also be used to evaluate strategies to decrease potential spread of oral pathogens in a real OR environment, as well as in other areas where anesthesiologists work such as postanesthesia care units, intensive care units, and pain clinics.

DISCLOSURES

Name: David J. Birnbach, MD, MPH.
Contribution: This author helped in design and conduction of study, data collection, data analysis, and manuscript preparation.
Attestation: David J. Birnbach reviewed the original study data and data analysis, attests to the integrity of the original data and analysis, approved the final manuscript, and is the archival author.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Lisa F. Rosen, MA.
Contribution: This author helped in study design, data analysis, and manuscript preparation.
Attestation: Lisa F. Rosen approved final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Maureen Fitzpatrick, MSN, ARNP-BC.
Contribution: This author helped in design and conduction of study, data collection, and manuscript preparation.
Attestation: Maureen Fitzpatrick approved final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
Name: Philip Carling, MD, MPH.
Contribution: This author helped in design and manuscript preparation.
Attestation: Philip Carling approved final manuscript.
Conflicts of Interest: Consulting fee and patent license with Ecolab, Inc.

Name: L. Silvia Munoz-Price, MD, PhD.
Contribution: This author helped in design and conduction of study, data collection, data analysis, and manuscript preparation.
Attestation: L. Silvia Munoz-Price approved final manuscript.
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This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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The Dynamics and Implications of Bacterial Transmission Events Arising from the Anesthesia Work Area

Randy W. Loftus, MD,* Matthew D. Koff, MS, MD,* and David J. Birnbach, MD, MPH†

Health care–associated infections are a hospital-wide concern associated with a significant increase in patient morbidity, mortality, and health care costs. Bacterial transmission in the anesthesia work area of the operating room environment is a root cause of 30-day postoperative infections affecting as many as 16% of patients undergoing surgery. A better understanding of anesthesia-related bacterial transmission dynamics may help to generate improvements in intraoperative infection control and improve patient safety. (Anesth Analg 2015;120:853–60)

THE HYPOTHESIS

Health care–associated infections (HCAIs) affect approximately 10% of patients admitted to acute care facilities, accounting for up to 500,000 infections and a cost of 30 billion dollars annually.[1] Despite advances in surgical techniques, sterilization, and disinfection programs, the U.S. health care system has not yet generated a sustained, overall improvement in HCAI rates.[2–5] Instead, HCAIs have become an increasing dilemma due to the evolving problem of multidrug-resistant bacteria and the increasing complexity of the health care environment.[6–8] The problem has been highlighted by the Centers for Medicaid and Medicare Services, which no longer reimburse for some costs related to HCAIs.[9] These infections are now a major public health concern, and as a result, the importance of gaining a better understanding of the various mechanisms of bacterial transmission in different hospital settings has been emphasized.[6,10,11] It is hypothesized that the anesthesia work environment (AWE) and anesthesia provider hygiene practices contribute to HCAIs. The purpose of this review is to summarize historical and recent literature pertaining to the magnitude and implications of AWE bacterial transmission dynamics (pathogen reservoir of origin, pathogen strain characteristics, mode of transmission, and portals of entry and exit to a susceptible host). This will highlight the potential areas for improvement in attenuation of intraoperative bacterial transmission and subsequent HCAI development.

ESTABLISHING THE HYPOTHESIS

The operating room (OR) environment includes health care tools and surfaces used within the AWE, air, and even anesthesia health care providers themselves.[12–18] It has long been known that syringes and intravascular catheters can become contaminated directly via bacterial contamination of the provider's hands or indirectly during connection to patient IV tubing.[19–22] In 1974, Blogg et al.[23] reported that syringes can become contaminated with bacterial pathogens after a single use, thereby providing a plausible mechanism for the bacterial contamination of propofol vials later linked to cases of severe sepsis[24] and a series of *Staphylococcus aureus* bloodstream infections occurring in patients undergoing electroconvulsive therapy.[25] An investigation of outbreaks associated with propofol at 7 different hospitals further characterized breaches in aseptic practice that could be associated with propofol contamination including failure to disinfect propofol vials before use, transfer of syringes between ORs and facilities, and syringe reuse (serial use of the same syringe for the same patient).[26] Conceptually, these breaches in aseptic practice could lead to bacterial transfer to propofol vials. This could subsequently contaminate syringes used for injection, the syringe connection ports (hubs) of peripherally and centrally inserted IV catheters, and the internal lumen of the central or peripheral devices. This contamination may therefore ultimately cause distal seeding of the bloodstream. This sequence of events has been characterized as a primary mechanism for central line–associated primary bloodstream infections.[27] However, infective agents cannot be seen and real-time testing for contamination is not available. This relative lack of feedback to the practitioner makes it difficult for them to appreciate the connection between practice and infection.

Laryngoscope blades and handles are contaminated with blood and mucus after use and standard disinfection procedures. Residual contamination of these airway devices associated with suboptimal disinfection practices has been linked to infectious outbreaks.[17] Additional work has confirmed the need for better disinfection of laryngoscope handles in today's OR environment.[28]

Contamination of anesthesia machine surfaces with blood, mucus, and bacterial organisms after standard cleaning processes was first characterized in the 1960s[12,13] and subsequently confirmed.[14,15] Many of these disinfection practices are still used today. Numerous early studies reported the ability of recovered bacterial pathogens to survive on anesthesia equipment for several days and to serve as potential sources of infection.[29–35] In addition, residual surface contamination was identified as a possible link to a cluster of follicular tonsillitis infections, all occurring in the same postoperative week.[34] Other reports have documented an association of residual contamination of the anesthesia machine circuit and Ambu-bag with outbreaks

From the *Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; and †Department of Anesthesiology, Obstetrics and Gynecology and Public Health Sciences, University of Miami Miller School of Medicine, Miami, Florida.

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Address correspondence to David J. Birnbach, MD, MPH, Department of Anesthesiology, Perioperative Medicine and Pain Management, University of Miami Miller School of Medicine, 1611 NW 12th Ave., Room C300, Miami, FL 33136. Address e-mail to DBirnbach@med.miami.edu.

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of *Pseudomonas aeruginosa* respiratory infections.[29,35] These early findings, however, were limited by the suboptimal bacterial typing methodology used. Thus, bacterial transmission events occurring in this distant era were not confirmed and were not directly linked, with reasonable certainly, to subsequent infections, with the data serving to present only a theoretical risk.

Bacterial contamination of the anesthesia machine circuit is also important to consider as a risk factor for bacterial transmission in the AWE. Early work by Albrecht and Dryden identified an association between combined preoperative decontamination of the external surface of anesthesia machine circuits and use of new absorbers with a reduction in postoperative pneumonia. These authors therefore concluded that contaminated anesthesia machines can indeed transmit bacteria to patients.[32,36] Several investigators have used laboratory models to confirm this mechanism.[37,38] Leijten et al.[39] published the results of a study in a simulated environment evaluating a matrix of factors that could potentially affect bacterial transfer to the patient circuit, and subsequently to the patient. They found that without an in-line circuit filter in place, bacterial organisms were universally transmitted to the patient circuit, with the greatest density of organisms lodged closest to the patient. They also found that the anesthetic gas (halothane) and soda lime were ineffective at preventing bacterial transfer.[39] Multiple studies have subsequently demonstrated the efficacy of in-line circuit filters in prevention of bacterial transfer to the patient circuit.[40,41] It has been suggested that filters be used routinely and changed between each case.[42]

Fukada et al.[18] sought to examine bacterial contamination on the hands of anesthesiologists during general anesthesia and found that they were heavily contaminated with bacterial pathogens throughout all phases of anesthesia care. These findings are concerning given that anesthesia providers have been shown to be particularly noncompliant with hand hygiene.[43] To determine how many anesthesia providers comply with practices recommended for preventing transmission of infectious agents to patients, Tait and Tuttle[43] surveyed anesthesiologists and reported the results in 1995. Ninety-five percent reported washing their hands after caring for "high-risk" patients, but only 58% washed their hands in "low-risk" situations. Although the OR environment and anesthetic practice characterized by Tait and Tuttle have likely evolved in the interim, more recent observational work has shown that lapses in hand hygiene compliance occur frequently in today's OR. Furthermore, they often involve failure to wash hands before and/or after aseptic tasks involving line insertions, bronchoscopy, or even after blood exposures.[44,45] Thus, when taken together, these data support the potential links between anesthesia providers and postoperative infectious outbreaks reported as early as the 1960s. One outbreak involved group A β-hemolytic streptococci–derived puerperal sepsis occurring in the postoperative period, whereas another involved 2 outbreaks of *S aureus* surgical site infections (SSIs) thought to originate with the contaminated hands of an anesthesia provider suffering from psoriasis.[46–52] Although these original infectious outbreak investigations were limited by the suboptimal typing methodology used at the time, a growing body of evidence provided a rationale for why they may have been true associations. However, the risk remained only theoretical.

Although not generally considered to be under direct control of the anesthesiologist, even intraoperative air poses some risk for bacterial transmission. In 2005, Edmiston et al.[53] published the results of a study whereby air samples were taken during 70 different vascular procedures from a single OR. Coagulase-negative *Staphylococcus* and *S aureus* were recovered from 86% and 64% of all samples, respectively, with Gram-negative bacteria recovered less frequently (33%). More contamination was found closer to the surgical field than those samples obtained farther away, but interestingly, some organisms were identical to those recovered from nasal samples of health care workers. These results raised questions pertaining to the efficacy of masks in prevention of bacterial transfer, but also highlighted a very important issue, that the bacterial inoculum brought to the OR can affect the patient via a vector outside of provider hands or the environment (surfaces/equipment); that is, aerosolization of particles.

This brings to question the evidence for the common practice of wearing masks in the OR for the purpose of decreasing the aerosolization of bacteria originating with providers. Unfortunately, a recent Cochrane review suggested that it is unclear whether the wearing of surgical masks by OR personnel during "clean" surgery either increases or reduces the risk of SSIs.[54] Based on this review, there are no data available to assess whether there is a benefit if a patient wears a surgical facemask. Furthermore, research is necessary to evaluate the potential benefit to having patients (and their spouses when present during initiation of neuraxial analgesia on the labor and delivery suite) wear masks during initiation of neuraxial blockade.

In summary, although we have known since 1963 that the AWE poses some risk for intraoperative bacterial transmission,[12–54] this early work provided only a theoretical risk for the occurrence of intraoperative bacterial transmission events and subsequent infection development. In all cases, suboptimal methodology failed to conclusively identify the source(s) for the causative organism of infection and transmission links or other aspects of transmission dynamics. As such, it is not surprising that infection control measures in the AWE have not historically involved targeted attenuation of intraoperative bacterial transmission events.

CONFIRMING THE HYPOTHESIS

Recently, this knowledge gap has been addressed by a newly developed model for study of intraoperative bacterial cross-contamination. This model measures the relative contribution of intraoperative bacterial reservoirs including anesthesia provider hands throughout care, patient skin surfaces, and proven representatives of the anesthesia environment, in parallel during the process of patient care, to high-risk bacterial transmission events. This approach leverages temporal association and systematic phenotypic analysis to examine the importance of bacterial reservoirs of origin, modes of transmission, portals of entry, and phenotypic strain characteristics in the incidence of transmission and subsequent infection development. Use of this model has helped to clarify the magnitude and importance of intraoperative bacterial transmission events in the intraoperative arena.[55–58]

In a study published in *Anesthesiology* in 2008,[55] this model for study of bacterial cross-contamination was used to examine the magnitude, rate, and implications of intraoperative bacterial transmission events involving the AWE during the first case of the day in 61 operative suites at a single medical center. Transmission of bacterial organisms, including vancomycin-resistant *Enterococcus* (VRE), to IV stopcock sets was shown to occur in 32% of ORs, thereby solidifying and expanding on results characterizing the risk of bacterial contamination of intravascular devices used in the AWE.[23–26]

Bacterial contamination of the AWE occurred very early (in as little as 4 minutes) and was also shown to increase significantly at the case conclusion with a mean difference of 115 colonies per surface area sampled ($P < 0.001$). Highly contaminated work areas (at a threshold of >100 colonies per surface area sampled) increased the odds of stopcock contamination by 4.7 ($P = 0.011$; Fig. 1), with the association remaining significant despite adjustment for multiple potentially confounding variables.[55] These results firmly established the relationship between AWE contamination and high-risk bacterial transmission events suggested by earlier work.[12–18]

Stopcock contamination events have been associated with increased patient mortality. Using pulsed-field gel electrophoresis techniques, the stopcock set has been shown to serve as an independent route to infection with introduction of VRE into the internal lumen of the patient IV stopcock set followed by VRE bacteremia and ultimately death from septic shock.[55] This work was supportive of earlier articles that similarly suggested that bacterial transmission events could lead to an increased patient morbidity.[12–52] The authors concluded that the next step was to further address bacterial transmission dynamics by examining the source and the reservoir(s) for these important transmission events.[55]

One of the sources investigated was anesthesia provider hands at baseline, before initiation of patient care.[56] The first and second operative cases in each of 92 ORs were initially randomly selected for observation with 82 paired samples included in the final analysis. Biotype analysis and temporal association were used to compare transmitted organisms to anesthesia provider hand reservoir isolates obtained before the start of each case. There were 2 key findings from this study: (1) anesthesia provider hands are frequently contaminated with major bacterial pathogens before patient care, and (2) the contaminated hands of anesthesia providers before patient care serve as a significant source of patient environmental and stopcock set contamination in the OR. Thus, this study provided the next step beyond early work showing that the hands of anesthesia providers are contaminated with bacterial organisms[18] by providing microbiological confirmation of the involvement of the anesthesia provider hand reservoir in high-risk bacterial transmission events to patient IV stopcock sets.

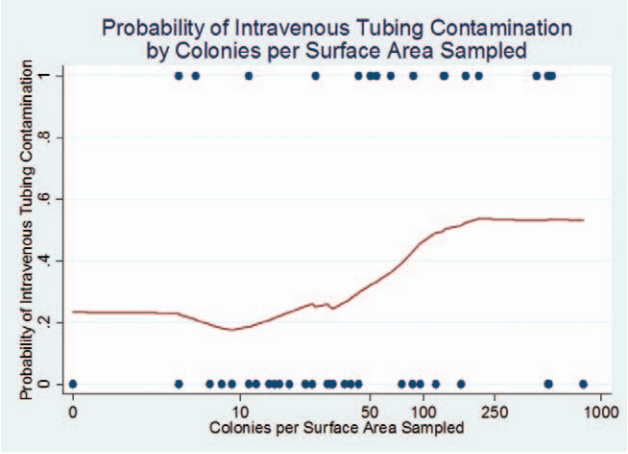

Figure 1. Increasing contamination of the surrounding patient environment is associated with an increased risk of stopcock contamination. A threshold of 100 colony-forming units of environmental contamination for increased risk of stopcock contamination is identified.

In a third study, the investigators sought to examine additional intraoperative reservoirs of transmission, to examine modes of transmission (processes by which bacteria get transmitted to susceptible patients), pathogen strain characteristics, and to further confirm the open-lumen stopcock set, a high-risk intravascular device, as an important portal for bacterial entry to the host.[57] In this multicenter study, 274 ORs were observed across 3 major academic medical centers, with the first and second cases of the day in each OR (548 surgical cases) studied in series to identify within- and between-case modes for transmission events. All patients were followed for 30 days for the development of infection and all-cause mortality. The authors verified that intraoperative bacterial transmission was a problem across 3 separate medical centers, with frequent contamination of high-risk intravascular devices (open-lumen stopcock sets) coupled with poor standard cleaning practices, including lack of active decontamination. Furthermore, multiple intraoperative bacterial reservoirs relevant to the AWE (e.g., the patient, provider hands, and the environment) contributed independently to the rate of bacterial contamination of patient open-lumen IV stopcock sets, yet were linked by residual contamination of the environment occurring despite routine cleaning between surgical cases occurring sequentially in the same OR environment. Of the 548 cases, the most frequent mode of transmission was found to involve transmission events originating from reservoirs within the same surgical case (within-case transmission), but an alarmingly high rate (approximately 30%) of transmission events linked to reservoirs from a prior surgical case (between-case transmission) was also confirmed. In 60% of between-case transmission events, residual contamination of the AWE occurring between cases after routine cleaning was implicated. All 3 reservoirs (anesthesia provider hands, the patient, and the patient environment) were shown to contribute to between-case (64% environment, 14% patient, and 21% providers) and within-case (47% environment, 23% patient, and 30% providers) transmission events. Thus, these results supported the earlier relation between increased probability of stopcock contamination occurring at a threshold of approximately 100 colony-forming units (CFUs).[55] Bacterial contamination of these devices was yet again associated with an increased patient morbidity and mortality, thereby supporting the earlier conclusion that the open-lumen stopcock sets and intravascular devices served as important portals of bacterial entry.[55]

Each intraoperative bacterial reservoir was also found to harbor a unique subset of bacterial pathogens known to cause HCAIs, for example, patient linked with *S aureus*, provider hands linked with *Enterococcus* and Gram-negative organisms, and the environment the unifying link between the patient and provider reservoirs.[57] Importantly, it was confirmed by pulsed-field gel electrophoresis, a validated typing method,[57] that at least 30% (6 of 20) of 30-day postoperative HCAIs were derived from these intraoperative bacterial reservoirs. Of great concern, provider hands were confirmed as vectors for transmission in 27% (12 of 44) of between-case and within-case stopcock transmission events.[57]

This work also led to the subsequent identification of bacterial pathogen strain characteristics facilitating increased resistance to preventive measures, and therefore intraoperative bacterial transmission and subsequent infection development.[58] In this study, 2 *S aureus* phenotypes were found to explain the majority of intraoperative *S aureus* transmission events. Furthermore, patients with prior exposure to the hospital ward or intensive care unit environments were at increased risk of colonization with this virulent pathogen. These findings are important because they may provide some insight into the success of Bode et al.[59] in reducing SSIs with patient decolonization efforts. Bode et al. enrolled patients from the hospital ward and demonstrated that patient decolonization significantly reduced SSIs.

These more recent studies together have addressed several important aspects of the pathophysiology of postoperative HCAI development, including the relative importance of various reservoirs in bacterial transmission events, various modes of transmission (between and within cases), pathogen strain characteristics, and an important portal of entry, the IV stopcock set.[55–58] In doing so, they have supported earlier work describing a theoretical risk of contamination by subsequently confirming the occurrence, magnitude, and importance of bacterial transmission events arising from the AWE. Collectively, these early and more recent findings strongly suggest that intraoperative bacterial transmission events arising from the AWE occur, that they occur rapidly, are of significant magnitude and are associated with increased patient morbidity and mortality. Furthermore, as illustrated by the interventions summarized in Table 1, bacterial transmission dynamics involving confirmed AWE transmission events strongly suggest that to see a significant reduction in intraoperative bacterial transmission and subsequent HCAI development, a multimodal approach targeting attenuation of provider hand, environmental, and patient skin surface reservoirs, in parallel during the process of patient care, is indicated.[57] Finally, given the association of bacterial contamination of patient IV stopcock sets with increased patient morbidity and mortality, improvements in intravascular catheter/stopcock set design and handling are also indicated. Figure 2 illustrates a multimodal approach for improvements in intraoperative infection control.

BUILDING AN EVIDENCE-BASED MULTIMODAL APPROACH

Targeting Anesthesia Provider Hand Contamination

Several studies have addressed the barrier of anesthesia provider hand contamination, designed to test the effectiveness of a personalized body-worn dispenser in improving intraoperative hand hygiene by anesthesia providers. The dispenser is capable of recording individual hand decontamination events by providers, dispenses 70% alcohol gel, includes an embedded computer chip to allow continuous monitoring, and provides an audible reminder to perform hand hygiene. In 1 study,[60] 111 ORs (58 control and 53 device-assigned operative suites) were evaluated in a controlled before and after study. Anesthesia was performed according to usual practice and bacterial transmission events were identified through the use of a previously validated protocol.[55] The implementation of the device significantly increased hourly hand decontamination events by 27-fold, reduced intraoperative transmission of pathogenic bacterial organisms to stopcock sets, reduced AWE contamination,

Table 1. Comprehensive Infection Control Program Targeting Bacterial Transmission in the Anesthesia Work Area

Intervention	Target(s)
Personalized alcohol dispenser for hand hygiene	• Independent reservoir for stopcock transmission events[56–58]
Personal feedback (hourly hand decontamination events)	• Highly transmissible and/or more virulent bacterial strains[58]
Peer pressure (group feedback)	• Augmentation of cleaning,[45,60–62] between-case transmission[56–58]
62% ethanol	• Direct microbiological links to postoperative HCAIs[57]
Environmental cleaning	• Independent reservoir for high-risk stopcock transmission events[57]
Frequency (induction and emergence)	• Critical link between patient and provider reservoirs[55–58,60,62,65]
Quality (double biocide, microfiber cloth)	• Augmentation of hand hygiene efforts[44–45,55,58,60,63]
Patient decolonization	• Independent contributor to high-risk stopcock transmission events[57]
Wide variety of surgical patients	• Primary reservoir for *Staphylococcus aureus* strain phenotype P[58]
Hospital ward or intensive care unit exposure	• Augmentation of hand hygiene and cleaning efforts[55–58,60,63]
S aureus, Gram-negative, *Enterococcal* pathogens	• A leading cause of 30-day postoperative HCAIs[57]
Vascular care bundle (open-lumen stopcock sets)	• Important portal for bacterial entry[55–57,70,72]
Improved design (disinfectable, needleless, closed)	• Downstream passive (in-line with current practice) safety device[72]
Improved handling (disinfection system) for syringes and hubs	• Augments patient, provider hand, and environmental cleaning efforts[55–57,63,70,72]
Infection surveillance	• Highly transmissible and/or more virulent bacterial pathogens[58]
Patient surveillance	• Patient-borne pathogens that can transmit between patients[57–59]
Environmental surveillance	• A potent transmission vehicle and the overall bacterial milieu[55–58,60,62,65]
Provider surveillance	• Improved education, hand hygiene, glove usage, and signage[45,57, 66,67,75]

HCAIs = health care–associated infections.

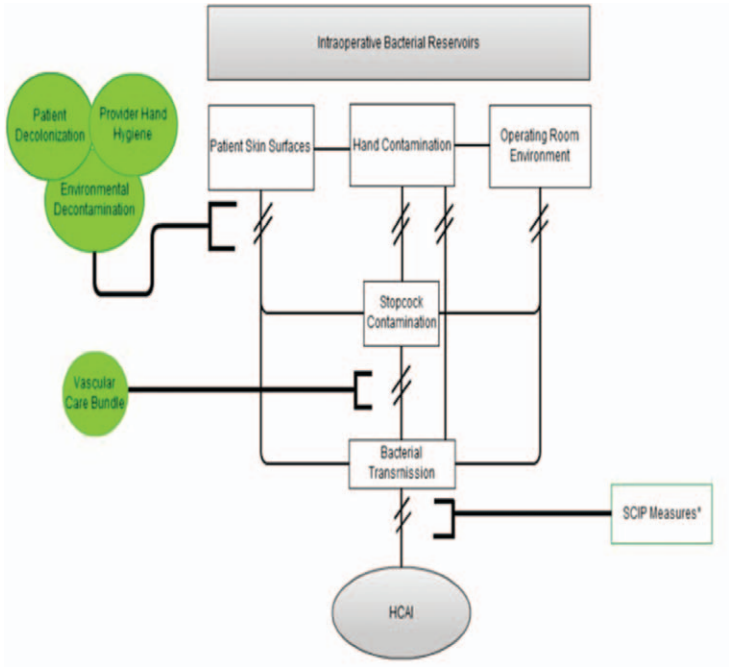

Figure 2. An evidence-based multimodal approach for improvements in intraoperative infection control. The upstream bacterial inoculum including provider hand, environmental, and patient skin contamination should be addressed in parallel in addition to downstream improvements in intravascular catheter design and handling. This program should be initiated along with surgical care improvement project measures to maximally attenuate the bacterial transmission and to attempt to optimize the host. HCAI = health care–associated infection; SCIP = Surgical Care Improvement Project.

and reduced 30-day postoperative HCAIs. This study helps to solidify the links between hand contamination, environmental contamination, high-risk stopcock contamination, and subsequent infection development. These results were verified in a subsequent study performed in the intensive care unit where use of the same device was associated with a significant decrease in the number of ventilator-associated pneumonias; from 6.9 to 3.7 ventilator-associated pneumonias/1000 ventilator days.[61]

Targeting Residual Environmental Contamination

There is clearly room for improvement in reducing contamination of the AWE[45,62] especially as relates to scrub-the-hub protocols.[63] Infection risk related to anesthesia providers may be related to hand hygiene[45,56] and may even be related to scrubs and jackets worn by anesthesia providers.[64,65] Recent work using a fluorescent marker[66] has identified glove use as a potentially beneficial practice, suggesting that the use of double gloves at the time of induction of anesthesia, with removal of the outer set after completion of induction but before touching the anesthesia cart or keyboard, could immediately reduce some of the workspace contamination that currently occurs.[67] This study has several implications, including a potential mechanism to avoid the increased risk of stopcock contamination with glove use.

Another study involved a combination of video observational and bacterial transmission tracking conducted to identify the rate and time at which the environment becomes contaminated during a procedure.[68] The authors found that bacterial contamination of high-risk objects within the AWE reached the previously determined threshold for increased probability of stopcock contamination at only 2 time points, induction and emergence of anesthesia (Fig. 3), periods that correlated with nadirs in hand hygiene compliance (Fig. 4). This indicates that an environmental cleaning strategy might be most effective when used during the times immediately after anesthesia induction and emergence.

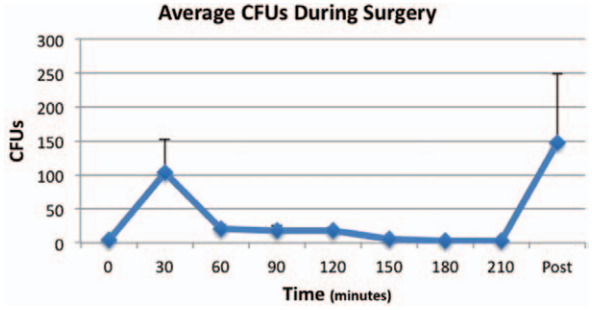

Figure 3. Bacterial contamination of the anesthesia environment reaches a peak during the 2 busiest phases of anesthesia care, induction and emergence of anesthesia. CFUs = colony-forming units.

Synthesis of the available literature pertaining to the personalized, body-worn alcohol dispenser suggests that the superior efficacy of the hand hygiene device may be derived from a simple concept; anesthesia providers could conveniently disinfect their hands during the complex phases of anesthesia, including induction and emergence. A recently published study compared the behavior of anesthesia providers during induction and maintenance of anesthesia in the OR. They reported that the frequency of contact with both the environment and patients was significantly higher during induction as compared with maintenance of anesthesia.[69] These more active periods are linked to increased probability of open-lumen IV stopcock contamination due to residual environmental contamination reaching a necessary threshold. Anesthesia providers cannot easily wash their hands during these high-risk periods without the immediate availability of hand sanitizer. This is further validated by data suggesting that placement of hand sanitizer in a more convenient location on the anesthesia machine increased the frequency of hand hygiene among anesthesia providers.[70] This argues strongly for the development and implementation of improvement

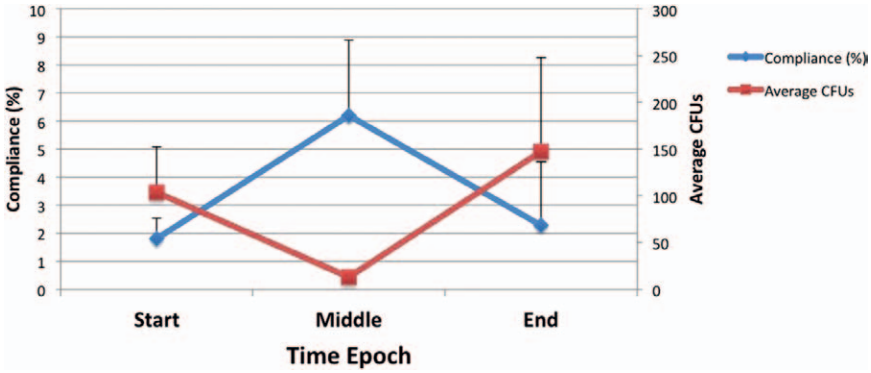

Figure 4. Anesthesia provider hand hygiene compliance reaches a nadir during induction and emergence of anesthesia. CFUs = colony-forming units.

strategies uniquely suited for the barriers of specific hospital environments.

Improved Patient Screening and Decolonization

As previously discussed, patients frequently arrive to the intraoperative environment with skin surfaces colonized with major bacterial pathogens that contribute significantly to bacterial contamination of patient IV stopcock sets, events associated with increased patient morbidity and mortality.[3,55,57] As such, improvements in patient decolonization strategies may be indicated. As the Perioperative Surgical Home model of care expands, these activities may belong in the domain of the anesthesiologist.

Because recent work suggests that more virulent bacterial organisms are associated with patients exposed to the hospital ward,[58] future research should be directed toward assessing the efficacy of improved screening and decolonization of patients exposed to the hospital ward, before OR entry, on 30-day postoperative SSI reduction.

Targeting Improved Intravascular Care Handling and Design

Downstream catheter care (including injection ports) is another important barrier to intraoperative infection control because many primary and secondary lumens of open-lumen intravascular devices have been shown to be contaminated with pathogenic bacteria.[71] An important question to consider is the relative importance of catheter design versus handling in bacterial contamination of intravascular catheters. In vitro work has concluded that catheter design supersedes handling technique.[72] This stands in contrast to work conducted in the clinical environment. In a randomized, controlled, ex vivo study, the relative incidence of bacterial injection by anesthesia providers after induction of anesthesia and patient stabilization was compared for a closed, disinfectable stopcock incorporating a split septum, with and without disinfection before injection, and the conventional open-lumen stopcock set.[73] A key finding of the study was that disinfection of the closed catheter before injection was absolutely necessary. Simple introduction of the closed system in place of the open lumen without disinfection actually increased the risk of bacterial injection (from 3.2% in the conventional design to 4% for the nondisinfected closed stopcock). However, when disinfected, the incidence of effluent bacterial contamination was 0% (0 of 152) and was associated with an absolute risk reduction of 3.2% (95% confidence interval [CI], 0.5%–7.4%) of bacterial injection. Thus, work in the clinical environment suggests that catheter handling supersedes design. The difference in these studies may be explained by the size of the bacterial inoculum before bacterial injection. The bacterial inoculum leading to contaminated effluent in the OR was estimated at 50,000 CFU,[73] whereas prior in vitro work evaluated the rates of bacterial injection after initial contamination with <100 CFU.[72] It may be that the split septum design fails under more heavily contaminated conditions occurring in the clinical environment, highlighting the importance of disinfection before injection to reduce the size of the bacterial inoculum.

In a follow-up clinical trial,[71] the efficacy of 2 interventions designed to augment anesthesia provider disinfection of intravascular devices and syringe tips, the HubScrub and DOCit (PSI Medical Catheter Care, Erie, PA), respectively, was investigated. The HubScrub is designed to clean needleless connectors, including open systems, with 70% isopropyl alcohol before access and to provide interim protection from bacterial transmission during subsequent use. Similarly, the DOCit is a device designed to simultaneously scrub the interior and exterior contact surface of luer connectors on IV tubing and syringes with 70% isopropyl alcohol, providing direct decontamination and interim protection from bacterial transmission to the luer connector of IV tubing and syringes. Conventional red caps are designed to close open-lumen stopcock systems at present. The HubScrub and DOCit are intended to be used together as part of a catheter care station attached to the IV pole in the OR and thus facilitating anesthesia provider access.

When implemented in the clinical environment, the incorporation of these 2 devices was associated with a significant reduction in intraoperative bacterial contamination of open-lumen IV stopcock sets (OR, 0.79; 95% CI, 0.63–0.98; $P = 0.034$) and a reduction in the combined incidence of 30-day postoperative infections and phlebitis (OR, 0.589; 95% CI, 0.353–0.984; $P = 0.040$) when adjusted for procedural covariates. The distribution of HCAIs involved 27% wound (deep and/or superficial), 8% bloodstream, 8% deep surgical site, 12% respiratory, and 46% catheter-associated urinary tract infections.[71] Thus, this study demonstrated that stopcock contamination was modifiable, and it closed the loop on the importance of the stopcock set as an important portal for bacterial entry.

CONCLUSIONS

HCAIs are of great concern across all health care arenas, including the intraoperative environment. The development of 30-day postoperative infections has been directly linked to bacterial transmission events originating from AWE reservoirs. As such, in addition to the following national guidelines adopted to reduce the risk of infection development during neuraxial procedures,[74] anesthesia providers should consider implementation of measures designed to target attenuation of bacterial transmission occurring during the routine administration of all anesthetics. Evidence suggests that a multimodal approach targeting improvements in intraoperative hand hygiene, patient screening and decolonization, and environmental decontamination, as well as improvements in intravascular handling and design, may reduce the risk of postoperative infections. Future work should evaluate the efficacy of the combined, evidence-based strategies as illustrated in Table 1 and described in this review.

DISCLOSURES

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Contribution: This author helped write the manuscript.
Attestation: Randy W. Loftus approved the final manuscript.
Name: Matthew D. Koff, MS, MD.
Contribution: This author helped write the manuscript.
Attestation: Matthew D. Koff approved the final manuscript.
Name: David J. Birnbach, MD, MPH.
Contribution: This author helped write the manuscript.
Attestation: David J. Birnbach approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon.).

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Transmission Dynamics of Gram-Negative Bacterial Pathogens in the Anesthesia Work Area

Randy W. Loftus, MD,* Jeremiah R. Brown, MS, PhD,† Hetal M. Patel, BS,* Matthew D. Koff, MD, MS,* Jens T. Jensen, MS,* Sundara Reddy, MD,‡ Kathryn L. Ruoff, PhD,* Stephen O. Heard, MD,§ Thomas M. Dodds, MD,* Michael L. Beach, MD,* and Mark P. Yeager, MD*

BACKGROUND: Gram-negative organisms are a major health care concern with increasing prevalence of infection and community spread. Our primary aim was to characterize the transmission dynamics of frequently encountered gram-negative bacteria in the anesthesia work area environment (AWE). Our secondary aim was to examine links between these transmission events and 30-day postoperative health care-associated infections (HCAIs).

METHODS: Gram-negative isolates obtained from the AWE (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing). The top 5 frequently encountered genera were subjected to antibiotic disk diffusion sensitivity to identify epidemiologically related transmission events. Complete multivariable logistic regression analysis and binomial tests of proportion were then used to examine the relative contributions of reservoirs of origin and within- and between-case modes of transmission, respectively, to epidemiologically related transmission events. Analyses were conducted with and without the inclusion of duplicate transmission events of the same genera occurring in a given study unit (first and second case of the day in each operating room observed) to examine the potential effect of statistical dependency. Transmitted isolates were compared by pulsed-field gel electrophoresis to disease-causing bacteria for 30-day postoperative HCAIs.

RESULTS: The top 5 frequently encountered gram-negative genera included *Acinetobacter*, *Pseudomonas*, *Brevundimonas*, *Enterobacter*, and *Moraxella* that together accounted for 81% (767/945) of possible transmission events. For all isolates, 22% (167/767) of possible transmission events were identified by antibiotic susceptibility patterns as epidemiologically related and underwent further study of transmission dynamics. There were 20 duplicates involving within- and between-case transmission events. Thus, approximately 19% (147/767) of isolates excluding duplicates were considered epidemiologically related. Contaminated provider hand reservoirs were less likely (all isolates, odds ratio 0.12, 95% confidence interval 0.03–0.50, $P = 0.004$; without duplicate events, odds ratio 0.05, 95% confidence interval 0.01–0.49, $P = 0.010$) than contaminated patient or environmental sites to serve as the reservoir of origin for epidemiologically related transmission events. Within- and between-case modes of gram-negative bacilli transmission occurred at similar rates (all isolates, 7% between-case, 5.2% within-case, binomial *P* value 0.176; without duplicates, 6.3% between-case, 3.7% within-case, binomial *P* value 0.036). Overall, 4.0% (23/548) of patients suffered from HCAIs and had an intraoperative exposure to gram-negative isolates. In 8.0% (2/23) of those patients, gram-negative bacteria were linked by pulsed-field gel electrophoresis to the causative organism of infection. Patient and provider hands were identified as the reservoirs of origin and the environment confirmed as a vehicle for between-case transmission events linked to HCAIs.

CONCLUSIONS: Between- and within-case AWE gram-negative bacterial transmission occurs frequently and is linked by pulsed-field gel electrophoresis to 30-day postoperative infections. Provider hands are less likely than contaminated environmental or patient skin surfaces to serve as the reservoir of origin for transmission events. (Anesth Analg 2015;120:819–26)

From the *Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; †The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; ‡Department of Anesthesiology, University of Iowa Hospitals and Clinics, Iowa City, Iowa; and §Department of Anesthesiology, UMass Memorial Medical Center, Worcester, Massachusetts.

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Address correspondence to Randy W. Loftus, MD, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756. Address e-mail to randy.w.loftus@hitchcock.org.

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Gram-negative pathogens contribute to the hospital-wide problems of health care-associated infections (HCAIs) and bacterial resistance.[1–3] They are associated with surgical site,[1] central line–associated,[4,5] and primary blood stream infections (BSIs)[6]; postoperative meningitis and epidural abscesses[7]; and a multitude of infections occurring in complex health care settings such as the intensive care unit.[8,9] These organisms have evolved to develop new and important mechanisms of antibiotic resistance and have extended beyond the acute health care settings to healthy members of the community.[10,11] In fact, the family Enterobacteriaceae (e.g., *Citrobacter*, *Enterobacter*, *Serratia*, *E coli*, *Klebsiella*, *Proteus*, *Shigella*, and others) has become a worldwide public health

concern associated with increased morbidity, mortality, and health care costs.[11] Because bacterial transmission is a root cause of HCAI development, it is important that we understand and attenuate the spread of these important pathogens across all health care arenas, including the operating room environment. The primary aim of this study was to identify and examine transmission dynamics (reservoirs of origin and modes of transmission) involving frequently encountered gram-negative bacterial organisms in the anesthesia work area environment (AWE). The secondary aim was to examine links between these transmission events and subsequent 30-day postoperative HCAIs.

METHODS

General Approach

A prospective, randomized, observational study was previously conducted over 12 consecutive months (from March 2009 to February 2010) at Dartmouth-Hitchcock Medical Center (DHMC) in New Hampshire, the University of Iowa Hospitals and Clinics in Iowa, and the UMass Memorial Medical Center in Massachusetts. The primary aim of this prior study was to characterize the frequency and implications of overall bacterial transmission events to intravascular devices in the intraoperative arena.[12] A model for study of intraoperative bacterial cross-contamination was used to identify bacterial isolates and transmission events involving AWE reservoirs across 274 operating rooms.[12] The distribution of number of study units and provider encounters across the 3 study sites is shown in Figure 1. The study unit was a case pair, with the first and second case of the day in each room observed to evaluate bacterial transmission occurring within and between operative cases (Fig. 2). Measured bacterial reservoirs included provider hands throughout care (before, during, and after), patient sites (nasopharynx and axilla) after induction of anesthesia, and baseline and case end environmental cultures. These sites were assessed in parallel during the process of patient care.[12] Health care provider hand hygiene, patient decolonization, and environmental cleaning processes were not altered during the study period, and aseptic practice procedures at each site were tracked and recorded.[12] A waiver for informed consent was obtained after approval at each study site from the respective IRBs for the protection of human subjects.[12] Additional approval was obtained from the Committee for Protection of Human Subjects at DHMC for the current study.

Evaluation of Gram-Negative Transmission Dynamics (Primary Aim)

In the prior study, >6000 bacterial pathogens were isolated and archived for later analysis including *Staphylococcal*,

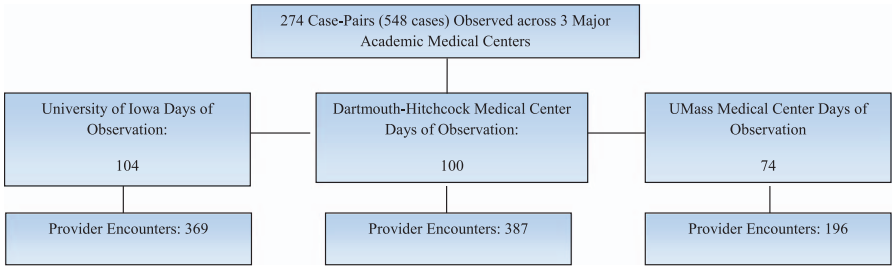

Figure 1. A summary of operating room number, days observed, and number of providers stratified by study site.

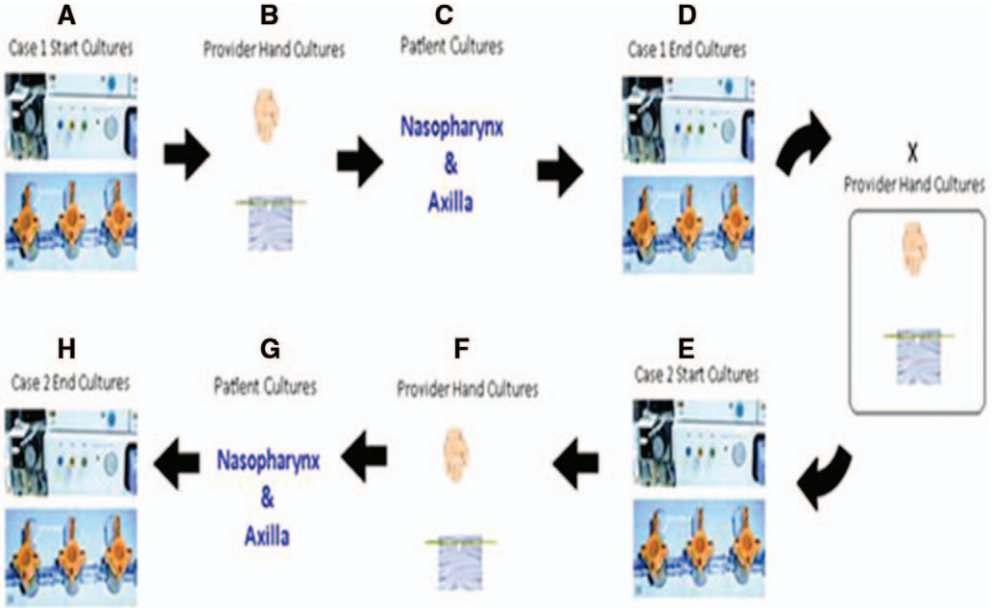

Figure 2. Schematic of culture sampling sequence. Culture samples were collected sequentially (A → H) from the operative environment (adjustable pressure-limiting valve and agent dial), patient IV tubing, provider hands, and the patient nasopharynx/axilla. Provider hands were also intermittently cultured throughout the case and upon provider return to the operating room following an absence during the case (X).

Enterococcal, and gram-negative organisms.[12] The primary focus of the current analysis is gram-negative bacilli. The experimental model used to obtain gram-negative isolates included reservoirs that could be potentially addressed by improvements in aseptic/disinfection practice conducted or facilitated by anesthesia providers, while also addressing the potential role of other more distal reservoirs, such as the patient's rectum, when organisms from distal reservoirs are transmitted to more proximal reservoirs contacted by the anesthesia provider. Rectal colonization with bacterial organisms commonly occurs in conjunction with skin colonization,[13] and the antecubital fossa and blood pressure cuff, often in contact with the axilla, have been shown to be significant predictors of bacterial transmission in colonized patients.[14] Thus, the patient sites measured in the model served to effectively measure the patient's contribution to transmission/infection involving gram-negative pathogens.[12–14]

A systematic analysis of gram-negative isolates (Fig. 3) was used to examine intraoperative gram-negative transmission dynamics. All previously archived major bacterial pathogens were classified according to colony morphology, gram stain, and simple rapid tests. Next, 274 case pairs (548 cases) were reviewed for evidence of possible gram-negative transmission defined by the presence of a gram-negative isolate in 2 or more reservoir sites across the case pair. Bacterial phenotype was then identified via use of a commercially available bioMerieux Analytical Profile Index (API) identification system (Marcy 1'Etoile, France) that generates a 7-digit profile number based on positive or negative reactions in a minimum of 20 phenotypic tests.[15] Temporal associations (the same class of pathogen isolated in >1 site surveyed in the same operating room on the same day at the same time with the same API phenotype) were then used to identify possible transmission events occurring within and between operative cases. Possible transmission events were further evaluated by disk diffusion antibiotic susceptibility testing analysis (antibiotic susceptibility profiling-same response to 12 commonly used prophylactic antibiotics potentially effective against gram-negatives, Appendix) to identify epidemiologically related transmission events. Reservoir(s) of origin and modes (within- and/or between-case transmission) of transmission were then characterized for the top 5 frequently encountered genera.

Definitions

Transmission event: The presence of a bacterial pathogen in a reservoir during the process of patient care that was not present in baseline cultures at case start. *Reservoir of origin: Provider origin* of a transmission event was assumed if the transmitted isolate was identical to an isolate from the hands of 1 or more anesthesia providers but not found in the patient or environmental reservoirs earlier in the sampling sequence. *Environmental origin* of contamination was assumed if the transmitted isolate was identical to an isolate from the environment sampled at baseline or at case end but not isolated either from the hands of providers or from the patient reservoirs earlier in the sampling sequence. The hands of all providers who would potentially interact with the anesthesia environment were sampled at baseline. *Patient origin* of contamination was assumed if the transmitted isolate was identical to an isolate from the patient sampled at case start but was not isolated from provider hands or environmental reservoirs earlier in the sampling sequence. *Epidemiologically related transmission events:* Two or more major bacterial pathogens present in >1 intraoperative site in a case series that were identical according to class of pathogen, standard microbiological tests, API, antibiotic susceptibility, and temporal association (appropriate reservoir of exposure and timing of the event occurring in the same operating room case pair, on the same operating day, during procedures whereby patients were undergoing care in the same environment, and with the same set of health care providers measured). *Mode of transmission*: Transmission occurring within or between operative cases. *Statistically dependent transmission events*: In study units where >1 within- and/or between-case transmission event involving the same bacterial genera for a study unit occurred, statistical dependence was assumed. As described further in the statistical methods, the primary analysis included all transmission events, statistically dependent or independent. For the exploratory analysis, duplicate within- and between-case transmission events were deleted to examine the sensitivity of the analyses to statistical dependence.

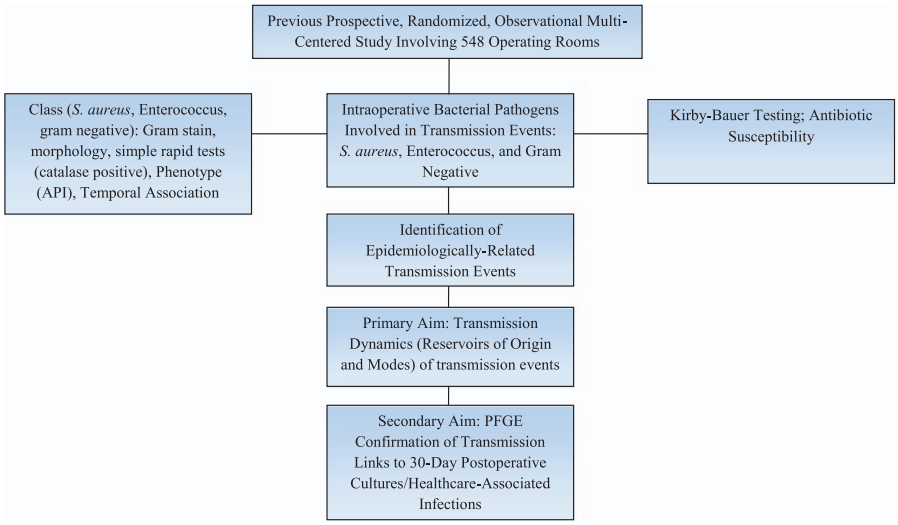

Figure 3. Systematic analysis of intraoperative gram-negative transmission. PFGE = pulsed-field gel electrophoresis; API = analytical profile indexing.

Evaluation for Microbiological Links Between Gram-Negative Transmission Events and 30-Day Postoperative Infections (Secondary Aim)

Epidemiologically related transmission events were compared to the causative organism of 30-day postoperative infections via temporal association, biotype, disk diffusion antibiotic susceptibility testing, and pulsed-field gel electrophoresis (PFGE) analysis.[16] HCAIs were defined according to National Healthcare Safety Network definitions.[17]

Demographic Information

Information pertaining to hospital site, age, sex, case 1 or case 2, ASA physical status classification, Study on the Efficacy of Nosocomial Infection Control (SENIC)[18] score (an index characterizing patient morbidity and associated with probability of postoperative HCAI development for a given patient), patient comorbidities, patient origin, patient discharge location, procedure type, and case duration of >2 hours was collected.

Statistical Analysis

The primary aim was to examine the primary reservoir of origin and mode of transmission for all epidemiologically related transmission events involving frequently encountered gram-negative pathogens in the AWE. An analysis involving deletion of duplicate transmission events (>1 within- and/or between-case transmission event involving the same bacterial genera for a study unit, the first and second case of the day) was also conducted to examine the potential effect of statistical dependence (Table 1).

For both analyses, reservoirs of origin were compared via forward and reverse stepwise multivariable logistic regression analysis models that included adjustment for potentially confounding site and exposure variables. For the analysis involving all isolates, significant variables from forward stepwise included discharge location to same day, case duration >2 hours (a component of SENIC score),[18] and case (first or second case of the day), while significant variables from reverse stepwise included discharge location to same day, case, orthopedic procedure, and SENIC >2. The final model for all isolates included all variables from forward and reverse regression at an α of ≤ 0.10, which were discharge location and case duration >2 hours, as well as hospital site. All first-order interactions were assessed, with only an interaction for discharge location and site 2 significant. Table 2a shows the results of the multivariable analysis for all isolates with and without the interaction term. An α level of $P < 0.05$ was defined as statistically significant. Table 2b shows the results of the analysis involving deletion of duplicate transmission events. Forward and backward stepwise logistic regression showed that case, duration >2 hours, and discharge location were significant, and they remained in the final model. There were no significant interaction terms. An α level of $P < 0.05$ was defined as statistically significant.

Intergenera differences in modes of transmission for the top 5 most frequently encountered genera were compared via Fisher exact test. To test whether transmission was equally likely by within- and between-case modes of transmission, a 2-sided binomial was used to test whether the proportion of total within-case events was 50% as a fraction of all transmissions, in which the transmission was defined as either within-case or between-case but not both. Analyses involved all isolates and deletion of duplicates, and the results were adjusted for multiple comparisons by multiplying the P value by 2. An α level of $P < 0.05$ was defined as statistically significant (Table 3).

The secondary aim was to examine links between transmission events and 30-day postoperative HCAIs. Gram-negative bacterial links to 30-day postoperative HCAIs were identified and reported qualitatively (Table 4).

Table 1. Gram-Negative Transmission Events

Species (spp.)	Possible transmission events (*N*), total = 945	Percent possible transmission events	Confirmed transmission events (*N*)	Percent confirmed transmission events
Acinetobacter	327	34.6	65	19.88
Pseudomonas	151	15.98	40	26.49
Brevundimonas	117	12.38	23	19.66
Enterobacter	111	11.75	29	26.13
Moraxella	61	6.46	10	16.39
Raoultella	35	3.7	4	11.43
Serratia	27	2.86	8	29.63
Klebsiella	22	2.33	4	18.18
Stenotrophomonas	22	2.33	4	18.18
Pantoea	20	2.12	6	30
Sphingomonas	11	1.16	3	27.27
Wautersia	6	0.63	2	33.33
Photobacterium	5	0.53	0	0
Salmonella	5	0.53	0	0
Pasturella	4	0.42	0	0
Psychrobacter	4	0.42	0	0
Proteus	3	0.32	2	66.67
Rhizobium	3	0.32	2	66.67
Acaligenes	3	0.3	0	0
Cedecea	2	0.21	0	0
Ewingella	2	0.21	0	0
Rahnella	2	0.21	0	0
Ralstonia	2	0.21	2	100
Total	945	100	204	21.59

Table 2. Reservoir of Origin Analysis of All Isolates, Multivariable Analysis, Deletion

Reservoir of Origin Analysis of All Isolates				Reservoir of Origin Multivariable Analysis, Deletion[a]			
Without interaction term				***Without interaction term***			
Transmission-any[b]	OR	95% CI	*P* value	Transmission-any[b]	OR	95% CI	*P* value
Reservoir isolate				Reservoir isolate			
Hand[c]	0.12	0.03–0.50	0.004	Hand[c]	0.05	0.01–0.49	0.010
Patient	0.64	0.14–2.96	0.569	Patient	0.29	0.03–2.96	0.295
Environment	1.94	0.67–5.59	0.219	Environment[d]			
Case duration >2 h	0.65	0.44–0.95	0.027	Case duration >2 h	0.60	0.40–0.90	0.015
Discharge location[e]	0.48	0.30–0.75	0.001	Discharge location[e]	0.42	0.26–0.68	0.000
Site 2	2.02	1.21–3.39	0.008	Site 2	2.25	1.31–3.87	0.003
Site 0	1.84	0.99–3.44	0.055	Site 0	2.15	1.12–4.11	0.022
				Case 2	1.44	0.98–2.09	0.060
With interaction term							
Transmission-any[b]	OR	95% CI	*P* value				
Reservoir isolate							
Hand	0.13	0.03–0.52	0.004				
Patient	0.65	0.14–2.96	0.578				
Environment	1.8	0.63–5.18	0.275				
Case duration >2 h	0.63	0.43–0.93	0.019				
Discharge location[e]	1.02	0.47–2.23	0.955				
Site 2	2.02	1.33–3.78	0.002				
Site 0	1.23	0.59–2.58	0.581				
Interaction discharge location	0.32	0.12–0.82	0.018				

OR = odds ratio; CI = confidence interval; OR = operating room.

[a]Isolates involving duplicate within- or between-case transmission events in a study unit (first and second case of the day in each operating room observed) removed from the analysis.

[b]Within-case or between-case.

[c]The lack of concordance for the OR and *P* values for the with- and without-duplicate analyses is presumed to be due to removal of duplicate events when isolates are present but the inability to remove corresponding controls when isolates are not present.

[d]Omitted due to collinearity.

[e]To same day holding.

Table 3. Mode of Transmission for Frequently Encountered Gram-Negative Genera

	All isolates							
Mode transmission	***Acinetobacter* (*N* = 327)**	***Enterobacter* (*N* = 111)**	***Brevundimonas* (*N* = 117)**	***Moraxella* (*N* = 61)**	***Pseudomonas* (*N* = 151)**	**Total number of isolates (*N* = 767)**	***P* value,[a] Fisher exact test**	***P* value,[b] binomial**
	N TE	N TE	N TE	N TE	N TE	N (%) TE	0.004	0.176
Within-case	15	6	14	1	5	41 (5.2)		
Between-case	20	12	2	4	16	54 (7.0)		
	Excluding duplicates							
Mode transmission	***Acinetobacter* (*N* = 321)**	***Enterobacter* (*N* = 107)**	***Brevundimonas* (*N* = 109)**	***Moraxella* (*N* = 61)**	***Pseudomonas* (*N* = 150)**	**Total number of isolates (*N* = 748)**	***P* value,[a] Fisher exact test**	***P* value,[b] binomial**
	N TE	N TE	N TE	N TE	N TE	N (%) TE	0.096	0.036
Within-case	11	4	7	1	5	28 (3.7)		
Between-case	18	9	1	4	15	47 (6.3)		

TE = Transmission Event.

[a]Intergenera comparison of the proportion of within- and between-case transmission events (TE) via Fisher exact test.

[b]Two-sided binomial to test whether the proportion of total within-case events was 50% as a fraction of all transmissions, in which the transmission was defined as either within-case or between-case but not both.

Table 4. Intraoperative Transmission Links to Patient Cultures and HCAI Association

Organism	Hospital site	Patient culture source	Possible transmission links	PFGE confirmed link to culture	Temporal association of link	HCAI
Enterobacter aerogenes	1	Sputum	Attending physician hand	Yes	Provider to patient	Yes
Proteus mirabilis	0	Urine patient case 1	Patient nasopharynx 2nd case	Yes	Patient to patient	Yes
Serratia liquefaciens	0	Sputum	Patient nasopharynx 2nd case	Yes	Patient to self	Yes

HCAI = health care-associated infection; PFGE = pulsed-field gel electrophoresis.

Sample Size

All gram-negative isolates obtained during the prospective, randomized, observational study previously conducted over 12 consecutive months (from March 2009 to February 2010) at DHMC in New Hampshire, the University of Iowa Hospitals and Clinics in Iowa, and the UMass Memorial Medical Center in Massachusetts were used in this analysis.

RESULTS

Gram-negative isolates (N = 2682) were obtained from 1448 AWE reservoirs and a subset (N = 945) identified as possible transmission events. *Acinetobacter*, *Pseudomonas*, *Brevundimonas*, *Enterobacter*, and *Moraxella* genera accounted for 81% (767/945) of possible transmission events. Twenty-two percent (167/767) of all isolates were considered epidemiologically related after antibiotic susceptibility testing (Table 1). There were 20 duplicates involving within- and between-case transmission events. Thus, approximately 19% (147/767) of isolates excluding duplicates were considered epidemiologically related.

Contaminated provider hands were less likely to serve as the reservoir of origin for transmission events (all isolates, odds ratio 0.12, 95% confidence interval 0.03–0.50, P = 0.004; without duplicates, odds ratio 0.05, 95% confidence interval 0.01–0.49, P = 0.010) than contaminated patient or environmental surfaces (Table 2). This difference remained significant with or without inclusion of the significant interaction term for the analysis including all isolates (Table 2a).

There were intergenera differences in modes of transmission for the analysis involving all isolates (P = 0.004), but this difference did not remain statistically significant in the analysis excluding duplicate transmission events (P = 0.096) (Table 3). Approximately 7% (54/767) and 5% (41/767) of all isolates implicated in an epidemiologically related intraoperative bacterial transmission sequence were involved in between- and within-case modes of transmission, respectively (binomial test of between- and within-case transmission event proportions, P = 0.178). After exclusion of duplicates, approximately 6% (47/748) and 4% (28/748) of isolates were involved in between- and within-case modes of transmission, respectively (binomial test of between- and within-case transmission event proportions, P = 0.036) (Table 3).

Overall, 4% (23/548) of patients suffered from HCAI development and had some intraoperative gram-negative exposure. In 8% (2/23) of those patients, gram-negative bacteria were linked by PFGE to the causative organism of infection. The organisms confirmed as causative for infection by PFGE were *Enterobacter aerogenes* and *S liquefaciens*. In the case of *E aerogenes* transmission, the infection was pneumonia, with the identified source as provider hands and the transmission location the patient. For *S liquefaciens*, the infection was pneumonia, with the identified source and transmission location as the patient. In addition, we were able to show how a patient infected and colonized with *Proteus mirabilis* in case 1 led to transmission of the organism to the nasopharynx of the second patient of the day (Table 4).

DISCUSSION

We have examined the transmission dynamics and associated morbidity of gram-negative bacteria frequently isolated from the AWE. This work may aide the development of improved intraoperative infection control measures targeting a reduction in the intraoperative spread of gram-negative pathogens.

We found that *Acinetobacter*, *Pseudomonas*, *Brevundimonas*, *Enterobacter*, and *Moraxella* genera are frequently encountered in and transmitted from anesthesia reservoirs. *Acinetobacter* spp. are considered a major problem for multidrug-resistant organisms in orthopedic military wounds[19,20] and have been identified as important pathogens in intensive care unit infections,[21] and environmental cleaning has been shown to be an important preventive measure for these organisms.[22] *Pseudomonas* spp. are major bacterial pathogens involved in ventilator-associated pneumonias,[23] BSIs,[24] and surgical site infections[25] and are associated with increased patient mortality.[23] Similarly, *Enterobacter* spp. are common pathogens involved in BSIs and respiratory and wound infections and are associated with increased morbidity and mortality.[6,11,26] In fact, *Enterobacter* spp. are an important cause of mediastinitis and sternal wound infections.[27] Though less pathogenic, *Moraxella* spp. and *Brevundimonas* have been implicated as the disease-causing pathogen for infectious complications.[28,29] Thus, all identified, frequently encountered genera in the surgical operating room have clinical relevance.

Our study of intraoperative gram-negative transmission dynamics shows that contaminated provider hands are a less potent transmission vehicle than contaminated patient or environmental sites. Thus, this work suggests that improvement measures targeting a reduction in intraoperative gram-negative transmission should consider not only the frequency of reservoir pathogen isolation but also the likelihood of transmission given reservoir contamination (potency of transmission). These results suggest that in addition to provider hands, patient and environmental reservoirs should be addressed.

This study shows that transmission of gram-negative pathogens within and between cases occurs at alarmingly high rates. Additionally, there may be significant overall and intergenera differences in the frequency of between- and within-case modes of transmission. Because there are differences in the analysis of all isolates as compared to the analysis excluding duplicates, and it is unclear which approach yields the correct answer, the finding of a significantly higher proportion of between-case transmission in the analysis excluding duplicates should be interpreted with caution. We have concluded that until further evaluation, the proportions are similar. This finding is however consistent with prior work highlighting the importance of intraoperative environmental reservoirs in transmission of bacterial pathogens,[12] and it supports the finding in this study that contaminated hands are a less potent transmission vehicle for intraoperative gram-negative pathogens. At the very least, these findings suggest that there is room for improvement in the environmental cleaning practices used during the study period which have been previously reported.[12]

Patients were followed prospectively to ascertain whether we could link transmitted organisms to infection. Using PFGE, we were able to link *E aerogenes* and *S marcescens* transmission to cases of postoperative pneumonia, and we were able to show how infected patients can bring organisms to the operating room (e.g., *P mirabilis*) that are subsequently transmitted to patients undergoing care in the same arena. In the case of *E aerogenes*, the transmission was provider hand-derived. In the case of *S marcescens* and *P mirabilis*, the transmission originated with the patient, endogenous in the case of *S marcescens* with transmission from a nonsterile site to a sterile site during instrumentation,

and exogenous in the case of *P mirabilis* transmission, likely via provider hands or the environment. Thus, prevention of all of these infections (between-case transmission in the case of *P mirabilis*) would have required addressing patient, environmental (between-case transmission), and provider reservoirs, that is, a multimodal program.

This study is limited by the insensitivity of the culture methods used, with the results likely underestimating the overall magnitude of transmission events and the subsequent development of infection. In addition, we recognize that a traditional approach to gram-negative transmission involves rectal swabs and as such, may not have identified all cases of patient colonization with gram-negative organisms. However, the intent of this study was to examine bacterial reservoirs relevant to the anesthesiologist, not to examine overall intraoperative bacterial transmission. We also recognize that a clonal relationship is not confirmed for transmission events, but our model is strengthened with an approach combining temporal association with a systematic analysis involving a series of phenotypic tests. PFGE was used to confirm clonal relationships in cases where transmission events were compared to the causative organism of infection, because this period lacked temporal association.

In conclusion, epidemiologically related gram-negative transmission events occur frequently within and between operative cases. Health care provider hands are less likely to serve as a reservoir of origin for transmission events than contaminated patient or environmental surfaces. Intraoperative gram-negative transmission events are linked to 30-day postoperative infections by PFGE. Improvement measures targeting gram-negative pathogens are indicated and should include the relative potency of reservoir transmission.

DISCLOSURES

Name: Randy W. Loftus, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Randy W. Loftus has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Jeremiah R. Brown, MS, PhD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jeremiah R. Brown has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Hetal M. Patel, BS.
Contribution: This author helped conduct the study.
Attestation: Hetal M. Patel has seen the original study data and approved the final manuscript.
Name: Matthew D. Koff, MD, MS.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Matthew D. Koff has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Jens T. Jensen, MS.
Contribution: This author helped conduct the study and analyze the data.
Attestation: Jens T. Jensen has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Sundara Reddy, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Sundara Reddy has seen the original study data and approved the final manuscript.
Name: Kathryn L. Ruoff, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Kathryn L. Ruoff has seen the original study data, and approved the final manuscript.
Name: Stephen O. Heard, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Stephen O. Heard has seen the original study data and approved the final manuscript.
Name: Thomas M. Dodds, MD.
Contribution: This author helped design the study and write the manuscript.
Attestation: Thomas M. Dodds approved the final manuscript.
Name: Michael L. Beach, MD.
Contribution: This author helped analyze the results.
Attestation: Michael L. Beach approved the final manuscript.
Name: Mark P. Yeager, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Mark P. Yeager has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

Appendix

Antibiotics tested in Kirby-Bauer analysis

Ampicillin
Cefazolin
Cefepime
Ceftazidime
Cefuroxime
Ciprofloxacin
Clindamycin
Gentamicin
Meropenem
Piperacillin/tazobactam
Sulfamethoxazole/trimethoprim
Penicillin

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The Dynamics of Enterococcus Transmission from Bacterial Reservoirs Commonly Encountered by Anesthesia Providers

Randy W. Loftus, MD,* Matthew D. Koff, MS, MD,* Jeremiah R. Brown, MS, PhD,† Hetal M. Patel, BS,* Jens T. Jensen, MS,* Sundara Reddy, MD,‡ Kathryn L. Ruoff, PhD,§ Stephen O. Heard, MD,|| Mark P. Yeager, MD,* and Thomas M. Dodds, MD*

BACKGROUND: Enterococci, the second leading cause of health care-associated infections, have evolved from commensal and harmless organisms to multidrug-resistant bacteria associated with a significant increase in patient morbidity and mortality. Prevention of ongoing spread of this organism within and between hospitals is important. In this study, we characterized Enterococcus transmission dynamics for bacterial reservoirs commonly encountered by anesthesia providers during the routine administration of general anesthesia.

METHODS: Enterococcus isolates previously obtained from bacterial reservoirs frequently encountered by anesthesiologists (patient nasopharynx and axilla, anesthesia provider hands, and the adjustable pressure-limiting valve and agent dial of the anesthesia machine) at 3 major academic medical centers were identified as possible intraoperative bacterial transmission events by class of pathogen, temporal association, and phenotypic analysis (analytical profile indexing). They were then subjected to antibiotic disk diffusion sensitivity for transmission event confirmation. Isolates involved in confirmed transmission events were further analyzed to characterize the frequency, mode, origin, location of transmission events, and antibiotic susceptibility of transmitted pathogens.

RESULTS: Three hundred eighty-nine anesthesia reservoir isolates were previously identified by gross morphology and simple rapid tests as Enterococcus. The combination of further analytical profile indexing analysis and temporal association implicated 43% (166/389) of those isolates in possible intraoperative bacterial transmission events. Approximately, 30% (49/166) of possible transmission events were confirmed by additional antibiotic disk diffusion analysis. Two phenotypes, E5 and E7, explained 80% (39/49) of confirmed transmission events. For both phenotypes, provider hands were a common reservoir of origin proximal to the transmission event (96% [72/75] hand origin for E7 and 89% [50/56] hand origin for E5) and site of transmission (94% [16/17] hand transmission location for E7 and 86% [19/22] hand transmission location for E5).

CONCLUSIONS: Anesthesia provider hand contamination is a common proximal source and transmission location for Enterococcus transmission events in the anesthesia work area. Future work should evaluate the impact of intraoperative hand hygiene improvement strategies on the dynamics of intraoperative Enterococcus transmission. (Anesth Analg 2015;120:827–36)

Health care-associated infections (HCAIs) have remained persistent despite advances in surgical technique, disinfection and sterilization procedures, and a multitude of infection control measures.[1–5] The persistent nature of HCAIs is connected to the evolution of bacterial resistance and to community health, because HCAIs, due to invasive, multidrug-resistant bacterial pathogens, are no longer confined to acute health care settings.[2] It is therefore important to understand the epidemiology of bacterial transmission across all health care settings to generate sustained reductions in HCAIs.[6–9] *Staphylococci*, *Enterococci*, and members of the family *Enterobacteriaceae* are classes of bacterial pathogens most commonly associated with HCAI development. In this study, we sought to characterize the potential role of the anesthesiologist in intraoperative spread of Enterococci by characterizing the dynamics of Enterococcus transmission involving bacterial reservoirs frequently encountered by anesthesiologists. Our primary aims were to examine the mode, frequency, probable sources, the location of bacterial transmission events, and antibiotic resistance patterns for the most prevalent Enterococcus phenotypes isolated from reservoirs routinely contacted by anesthesia providers. These reservoirs included patient skin sites strongly associated with surgical site infections (SSIs),[10,11] anesthesia provider hands (transiently colonized by bacterial contaminants of other potential reservoirs and as such, a reasonable alternative to rectal swabs),[12,13] and proven representatives of the anesthesia environment (adjustable pressure-limiting valve and agent dial).[6,7,9] Our secondary aims were to examine

From the *Department of Anesthesiology, Dartmouth-Hitchcock Medical Center; †The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; ‡Department of Anesthesiology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa; §Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; and ||Department of Anesthesiology, UMass Memorial Medical Center, Worcester, Massachusetts.

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Address correspondence to Randy W. Loftus, MD, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756. Address e-mail to randy.w.loftus@hitchcock.org.

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whether Enterococcus isolates transmitted from these reservoirs could be linked by pulsed-field gel electrophoresis (PFGE) to 30-day postoperative patient cultures and to determine the incubation periods (growth rates) for these same Enterococcus phenotypes.

METHODS

General Approach

We previously conducted a prospective, randomized, observational study at 3 major academic medical centers, Dartmouth-Hitchcock Medical Center in New Hampshire, the University of Iowa Hospitals and Clinics in Iowa, and the UMass Memorial Medical Center in Massachusetts to characterize the frequency and implications of bacterial transmission events to intravascular devices in the intraoperative arena.[9] The study took place over 12 consecutive months (from March 2009 to February 2010). Approval was obtained at each study site from the respective IRB for the protection of human subjects with a waiver for informed patient consent. For the current study, additional approval was obtained from the Committee for Protection of Human Subjects at Dartmouth-Hitchcock Medical Center.

Experimental Model for Study of Bacterial Cross Contamination

We examined 2170 environmental bacterial culture sites, 2640 health care provider hand cultures, and 1087 patient skin cultures in 274 case-pairs representing 548 operating rooms across the 3 major academic medical centers. The unit of randomization was the operating room environment accomplished via use of a computer-generated list. The first and second patients of the day in each operating room environment were selected for analysis (the study unit a case-pair), with the above reservoirs sampled in parallel (according to the sequence described in Fig. 1) during the routine administration of general anesthesia. Operating rooms were randomized in order that the study results reflect the usual process of general anesthesia across a wide variety of environments, providers, and operative procedures. The patient, provider, and procedural demographics for operating rooms observed have been reported.[9] From these reservoirs, >6000 potential and 2184 true bacterial pathogens were isolated and archived for later analysis. Each pathogen received a unique identification number linked to a specific date, operating room, reservoir, patient, and provider.

The potential association of each pathogen with patient, provider and environmental characteristics, and patient bacterial cultures in those patients with 30-day postoperative infections was assessed. Basic demographic information collected and linked to each frozen pathogen included the hospital site, age, sex, case 1 or case 2, ASA physical status classification, Study on the Efficacy of Nosocomial Infection control (SENIC)[14] score (an index predicting the probability of postoperative HCAI development for a given patient), case duration, patient comorbidities, patient origin, patient discharge location, and procedure type.[9]

We used a validated model for study of intraoperative bacterial cross contamination (Fig. 1) in this previous study. Bacterial reservoirs including anesthesia provider hands, patient skin sites strongly associated with SSIs[10,11] and increased risk of Enterococcus transmission events,[12,13] the adjustable pressure-limiting valve and agent dial of the anesthesia machine, and proven representatives of the anesthesia environment[6,7,9] were selected for evaluation in order that the results represent reservoirs within the purview of anesthesia providers. We prospectively evaluated the relative contribution of these bacterial reservoirs to intraoperative bacterial transmission events to high-risk intravascular devices (stopcocks) and to the subsequent development of 30-day postoperative patient cultures, and in some cases, HCAIs. Our focus in the initial study was on bacterial organisms transmitted to intravascular devices, and we used the combination of class of organism, phenotype defined by a series of biochemical reactions (Analytical Profile Index [API]), and temporal association given the timed sequence of bacterial culture acquisition during the process of patient care in each operating room (Fig. 1) to identify epidemiologically related transmission events. PFGE was used to examine potential links between intraoperative transmission events and subsequent infection development.

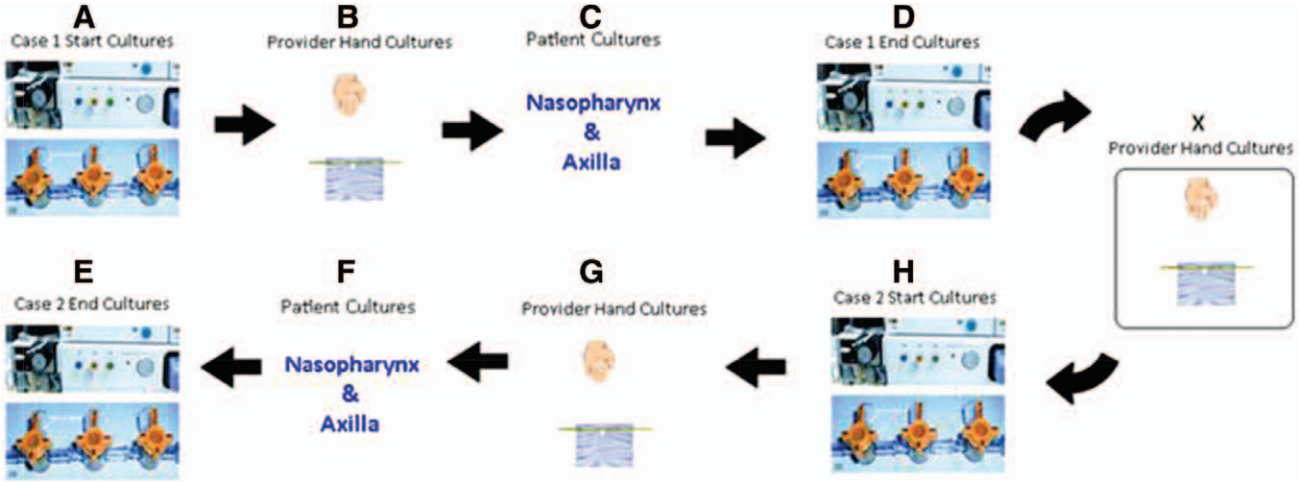

Figure 1. Schematic of culture sampling sequence. Culture samples were collected sequentially (A → H) from the operative environment (adjustable pressure-limiting valve and agent dial), patient IV tubing, provider hands and the patient nasopharynx/axilla. Provider hands were also intermittently cultured throughout the case and on provider return to the operating room following an absence during the case (X).

Systematic Evaluation of the Epidemiology of Transmission for Major Bacterial Pathogens

We have since conducted a systematic analysis of bacterial pathogens that are most likely to cause SSIs, including *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant), Enterococcus (vancomycin-resistant [VRE] and vancomycin-susceptible [VSE]), and gram negative pathogens to characterize the potential role of the anesthesiologist pertaining to intraoperative transmission of these important disease-causing organisms. Consistent with the framework established by the Centers for Disease Control and Prevention,[15] we sought to characterize the overall mode, frequency, probable sources and the location of transmission events, and antibiotic resistance patterns for frequently transmitted Enterococci phenotypes as they pertain to bacterial reservoirs engaged by the anesthesia provider during routine practice. We also sought to examine the potential association with 30-day postoperative patient cultures and potential phenotypic differences in incubation period (growth rate) for these same organisms to ascertain whether anesthesiologists participate significantly in the intraoperative spread of Enterococcus pathogens later causing infection, and so that we could begin to understand the mechanisms for evasion of current disinfection practices, respectively. The sequence of this systematic analysis focused on Enterococci is shown in Figure 2.

Microbiological Analysis

As the first step in this analysis, we had previously classified all major bacterial pathogens isolated from these reservoirs according to colony morphology, gram stain, and simple rapid tests. As such, we were able to identify and archive all Enterococcus isolates obtained from anesthesia reservoirs during the study period. In this study, we reviewed 274 case-pairs (548 cases) for evidence of possible Enterococcus transmission defined by the presence of an Enterococcus isolate in 2 or more reservoir sites across the case-pair. We then used a commercially available bioMerieux API identification system (Marcy 1′ Etoile, France) to identify phenotype. Each API-derived phenotype represents observable characteristics of bacterial organisms in uptake and use of elemental nutrients required for cell survival. Each API test comprised at least 20 different biochemical assays. The response of the organism tested to each assay yields a unique 7 digit number (biotype, API phenotype) that can be used for species identification via input into a large database

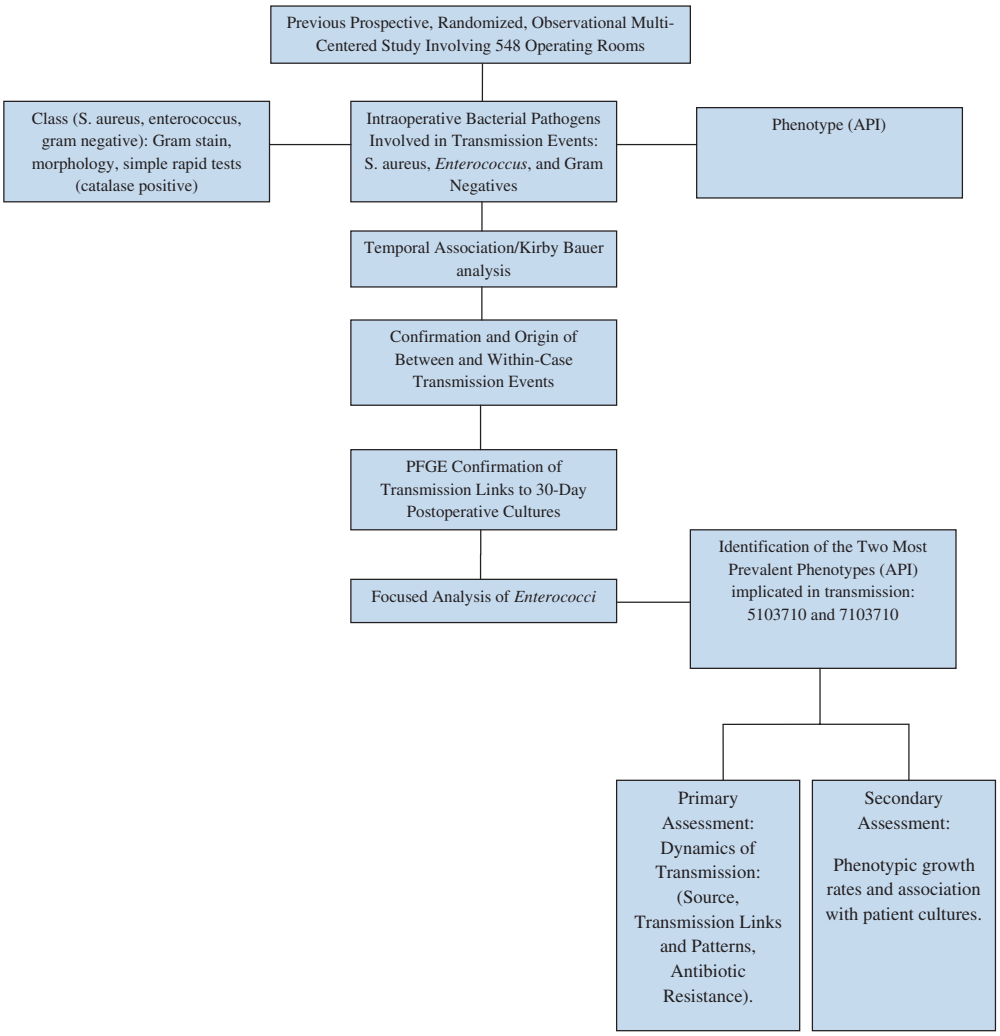

Figure 2. Systematic analysis of intraoperative Enterococcus transmission and subsequent infection development.

and/or to compare bacterial strains. Isolates of the same class with an identical biotype are thought to be epidemiologically related. With identification of the class of organism and API phenotype, we then used temporal association (the same class of pathogen isolated in >1 site surveyed in the same operating room on the same day at the same time with the same biotype, Fig. 1) to identify possible transmission events occurring within and between operative cases. This initial methodology was previously validated.[9] We added disk diffusion antibiotic susceptibility testing analysis (antibiotic susceptibility profiling-same response to methicillin and 15 commonly used prophylactic antibiotics, Appendix) to this model to provide further support for the identification of transmission events and the most proximal reservoir origin (provider, environment or patient) for these events. Because susceptibility to antibiotics is another observable characteristic intimately related to the bacterial genome, a similar API phenotype combined with diffusion antibiotic susceptibility analysis and an appropriate temporal exposure allowed us to identify with reasonable certainty intraoperative bacterial transmission events involving Enterococci between and within operative cases (mode of transmission) and to examine the most proximal origin and location of these transmission events. Bacterial sensitivity was recorded and subsequently analyzed as sensitive or resistant (intermediate resistance was considered resistant due to clinical relevance).[16]

This experimental model serves to examine reservoirs proximal to anesthesia providers during routine administration of general anesthesia, reservoirs that could be potentially addressed by improvements in aseptic practice, while also addressing more distal reservoirs, such as the patient rectum, when organisms from distal reservoirs are transmitted to proximal reservoirs contacted by the anesthesia provider. A positive rectal site for Enterococcus commonly occurs in conjunction with skin colonization (in patients with VRE bacteremia, 100% of study patients had rectal colonization and 86% skin colonization),[12] and the antecubital fossa and blood pressure cuff, often in contact with the axilla, have been shown to be the best predictors of VRE transmission.[13] Further, most patients with positive rectal swabs for VRE will test positive at other skin sites with the same organism.[13] Thus, the patient skin sites cultured in this model not only serve to assess the dynamics of Enterococcus transmission in reservoirs pertinent to anesthesia providers but also effectively assess distal reservoirs for this organism.

Provider hand contamination was assumed to be the most proximal reservoir if the transmitted isolate was identical to an isolate from the hands of 1 or more anesthesia providers but not found in the examined patient skin sites or environmental reservoirs earlier in the sampling sequence. Environmental contamination was assumed to be the most proximal reservoir if the transmitted isolate was identical to an isolate from the environment sampled at baseline or at case end but not isolated either from the hands of providers or from the patient reservoirs earlier in the sampling sequence. The hands of all providers who would potentially interact with the anesthesia environment were sampled at baseline (Fig. 1). Patient skin contamination was assumed to be the most proximal reservoir if the transmitted isolate was identical to an isolate from the patient nasopharynx or axilla sampled at case start but was not isolated from provider hands or environmental reservoirs earlier in the sampling sequence.

Transmission events were then compared, by temporal association, biotype, and disk diffusion antibiotic susceptibility testing analysis, with all patient cultures obtained in the 30-day postoperative period. Probable patient bacterial culture links, defined by the same class of pathogen, the same biotype, the same response to commonly used prophylactic antibiotics, and an appropriate temporal exposure, were then confirmed with PFGE.[17]

Evaluation of Bacterial Growth Rates

In addition, the 2 most prevalent Enterococci phenotypes encountered in the intraoperative anesthesia work area (E5 and E7, [Table 1]) were subjected to growth rate analysis under ideal growth conditions by using a previously reported technique (time to positivity).[8]

In order that the growth rates accounted for vancomycin resistance (each phenotype comprised vancomycin-sensitive and resistant isolates) and reservoir of origin, 10 VSE and 10 VRE isolates were randomly selected from the available pool of isolates for both E5 and E7 phenotypes. In addition, a negative control was prepared for each phenotype group. Thus, each experimental phenotype group comprised 11 samples for a total of 22 samples. Selected organisms were grown on blood agar plates for 24 hours at 36.5°C. A 0.5 McFarland standard dilution was then prepared for each organism and serially diluted to a final concentration of 50,000 colony forming units/mL. A BacT/Alert bottle containing aerobic culture media (BacT/Alert, Biomerieux Inc., Durham, NC) was then disinfected with an alcohol prep for 30 seconds and allowed to air dry. One mL 50,000 colony forming units/1.0 mL test concentration for each sample was then drawn up by using aseptic technique and injected into the aerobic culture media contained within the BacT/Alert bottle. All inoculated bottles were then placed into the BacT/Alert machine and incubated at 36.5°C for 5 days or until positive. The BacT/Alert incubator identified a positive bottle based on colorimetry; a color change in the media secondary to CO_2 production from the growing bacteria was detected via spectroscopy occurring

Table 1. Overall Intraoperative Phenotypic Prevalence for Enterococci Species Implicated in Transmission

Species	Phenotype	*N*	Percent	Vancomycin-resistant (%)
E. faecalis	E1	2	1.20	0
E. sp	E2	3	1.81	0
E. faecium	E3	8	4.82	0
E. faecium	E4	2	1.20	0
E. faecalis	E5	56	33.73	0
E. faecium	E6	2	1.20	0
E. faecalis	E7	75	45.18	1 (1/75)
E. avium	E8	2	1.20	0
E. faecalis	E9	5	3.01	0
E. sp	E10	2	2.00	0
E. faecium	E11	3	1.81	0
E. faecium	E12	3	1.81	100 (3/3)
E. faecium	E13	3	1.81	100 (3/3)

N = 166.

every 10 minutes. If the color change did not occur within 5 days, the bottle was determined to be negative. For positive samples, the time to positivity was recorded. For negative samples, the BacT/Alert bottle was removed from the incubator, and sterility was confirmed by aspirating 1 mL fluid by using standard, aseptic technique, spreading the solution onto standard blood agar plates and incubating for 72 hours at 36.5°C. Time to positivity in hours was then compared for each VSE phenotype.

Statistical Analysis

In this study, we sought to examine transmission dynamics for Enterococcus isolates frequently encountered in reservoirs relevant to the routine administration of general anesthesia. Our primary aims were to examine the mode, frequency, probable sources, and the location of intraoperative bacterial transmission events and to examine antibiotic resistance patterns for the most prevalent Enterococci phenotypes isolated from patient skin sites (the nasopharynx and axilla), anesthesia provider hands (transiently colonized and a reasonable alternative to rectal swabs), and proven representatives of the anesthesia environment (the adjustable pressure-limiting valve and agent dial). Our secondary aims were to examine the phenotypic association of frequently transmitted pathogens with subsequent 30-day postoperative patient cultures and to examine the incubation periods for these same Enterococci phenotypes.

The relative contributions of the patient, environmental, and provider hand bacterial reservoirs to Enterococci transmission events (reservoir source and/or transmission location between and within operative cases) involving the 2 most prevalent Enterococci phenotypes were compared by using the χ^2 or Fisher exact test where appropriate. For cell counts <5, Fisher exact test was used. As transmission dynamics were the primary outcome, fixed effects logistic regression analysis was used to adjust all transmission dynamic comparisons for ASA physical status and SENIC as ordinal variables and for hospital site, as these factors were previously associated with increased risk of 30-day postoperative infection.[9] An α level of $P < 0.05$ was defined as statistically significant.

Differences in antibiotic resistance profiles for Enterococci phenotypes were compared by using the χ^2 or Fisher exact test for categorical data. For cell counts <5, Fisher exact test was used. Phenotypic comparisons were reported as relative risk unless cell size was zero, in which case odds ratios were reported. We addressed multiple comparisons by defining P values of <0.003 as statistically significant (0.05/15). Fixed effects logistic regression analysis was then used to adjust significant differences for ASA physical status and SENIC as ordinal variables and for hospital site: factors previously associated with increased risk of 30-day postoperative infection.[9] An α level of $P < 0.05$ after adjustment was defined as statistically significant.

Phenotypic contributions to 30-day postoperative patient cultures were compared by using Fisher exact test. To assess phenotypic differences in growth rates, Kaplan-Meier time to event analysis was conducted to evaluate the difference between phenotypes in time to critical growth threshold (that required for detection) after injection. We used the log-rank test for equality of time to critical threshold of contamination differences across the 2 phenotypes. An α level of P <0.05 was defined as statistically significant.

RESULTS

A total of 389 bacterial isolates obtained from anesthesia reservoirs were previously identified as Enterococcus by gross morphology and simple rapid tests. In this study, API biotype analysis and temporal association implicated 43% (166/389) of these isolates in possible intraoperative bacterial transmission events.

As shown in Table 1, possible Enterococcus transmission events involved 13 different API biotypes. *E faecalis* (Biotype E5, $N = 56$) and *E faecalis* (Biotype E7, $N = 75$) explained 79% (131/166) of these events. Only 4% (7/161) of possibly transmitted Enterococci isolates were resistant to vancomycin and were all *E faecium* (VRE). As shown in Figure 3, 89% (149/166) of Enterococcus organisms implicated in probable transmission events were isolated from anesthesia provider hand reservoirs.

Thirty-six (60/166) percent, 20% (34/166), and 43% (72/166) isolates were obtained from sites 0, 1 and 2, respectively. There were no significant differences in the rates of Enterococcus transmission among sites (data not shown).

Approximately, 30% (49/166) of probable transmission events were further supported via the same class of pathogen, temporal association, identical biotypes, and additional antimicrobial susceptibility testing. As shown in Figure 4, residual contamination of provider hands was the reservoir of isolation for 86% (42/49) of organisms implicated in confirmed transmission events.

E faecalis phenotypes E5 and E7 explained 80% (39/49) of transmission events (Table 2) supported by antimicrobial susceptibility. Both phenotypes were transmitted similarly of the overall rate and mode (between or within case transmission) (Table 3). For both phenotypes, provider hands were a frequent proximal reservoir of origin (96% [72/75] for E7 and 89% [50/56] for E5). Similarly, provider hands

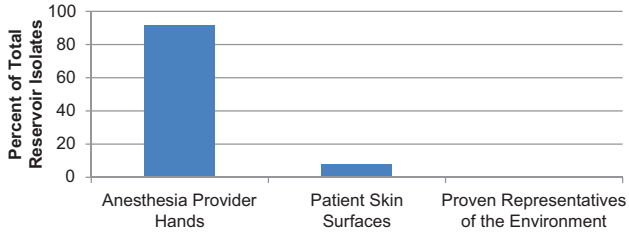

Figure 3. Reservoir Enterococcus isolate locations for possible transmission events.

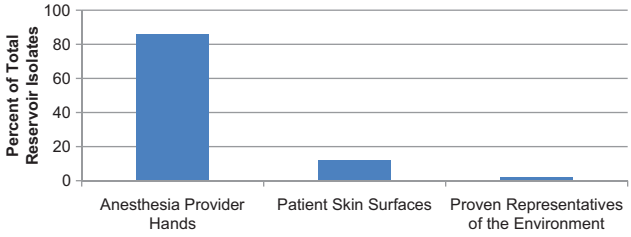

Figure 4. Reservoir Enterococcus isolate locations for confirmed transmission events.

were a frequent site of transmission for both phenotypes (94% [16/17] for E7 and 86% [19/22] for E5) (Table 3).

Phenotype E5 was more likely than phenotype E7 to be resistant to penicillin (relative risk 2.15, 1.54–3.00, $P = 0.001$), (Table 4).

Six of 548 patients (1%) had cultures positive for Enterococci in the 30-day postoperative period. There was no difference between those E7 and E5 phenotypes implicated in transmission events of the overall incidence of positive postoperative patient cultures. We were unable to demonstrate any PFGE links of patient cultures to intraoperative bacterial transmission events. There was no difference between phenotypes in inadequate prophylactic antibiotic coverage (Table 5). One patient was diagnosed with a confirmed HCAI due to *E faecalis*.

Finally, as shown in Figure 5, there was no difference in incubation periods for each of the frequently transmitted *E. faecalis* phenotypes under ideal, aerobic conditions.

Table 2. Overall Intraoperative Phenotypic Prevalence for Confirmed Enterococci Transmission Events

				Vancomycin-resistant (%)		
Species	Phenotype	*N*	Percent	S	I	R
E. faecalis	E1	2	4		100	
E. faecalis	E2	2	4		100	
E. faecium	E3	1	2	100		
E. faecalis	E4	1	2		100	
E. faecalis	E5	22	45	100		
E. faecalis	E9	1	2		100	
E. faecalis	E7	17	35	94		6
E. faecium	E11	1	2	100		
E. faecium	E13	2	4			100

N = 49.

DISCUSSION

We have previously systematically evaluated the relative contributions of known intraoperative bacterial reservoirs to high-risk bacterial transmission events involving IV stopcock sets.[9] We have extended this analysis by examining the dynamics of Enterococcus transmission from bacterial reservoirs frequently encountered by anesthesia providers.

Enterococci, bacterial organisms once thought to be of low virulence, harmless, and commensal, have evolved to the extent that they are now the second leading cause of hospital-acquired infections. In fact, they now explain up to 14% of hospital-acquired urinary tract infections, 11% of SSIs, and 7% of bloodstream infections.[18] They are especially problematic for immunocompromised patients such as those undergoing renal, hepatic, and bone marrow transplantation accounting for up to 50% of cases of sepsis that ultimately lead to patient death.[19–22]

The evolution of this organism to its current state is thought to be derived from several mechanisms, including the development of multidrug resistance. While there are up to 14 different species of *Enterococcus*, only 2 are considered to be of significant clinical relevance, *E faecalis* and *E faecium*.[23] *E faecalis* causes approximately 80% of hospital-acquired infections attributed to Enterococci, while *E faecium* explains most of the remainder. While the importance of *E faecalis* is highlighted due to its ability to cause infection, *E faecium* is also very important because it has expanded greatly in antibiotic resistance; the incidence of vancomycin-resistant *E faecium* isolates increased 20-fold from 1987 to 1993.[24] Therefore, it is important that we gain a better understanding of *E faecalis* and *E faecium* transmission in all health care environments to attenuate the spread of this evolving pathogen.

Table 3. The Epidemiology of Confirmed EnterococcusTransmission Events for Frequently Transmitted Isolates (E5 and E7) in the Anesthesia Work Area

	Phenotype		Comparison			Adjusted[d]		
	5103710 (*N* = 56)	7103710 (*N* = 75)	OR	95% CI	*P*	OR	95% CI	*P*
	N (%)	*N* (%)						
Vertical[a] transmission event[b]	13 (23)	9 (12)	2.21	0.872–5.63	0.089	1.13	0.401–3.230	0.806
Horizontal[c] transmission event	9 (16)	8 (11)	1.6	0.577–4.46	0.362	1.57	0.568–4.390	0.381
Any transmission event	22 (39)	17 (23)	2.21	1.03–4.73	0.039	1.10	0.457–2.650	0.831
						SENIC 1.72	0.975–3.040	0.061
						ASA 1.66	0.799–3.440	0.175
						Site 0.512	0.310–0.842	0.008
Vertical transmission source	8 (14)	5 (7)	2.33	0.71–7.56	0.149	1.42	0.387–5.18	0.600
Horizontal transmission source	7 (13)	6 (8)	1.64	0.52–5.19	0.392	1.28	0.331–4.97	0.719
Vertical transmission location								
Environment	0 (0)	0 (0)						
Patient	0 (0)	0 (0)						
Provider	13 (100)	9 (100)	2.22	0.872–5.63	0.072	1.13	0.401–3.23	0.806
Horizontal transmission location								
Environment	0 (0)	0 (0)						
Patient	3 (33)	1 (13)	4.19	0.424–41.39	0.313	1.02	0.061–15.9	0.991
Provider	6 (67)	7 (87)	1.17	0.369–3.68	0.791	0.877	0.240–3.20	0.842
Overall reservoir source								
Environment	0 (0)	0 (0)						
Patient	6 (12)	3 (4)	2.88	0.688–12.06	0.17	2.59	0.351–19.0	0.351
Provider	50 (89)	72 (96)	0.374	0.083–1.45	0.17	0.386	0.053–2.850	0.351

[a]Within a case.

[b]Transmission of 1 or more Enterococcus isolates not present at baseline to 1 or more\intraoperative reservoirs.

[c]Case 1 reservoir to case 2 reservoir.

[d]Adjusted for American Society of Anesthesiologists physical status classification (ASA) I-IV, Study on the Effect of Nosocomial Infection Control (SENIC), and hospital site.

Table 4. Antimicrobial Resistance of Confirmed Intraoperative EnterococcusTransmission Events for Phenotypes E5 and E7

	Phenotype		Difference		
	5103710 (*N* = 56)	7103710 (*N* = 75)	OR (RR)[a]	95% CI OR (RR)	*P*-Value OR (RR)/Adj[b]
	N (%)	*N* (%)			
Ampicillin	3 (5)	4 (5)	(1.57)	(0.687–3.58)	(0.404)
Cefazolin	1 (2)	1 (1)	1.35	0.082–21.99	0.397
Cefepime	23 (41)	31 (41)	1.42	0.678–2.97	1
Ceftazidime	56 (100)	75 (100)		Na-infinity	1
Cefuroxime	56 (100)	73 (97)		Na-infinity	1
Ciprofloxacin	43 (77)	60 (80)	(0.408)	(0.330–0.505)	(0.008)
Clindamycin	56 (100)	69 (92)	1.09	1.02–1.16	0.032
Gentamicin	14 (25)	14 (19)	1.45	0.627–3.36	0.38
Meropenem	1 (2)	1 (1)	1.35	0.082–21.99	1
Penicillin	13 (23)	3 (4)	(2.15)	(1.54–3.01)	(0.001)/0.039
Piperacillin/tazopbactam	1 (2)	1 (1)	1.35	0.082–21.99	1
Trimethoprim sulfamethoxazole	44 (79)	70 (93)	0.262	0.086–0.794	0.013
Linezolid	56 (100)	75 (100)			
Tetracycline	54 (96)	55 (73)	9.82	2.19–44.06	<0.001
Vancomycin	0 (0)	1 (1)	(2.49)	(0.702–9.88)	(0.081)

RR = relative risk.

[a]Risk ratio.

[b]Adjusted for American Society of Anesthesiology (ASA) physical status classification, hospital site, and Study on the Efficacy of Nosocomial Infection Control (SENIC) score.

Table 5. Antibiotic Resistance and Infection Related to Confirmed Intraoperative Enterococcus Transmission Events (E5 and E7)

	Phenotype		Difference		
	5103710 (*N* = 56)	7103710 (*N* = 75)	OR	95% CI	*P*
	N/%	*N*/%			
Inadequate antibiotics	11/19	23/31	0.553	0.243–1.26	1
Postoperative bacterial culture	0/0	3/4	0	0-infinity	0.26
PFGE Links	0/0	0/0			

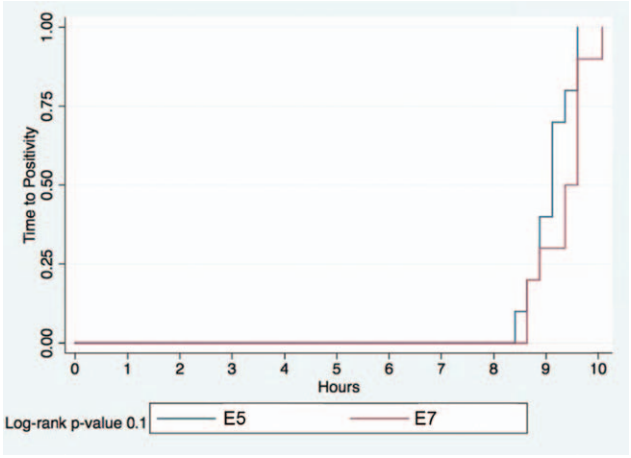

Figure 5. A comparison of the growth rate (hours) for vancomycin-susceptible *E faecalis* phenotypes E5 and E7.

Previous studies evaluating Enterococcus transmission have focused mainly on VRE in the intensive care unit setting and have shown that VRE commonly colonizes the skin (axilla, upper arm in the area of the blood pressure cuff, hands, and groin) of patients infected with the organism, that contamination of the axilla frequently correlates with positive rectal swabs in patients colonized with VRE, and that health care provider contact with patients infected or colonized with VRE leads to contamination of provider hands and/or the surrounding patient environment in up to 40% of cases after a single contact.[12,13] In addition, previous work has described a case of intraoperative VRE transmission that ultimately led to postoperative bacteremia as confirmed by PFGE.[6]

In this study, we used a previously validated experimental model to examine the dynamics of VRE and VSE transmission from intraoperative bacterial reservoirs relevant to anesthesia providers in the anesthesia work area environment. Reservoirs including anesthesia provider hands, patient skin sites strongly correlated with SSIs, and the surrounding patient environment were assessed in parallel during the routine administration of general anesthesia under a wide variety of conditions consistent with the overall practice of general anesthesia.[9] We found that most Enterococcus isolates obtained from these reservoirs were *E faecalis*, consistent with the epidemiology of hospital-wide enterococci isolates.[24]

We identified anesthesia provider hand contamination as a frequent proximal reservoir of origin and transmission location for possible and confirmed transmission events involving *E faecalis* phenotypes (E5 and E7) commonly isolated from anesthesia work area reservoirs. We found that between and within case modes of transmission for these phenotypes occurred at similar rates ranging from 11% to 23%. This rate of transmission is alarming, given issues pertaining to spread of major bacterial pathogens within and between operative cases, potentially to compromised hosts, and potential residual contamination of environmental surfaces in the surrounding patient environment

given previous reports of bacterial resilience.[13] While initial univariate analysis suggested that phenotype E5 was more likely to be transmitted than E7, adjustment for ASA physical status, site, and SENIC, factors previously associated with postoperative infection,[9] revealed that hospital site was a major confounder. The reason for impact of hospital site on Enterococcus transmission remains unknown and warrants further study, but we hypothesize that it is related to variability in aseptic practice among institutions. The findings of this study showing that hand contamination of anesthesia providers is an important proximal reservoir and transmission location for Enterococcus in the anesthesia work area, combined with evidence as reported previously that intraoperative hand hygiene is in need of improvement,[9] suggest that future work should evaluate the impact of hand hygiene improvement strategies on Enterococcus transmission in the intraoperative setting.

We were unable to show that patient skin contamination significantly increased the risk of Enterococcus transmission as compared with provider hands with or without adjustment for potentially confounding variables, and we were unable to identify a single case of between or within case Enterococcus transmission via the contaminated environment. These are different findings than that derived for the epidemiology of *S aureus* transmission, where patient and environmental reservoirs played a much larger role in transmission within and between cases.[9,25]

Phenotype E5 was more likely than phenotype E7 to be resistant to penicillin. As the acquisition of drug resistant traits has been shown to offer a survival advantage,[18] we hypothesized that E5 might also have a growth advantage potentially facilitating its colonization and survival in the anesthesia work area environment. We tested this hypothesis by evaluating the growth rates (incubation periods) of randomly selected E5 and E7 phenotype isolates, with the random selection intended to normalize isolates across vancomycin resistance and isolation site. We found that there was no difference in growth rates between phenotypes under the experimental conditions that we tested. Thus, this finding supports the results of the logistic regression analysis demonstrating no difference between transmission rates between the frequently encountered E5 and E7 Enterococcus isolates.

We were unable to establish a link between intraoperative Enterococci transmission events and postoperative patient cultures. Given the limitations of the methodology used, these findings do not eliminate the possibility that transmission of Enterococcus from reservoirs encountered by anesthesiologists can lead to infection development. In fact, this has been shown before.[6] However, the overall frequency at which this occurs is probably less than that of *S aureus*.[25] Furthermore, frequent intraoperative transmission events involving Enterococcus, as demonstrated in this study, could, in theory, lead to patient colonization and ultimately result in infection early or late in the patient's hospital course, especially if the transmission events involve a compromised host.

A limitation of this study is that it addresses the dynamics of Enterococcus transmission pertaining to the practice of anesthesiology but does not address overall intraoperative Enterococcus transmission. However, the focus of this study was to examine the dynamics of Enterococcus transmission from reservoirs frequently encountered by anesthesiologists to ascertain the "finger print" of the anesthesia provider in the spread of this organism. Our model not only accounted for these more proximal, relevant reservoirs to the practice of anesthesiology but also accounted for spread of Enterococcus to these sites from more distal reservoirs such as the rectum by including a reasonable surrogate for positive rectal samples, the axilla, a skin site commonly contaminated in conjunction with the rectum and a potent transmission site for Enterococcus.[12,13] Finally, as we have discussed previously,[9] transmission links in this study were identified by using a previously validated model combining standard microbiological techniques, temporal resolution, bacterial typing, and in this study, antibiotic sensitivity patterns. PFGE was used in cases for evaluation of potential links to patient cultures but not for transmission: the major outcome of the study. While PFGE has been shown to be more discriminating than biotype analysis alone, the benefit of this technique has not been proven superior to the combination of biotype analysis and temporal resolution as used in this study, and PFGE has its own limitations.[9]

In conclusion, we have shown that anesthesia provider hand contamination is an important proximal source and transmission location for within and between case Enterococcus transmission events in the intraoperative setting. Future work should examine the impact of improved intraoperative hand hygiene compliance on the dynamics of Enterococcus transmission in the anesthesia work area.

Appendix

Antibiotics tested in Kirby-Bauer analysis

Ampicillin
Cefazolin
Cefepime
Ceftazidime
Cefuroxime
Ciprofloxacin
Clindamycin
Gentamicin
Meropenem
Piperacillin/tazobactam
Sulfamethoxazole/trimethoprim
Linezolid
Tetracycline
Vancomycin
Methicillin
Penicillin

DISCLOSURES

Name: Randy W. Loftus, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Randy W. Loftus has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Matthew D. Koff, MS, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Matthew D. Koff has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Jeremiah R. Brown, MS, PhD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jeremiah R. Brown has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Hetal M. Patel, BS.
Contribution: This author helped conduct the study.
Attestation: Hetal M. Patel has seen the original study data and approved the final manuscript.
Name: Jens T. Jensen, MS.
Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
Attestation: Jens T. Jensen has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Sundara Reddy, MD.
Contribution: This author helped design and conduct the study and write the manuscript.
Attestation: Sundara Reddy has seen the original study data and approved the final manuscript.
Name: Kathryn L. Ruoff, PhD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Kathryn L. Ruoff has seen the original study data and approved the final manuscript.
Name: Stephen O. Heard, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Stephen O. Heard has seen the original study data and approved the final manuscript.
Name: Mark P. Yeager, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Mark P. Yeager has seen the original study data and approved the final manuscript.
Name: Thomas M. Dodds, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Thomas M. Dodds has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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Hand Hygiene Knowledge and Perceptions Among Anesthesia Providers

Patrick G. Fernandez, MD,* Randy W. Loftus, MD,* Thomas M. Dodds, MD,* Matthew D. Koff, MS, MD,* Sundara Reddy, MD,† Stephen O. Heard, MD,‡ Michael L. Beach, MD, PhD,* Mark P. Yeager, MD,* and Jeremiah R. Brown, MS, PhD§

BACKGROUND: Health care worker compliance with hand hygiene guidelines is an important measure for health care–associated infection prevention, yet overall compliance across all health care arenas remains low. A correct answer to 4 of 4 structured questions pertaining to indications for hand decontamination (according to types of contact) has been associated with improved health care provider hand hygiene compliance when compared to those health care providers answering incorrectly for 1 or more questions. A better understanding of knowledge deficits among anesthesia providers may lead to hand hygiene improvement strategies. In this study, our primary aims were to characterize and identify predictors for hand hygiene knowledge deficits among anesthesia providers.

METHODS: We modified this previously tested survey instrument to measure anesthesia provider hand hygiene knowledge regarding the 5 moments of hand hygiene across national and multicenter groups. Complete knowledge was defined by correct answers to 5 questions addressing the 5 moments for hand hygiene and received a score of 1. Incomplete knowledge was defined by an incorrect answer to 1 or more of the 5 questions and received a score of 0. We used a multilevel random-effects XTMELOGIT logistic model clustering at the respondent and geographic location for insufficient knowledge and forward/backward stepwise logistic regression analysis to identify predictors for incomplete knowledge.

RESULTS: The survey response rates were 55.8% and 18.2% for the multicenter and national survey study groups, respectively. One or more knowledge deficits occurred with 81.6% of survey respondents, with the mean number of correct answers 2.89 (95% confidence interval, 2.78–2.99). Failure of providers to recognize prior contact with the environment and prior contact with the patient as hand hygiene opportunities contributed to the low mean. Several cognitive factors were associated with a reduced risk of incomplete knowledge including providers responding positively to washing their hands after contact with the environment (odds ratio [OR] 0.23, 0.14–0.37, $P < 0.001$), disinfecting their environment during patient care (OR 0.54, 0.35–0.82, $P = 0.004$), believing that they can influence their colleagues (OR 0.43, 0.27–0.68, $P < 0.001$), and intending to adhere to guidelines (OR 0.56, 0.36–0.86, $P = 0.008$). These covariates were associated with an area under receiver operator characteristics curve of 0.79 (95% confidence interval, 0.74–0.83).

CONCLUSIONS: Anesthesia provider knowledge deficits around to hand hygiene guidelines occur frequently and are often due to failure to recognize opportunities for hand hygiene after prior contact with contaminated patient and environmental reservoirs. Intraoperative hand hygiene improvement programs should address these knowledge deficits. Predictors for incomplete knowledge as identified in this study should be validated in future studies. (Anesth Analg 2015;120:837–43)

Overall hand hygiene compliance across health care providers remains <50%, with anesthesia providers identified as a particularly noncompliant group.[1] Bacterial contamination of anesthesia providers has been directly linked to high-risk bacterial transmission events to IV stopcock sets and 30-day postoperative infections.[2,3]

Social cognitive models of human behavior have been used to identify individual factors that might be targeted in hand hygiene improvement strategies, including knowledge deficits, perceptions, attitudes, awareness of individual and group performance, workload and type (complexity of care), and accessibility of hand hygiene agents.[1,4,5] Complete provider knowledge regarding indications for hand decontamination according to types of contacts (answering 4 of 4 questions correctly) has been associated with better hand hygiene compliance as compared to health care providers missing 1 or more questions.[1] Our primary aim was to characterize and identify risk factors for knowledge deficits among anesthesia providers. Our secondary aims were to characterize anesthesia provider perceptions, attitudes, awareness of individual group performance, workload and type, and accessibility of hand hygiene agents.

From the *Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; †Department of Anesthesiology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa; ‡Department of Anesthesiology and Critical Care Medicine, UMass Memorial Medical Center, Worcester, Massachusetts; and §The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire.

Patrick G. Fernandez, MD, is currently affiliated with the Department of Anesthesia, Children's Hospital Colorado, Aurora, Colorado, and the Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado.

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Address correspondence to Randy W. Loftus, MD, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr., Lebanon, NH 03756. Address e-mail to randy.w.loftus@hitchcock.org.

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METHODS

General Survey Methodology

A previously used survey instrument characterized provider knowledge of hand hygiene indications as "good" or "not good" via structured questions pertaining to 4 types of contacts. They found that a correct answer to all 4 structured questions was associated with increased provider hand hygiene compliance (odds ratio [OR] 1.61; 95% confidence interval [CI], 1.01–2.58; compliance 62.3%) as compared to failure to answer 1 or more questions correctly (OR 1, compliance 47%).[1]

For this study, the survey instrument was updated to include structured questions pertaining to types of contacts based on the 5 moments of hand hygiene (before patient contact, after patient contact, before an aseptic task, after patient skin site or bodily fluid exposure, and after contact with the patient surroundings).[6,7] We considered complete knowledge as a correct answer to all 5 questions and incomplete knowledge as 1 or more incorrect answers.[1] We included anesthesia provider perceptions, attitudes, awareness of individual group performance, workload and type, and accessibility of hand hygiene agents as secondary outcomes.

The revised survey instrument was developed in 2 stages. First, it was reviewed by 10 departmental faculties to determine the appropriateness of the questions, to discern any ambiguity, and to suggest relevant content areas that may have been overlooked. We then conducted a pilot study across all active members of the anesthesia department at Dartmouth-Hitchcock Medical Center (Lebanon, NH). This was accomplished via an Internet-based survey system (SurveyMonkey.com, Palo Alto, CA). The requirement for written informed consent was waived by the IRB.

We then emailed the survey instrument to active members across 3 major academic medical centers and to a randomly selected group of active American Society of Anesthesiology (ASA) members to generate an adequate sample frame. The local multicenter group consisted of practicing members of 3 academic anesthesiology departments: Dartmouth-Hitchcock Medical Center, University of Massachusetts (Worcester, MA), and the University of Iowa (Iowa City, IA), totaling 396 survey participants. The national group originally consisted of 5449 randomly selected active members of the ASA. These potential participants were selected from an up-to-date ASA membership list including approximately 40,000 active anesthesia providers via systematic sampling using a random start, with the computer-generated list intended to capture a sampling frame including both anesthesiologists and certified registered nurse anesthetists. Both survey assessments were accomplished via an Internet-based survey system (SurveyMonkey.com).

While no incentives were offered to the local multicenter group, an incentive involving the random selection of 2 responders to receive $250 was provided to minimize the nonresponse rate of the national survey study group. Alternatively, top-down support from the departmental chairs was used for the multicenter group. Nonresponders received 2 additional survey requests via email to further minimize nonresponse rates for both the national and local multicenter surveys. The final total pool of participants for the national and local multicenter study groups was obtained after 3 rounds of electronic mail.

For both the local multicenter and national surveys, anesthesia providers who provided any response to the initial survey request were considered participants and were initially divided into 1 of 3 groups: (1) responders—completed the survey, (2) nonresponders—said no to the survey, or (3) partial responders—partly completed the survey. In those cases where an invalid email address had been provided, identified by a survey return to the Survey Monkey server, or where anesthesia providers said no to the survey request, email addresses were removed from the master list of emails and were not sent subsequent requests for participation. Invalid email addresses were subtracted from the initial study participant population and not included in calculation of survey response rates. For partial responders, a fourth request for survey participation was sent in order to address technical difficulties encountered while attempting survey completion. Once completed, the partial responders were added to the responder group. For those participants who may have received the survey more than once, only their initial survey was included in the results.

Basic demographic information including age and gender was obtained for all potential survey participants (responders and nonresponders) for both survey populations to estimate potential nonresponse bias. Nonresponse bias was calculated for the multicenter and national groups by multiplying the proportion of nonresponse for each group by the difference in age and gender across the responder and nonresponder populations.[8]

Inclusion criteria included active members of the anesthesiology department for each respective institution of the multicenter group and active members of the ASA residing within the United States for the national group.

Primary and Secondary Outcome Measurements

Primary Outcomes

The primary outcomes of this study included the incidence of and predictors for incomplete anesthesia provider knowledge pertaining to the 5 types of contacts as described by the 5 moments of hand hygiene. The structured items were as follows: (1) the importance of hand hygiene before a preoperative examination, (2) the importance of hand hygiene before placing a peripheral IV catheter, (3) the importance of hand hygiene after intubating, (4) the importance of hand hygiene after palpating a pulse, and (5) the importance of hand hygiene after adjusting operating room bed height. Thus, these items tested the application of the World Health Organization (WHO) guidelines[6,7] in the intraoperative arena. Complete knowledge was defined as a correct answer to all 5 conceptual inquiries into WHO moments for hand hygiene. Where appropriate, a 7-point scale was used, with the last 2 points of the scale closest to the positive perceptive evaluation (never to always) considered positive answers and the remainder negative.[1]

Secondary Outcomes

Secondary outcomes included providers' perception of knowledge of hand hygiene indication (what health care providers think they know without a requirement for clinical application), perception of social norms concerning

hand hygiene (behavioral and subjective, what health care providers think their colleagues know), perception of ease of adhering to hand hygiene, perception of the risk for intraoperative cross-transmission of bacteria linked to nonadherence (attitude toward hand hygiene importance), and perception of hand hygiene behavior (how health care providers think they perform during administration of patient care). A 7-point scale was used, with the last 2 points of the scale closest to the positive perceptive evaluation (never to always) considered positive answers and the remainder negative.[1] In addition, we assessed whether anesthesia providers felt that they could improve their hand hygiene compliance with a 3-point scale (no/possibly/yes), with only "yes" considered a positive answer. This was intended to address intrinsic motivation to improve within the anesthesia provider population. We also asked anesthesia providers to estimate their personal hourly hand decontamination rate, with >3/h considered a positive response.[1] Finally, the survey instrument asked anesthesia providers to estimate their personal hourly hand decontamination rate.

Demographic Information

Age, gender, professional status (attending physician, resident physician, certified registered nurse anesthetists), practice type, and years of anesthetic practice were obtained for all study participants.

Statistical Analysis

The primary aims of this study were to evaluate the frequency of and predictors for anesthesia provider incomplete knowledge pertaining to the application of WHO opportunity-based hand hygiene guidelines[6,7] in the intraoperative arena. The secondary aims were to characterize additional cognitive factors pertaining to anesthesia provider hand hygiene compliance. Complete knowledge was defined by correct answers to 5 questions addressing the 5 moments for hand hygiene and received a score of 1. Incomplete knowledge was defined by an incorrect answer to 1 or more of the 5 questions and received a score of 0. Descriptive statistics, a multilevel random-effects XTMELOGIT logistic model for incomplete knowledge clustering at the respondent and geographic location, and forward/backward stepwise logistic regression analysis were used to report the main results of this study. Covariates used in multivariable models included regional or national responder, age (normally distributed), gender, professional status, board certification, years of anesthesia practice (normally distributed), practice setting, geographic location, correct responses to sanitizing soiled and unsoiled hands, correct response to the minimum time required for soap and water washing, positive perception of knowledge, intention to adhere to hand hygiene guidelines, perception of colleagues to adhere to hand hygiene guidelines, positive response to the ability to influence colleagues, achieve excellent compliance, improve compliance, that poor hand hygiene compliance is a risk factor for infection and/or contamination, frequency of hand hygiene per hour of anesthesia time, location of the closest hand hygiene dispenser, glove use, washing hands after glove removal, disinfecting the environment, designating a clean/contaminated area, and positive responses to washing hands before patient contact, before aseptic practice, after a bodily exposure, after patient contact, and after exposure to the environment (direct questions pertaining to the WHO guidelines). All risk factors found to be statistically significant with an alpha of 0.05 P values did not vary (e.g., <0.001 change) between forward and reverse logistic regression analysis. We also assessed for all pairwise interaction terms. There were no significant interactions with P values ranging from 0.105 to 0.994. Finally, the impact of transformation of continuous variables to achieve linearity was assessed. All P values were the same in the non-parsimonious models within 0.078 (all not statistically significant). The use of other transformations did not change the inclusion of significant risk factors in the final model from the forward and backward step models.

Sample Size Calculation

For the regional survey, we attempted to survey all active members of each of the 3 anesthesiology departments. For the national survey, we hypothesized based on pilot data that only 20% of anesthesia providers would have complete knowledge. This hypothesis was based on pilot results where only 13.8% of pilot responders felt that they knew the 5 moments of hand hygiene, and only 23.8% and 38% of responders recognized the importance of hand hygiene after contact with patient surroundings and before patient contact, respectively, as important opportunities. Assuming a 50% positive response from a population of 40,000, the anticipated CI around the providers with complete knowledge was calculated to be 1.3. Given this CI, we required approximately 200 completed surveys to have a reasonable standard error around our proportions for the national survey.

RESULTS

Study Group

The local multicenter survey response rate was 55.8% (221/396). The national survey response rate was 18.2% (609/3346 participants). Tables 1 and 2 detail the participants and responder numbers for each study site and a summary of demographic information for each group, respectively.

Primary Outcomes: Incomplete Hand Hygiene Knowledge (Incidence and Predictors)

The majority of survey respondents (81.6%) met criteria for incomplete knowledge with the mean number of correct answers 2.89 (95% CI, 2.78–2.99). Table 3 shows the percentage of responders who answered correctly the 5 questions pertaining to the application of WHO guidelines. Table 4 shows predictors for incomplete knowledge. A positive response to " I wash my hands after contact with the environment," "I

Table 1. Survey Response Rates

Survey group	No. of participants	No. of responders	% response
National	3346	609	18.2
Multicenter—group 1	106	82	77.3
Multicenter—group 2	98	62	63
Multicenter—group 3	192	77	40
Multicenter—total	396	221	55.80

Table 2. Demographic Data

	National (%)	Regional multicenter			
		Group 1 (%)	Group 2 (%)	Group 3 (%)	Total (%)
Age range					
20–29 y	0.0	8.8	9.8	21.3	3.6
30–39 y	17.1	35	42.6	37.3	22.7
40–49 y	39.1	20	19.7	16	33.6
50–59 y	32.8	27.5	21.3	14.7	29.7
60+ y	11	8.8	6.6	10.7	10.4
Gender (male)	76.8	55	64	56	71.7
Professional status					
Attending	99.8	39.7	53.3	37.5	84.8
Resident	0.0	28.2	21.7	22.2	6.4
Fellowship trained	14.6	3.8	10.0	6.9	12.4
CRNA	0.0	29.5	23.3	20.8	6.5
SRNA	0.0	2.6	1.7	18.1	2.0
AA student	0.2	0.0	0.0	1.4	0.3
Board certification					
Anesthesiology	96.40	40	44.30	34.70	81.20
CRNA	0	28.80	24.60	20	6.60
Not board certified	3.60	31.30	31.10	45.30	12.30
Years in practice					
1–5	11.4	50	50.8	50.7	21.8
5–10	17.1	6.3	13.1	10.7	15.1
10–15	21.2	6.3	8.2	12.0	17.8
15–20	14.6	6.3	6.6	5.3	12.3
20–30	26.9	22.5	16.4	14.7	24.5
>30	9.0	8.8	4.9	6.7	8.4
Practice setting					
Academic	40	98.8	100	98.7	68.2
Private	64.5	1.3	0.0	0.0	47.3
VA	2.7	0.0	0.0	1.3	21.0
Industry	0.8	0.0	0.0	0.0	0.6
Geographic location					
Northeastern US	23.7	100	100	0.0	34.8
Southeastern US	21.5	0.0	0.0	0.0	15.7
Midwestern US	14.4	0.0	0.0	98.7	19.7
Southwestern US	6.8	0.0	0.0	1.3	5.1
Western US	33.7	0.0	0.0	0.0	24.7

CRNA = certified registered nurse anesthetists; VA = veterans administration; SRNA = student registered nurse anesthetists.

Table 3. Measured Knowledge Regarding WHO Opportunity-Based Hand Hygiene

Opportunity	Correct *N*	Incorrect *N*	Percent guidelines[6]
Placing a peripheral IV catheter (aseptic task)	658	137	82.77
After intubation (exposure to secretions)	521	274	65.53
After adjusting OR bed height (exposure to environment)	167	628	21.01
Before a preoperative exam (before patient contact)	638	157	80.25
After palpating a pulse (after patient contact)	310	485	38.99

WHO = World Health Organization.

Table 4. Mixed-Effects Logistics Regression Model for Incomplete Knowledge (*N* = 761)

Covariate	OR	95% confidence interval	*P* value
I wash after contact with the environment	0.23	0.15–0.37	<0.001
I can influence my colleagues	0.43	0.27–0.68	<0.001
I disinfect my environment	0.55	0.35–0.82	0.004
I intend to adhere to guidelines	0.56	0.36–0.86	0.008

can influence my colleagues," "I disinfect my environment," and "I intend to adhere to guidelines" was associated with a reduced risk of incomplete knowledge. These covariates were associated with an area under receiver operator characteristics (ROC) curve of 0.79 (95% CI, 0.74–0.83).

Secondary Outcomes

A positive perception of hand hygiene knowledge, as assessed by asking about awareness of the WHO 5 moments of hand hygiene (do you know the 5 moments of hand hygiene?), was seen on average only 25% of the time. Inquiry into perceptions of social norms was accomplished by asking whether people followed the WHO 5 moments and whether they believed that their colleagues followed these guidelines. Thirty-two percent of survey responders believed that they personally followed the WHO guidelines.

Table 5. Perceptions of Anesthesia Providers Pertaining to Hand Hygiene

	National (%)	Regional multicenter			
		Group 1 (%)	Group 2 (%)	Group 3 (%)	Total (%)
Perception of hand hygiene knowledge					
"... I know the WHO five moments ..."	24.5 (139/567)	28 (21/75)	27.6 (16/58)	24.7 (18/73)	25.1 (194/773)
Perception of hand hygiene social norms					
"... I follow the WHO five moments ..."	31.4 (178/567)	38.7 (29/75)	41.4 (24/58)	24.7 (18/73)	32.2 (249/773)
"... my colleagues follow the WHO five moments ..."	10.9 (62/567)	12 (9/75)	17.2 (10/58)	8.2 (6/73)	11.3 (87/773)
Perception of ease adhering to hand hygiene					
"... achieving excellent hand hygiene compliance is easy ..."	39.9 (226/567)	38.7 (29/75)	36.2 (21/58)	34.2 (25/73)	38.9 (301/773)
Perception of need to improve hand hygiene compliance					
"... I can improve my hand hygiene compliance ..."	64.6 (366/567)	68 (51/75)	62 (36/58)	71.2 (52/73)	65.3 (505/773)
Perception of infectious risk linked to nonadherence					
"... poor hand hygiene is a risk of contamination to patients ..."	85.2 (483/567)	89.3 (67/75)	86.2 (50/58)	76.7 (56/73)	84.9 (656/773)
Perception of hand hygiene behavior					
"I wash my hands before patient contact."	73 (408/559)	89.2 (66/74)	80.4 (45/56)	75 (54/72)	75.3 (573/761)
"I wash my hands before an aseptic task."	80.5 (450/559)	82.4 (61/74)	87.5 (49/56)	84.7 (61/72)	81.6 (621/761)
"I wash my hands after body fluid exposure risk."	98.2 (549/559)	97.3 (72/74)	96.4 (54/56)	95.8 (69/72)	97.8 (744/761)
"I wash my hands after patient contact."	82.3 (460/559)	85.1 (63/74)	87.5 (49/56)	73.6 (53/72)	82.1 (625/761)
"I wash my hands after contact with patient surroundings."	43.8 (245/559)	52.7 (39/74)	67.9 (38/56)	34.7 (25/72)	45.6 (347/761)
Perception of hand hygiene performance					
"... frequency of hand hygiene per hour of anesthesia time ..."	28.8 (161/559)	32 (24/75)	22.3 (13/57)	17.8 (13/73)	29.1 (222/763)

WHO = World Health Organization.

Nearly 40% of study participants had a positive perception with regard to their ability to adhere to hand hygiene recommendations. Universally, those studied perceived poor hand hygiene as an infectious risk to patients. When asked specifically about behaviors reflecting the WHO guidelines, the majority of study participants perceived their behaviors as congruent with the guidelines, except for hand hygiene after contact with patient surroundings. Overall, 65% of anesthesia providers believe that they can improve their hand hygiene compliance. Only approximately one-third of anesthesia providers estimated their hand decontamination events at >3/h (Table 5).

Nonresponse Bias Estimates

For the multicenter survey, the nonresponse bias was estimated at 3%. Among this group, there was no difference between total providers observed and those surveyed in gender, but there was a significant age difference. Those who responded to the survey were more likely to be younger than 40 years old. The estimated nonresponse bias for the national survey was 8% based on population differences in age. There was no difference in gender between responders and nonresponders for the national survey.

DISCUSSION

Overall hand hygiene compliance remains low among physicians.[9] Complete health care provider knowledge of hand hygiene indications according to types of contacts (answering 4 of 4 structured questions correctly) has been associated with improved hand hygiene compliance when compared to incomplete knowledge (answering 1 or more questions incorrectly).[1] This study sought to characterize anesthesia provider knowledge pertaining to WHO opportunity-based hand hygiene guidelines and to identify predictors for incomplete knowledge. This study shows that anesthesia providers underemphasize the importance of hand decontamination after prior contact with the patient and with the patient environmental surroundings, highlighting key areas for improvement in educational initiatives. Identified risk factors for incomplete knowledge may help to develop targeted improvement strategies.

Hand hygiene compliance among all physicians has been consistently reported at <50% despite extensive improvement efforts.[1] In response, much work has been done to characterize risk factors for hand hygiene noncompliance. Identified risk factors include but are not limited to time constraints, work pressure (task density), use of irritating agents, development of altered tactile sensation, gender, geographic location, attitudes and beliefs, and knowledge deficits.[1,4,5]

Anesthesiologists have been identified as a particularly noncompliant group, with a reported compliance rate of 23% as compared to an average compliance rate of 54% across all physicians.[1,10,11] This is not at all surprising given the complexity of care provided in the intraoperative arena. While the average physician has been reported to have 4 opportunities (ranging from 1 to 28) per episode of patient care,[1] anesthesiologists have recently been shown to have up to 54 opportunities per hour of patient care.[12] While achieving a 100% WHO opportunity-based hand hygiene compliance rate may not be a reasonable goal for anesthesiologists, generating baseline improvements in hand hygiene compliance as part of a multimodal program designed to attenuate bacterial transmission is reasonable. This is especially important considering recent evidence linking hand contamination of anesthesia providers to bacterial transmission events within and between patients, events that ultimately lead to infection.[2,3] As a first step, it is important to identify reasonable targets for improvement. While task density and time constraints are clearly important factors attenuating hand hygiene compliance in the intraoperative arena that should be addressed,[13] anesthesia provider knowledge and attitudes pertaining to hand hygiene indications have not been well described. In this study, we sought to characterize these factors.

Overall, approximately 20% of anesthesia providers surveyed in this study were able to demonstrate complete knowledge regarding WHO hand hygiene guidelines. This

appears to be relatively low compared to prior reports where 67% of health care providers had "good" measured (requiring application of concepts) knowledge defined by correct answers to 4 types of contacts.[1] However, this earlier work did not consider the 5 types of contacts as currently emphasized by the Centers for Disease Control and WHO.[6,7] Therefore, it is difficult to compare anesthesia provider measured knowledge to that of other health care providers. However, there is room for improvement, especially as it pertains to recognizing prior contact with the patient and the surrounding patient environment as hand hygiene opportunities. Knowledge deficits in these areas may partially explain the importance of patient skin and environmental reservoirs in high-risk intraoperative bacterial transmission events.[2,3,14] Thus, as part of intraoperative hand hygiene improvement strategies, the importance of hand decontamination after contact with patient skin surfaces and the surrounding environment should be better emphasized.

While much work has been done to identify risk factors for hand hygiene noncompliance,[1,4,5] little work has been done to characterize risk factors for incomplete hand hygiene knowledge. In this study, we developed a predictive model for incomplete knowledge that incorporated responder demographic information, cognitive and social factors previously associated with hand hygiene compliance,[1] and factors previously identified as perceived barriers to hand hygiene compliance.[1] Overall, this model is highly predictive for incomplete knowledge and could be used in future studies as a research tool to investigate targeted educational initiatives. It is not surprising that a positive response to washing hands after contact with the environment or disinfecting the environment during anesthetic practice is protective against incomplete knowledge because both highlight the importance of the contaminated environment as a hand hygiene opportunity, a major knowledge deficit highlighted by this work. The protective effect of a positive perception of the ability to influence colleagues is consistent with social cognitive models of behavior because this can lead to an intent to adhere, which ultimately influences behavior. Not surprising then was the protective effect of intention to adhere.

These survey results suggest that anesthesia providers realize that hand hygiene is an important preventive measure. Universally, providers recognized noncompliance with appropriate hand hygiene as an infectious risk to patients, demonstrated willingness to improve, and demonstrated a positive attitude toward the importance of hand hygiene. These are promising results that suggest an environment poised for behavioral change.[4] Such change might involve addressing knowledge deficits as highlighted in this study, or even work pressure and time constraints in the anesthesiology environment.

This study was limited by a low response rate. However, we estimate a nonresponse bias of only 8% for national and 3% for regional surveys. The survey results also reflect the appropriate sample frame for the population of interest, and both the national and regional survey studies were sufficiently powered. Further, the survey methodology, including design, implementation, and analysis, was based on previous descriptions of the various aspects of quality survey reports.[8] In addition, while we assume that honest answers were provided, we have no way of proving this assumption.

In conclusion, this research report suggests that anesthesia providers have significant knowledge deficits pertaining to opportunity-based hand hygiene in the intraoperative arena, specifically after interactions with patient skin surfaces and the surrounding environment, 2 important reservoirs of intraoperative bacterial transmission.[2,3,14] However, providers maintain an overall positive attitude toward hand hygiene as an important preventive measure for heath care–associated infections and demonstrate a willingness to improve. These results suggest that efforts directed toward the development of educational initiatives pertaining to intraoperative hand hygiene compliance may be met with a favorable response by anesthesia providers. The predictive model as outlined may serve to augment these efforts via implementation of targeted improvement strategies.

DISCLOSURES

Name: Patrick G. Fernandez, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Patrick G. Fernandez has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Randy W. Loftus, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Randy W. Loftus has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Thomas M. Dodds, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Thomas M. Dodds has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Matthew D. Koff, MS, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Matthew D. Koff has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Sundara Reddy, MD.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: Sundara Reddy approved the final manuscript.
Name: Stephen O. Heard, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Stephen O. Heard approved the final manuscript.
Name: Michael L. Beach, MD, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Michael L. Beach has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Mark P. Yeager, MD.
Contribution: This author helped write the manuscript.
Attestation: Mark P. Yeager has seen the original study data and approved the final manuscript.

Name: Jeremiah R. Brown, MS, PhD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jeremiah R. Brown has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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Leaving More Than Your Fingerprint on the Intravenous Line: A Prospective Study on Propofol Anesthesia and Implications of Stopcock Contamination

Devon C. Cole, MD,* Tezcan Ozrazgat Baslanti, PhD,* Nikolaus L. Gravenstein, BS,† and Nikolaus Gravenstein, MD*

BACKGROUND: Acute care handling of IV stopcocks during anesthesia and surgery may result in contaminated IV tubing sets. In the context of widespread propofol use, a nutrient-rich hypnotic drug, we hypothesized that propofol anesthesia increases bacterial contamination of IV stopcocks and may compromise safety of IV tubing sets when continued to be used after propofol anesthesia.

METHODS: We conducted an in vitro trial by collecting IV tubing sets at the time of patient discharge from same-day ambulatory procedures performed with and without propofol anesthesia. These extension sets were then held at room temperature for 6, 24, or 48 hours. We cultured 50 samples at each interval for both cohorts. Quantitative cultures were done by aspirating the IV stopcock dead space and plating the aspirate on blood agar for colony count and speciation.

RESULTS: Positive bacterial counts were recovered from 17.3% of propofol anesthesia stopcocks (26/150) and 18.6% of nonpropofol stopcocks (28/150). At 6 hours, the average bacterial counts from stopcocks with visible residual propofol was 44 colony forming units (CFU)/mL, compared with 41 CFU/mL with no visible residual propofol and 37 CFU/mL in nonpropofol anesthesia stopcocks. There was a 100-fold increase in bacterial number in contaminated stopcock dead spaces at 48 hours after propofol anesthesia. This difference remained significant when comparing positive counts from stopcocks with no visible residual propofol and nonpropofol anesthesia ($P = 0.034$).

CONCLUSIONS: There is a covert incidence and degree of IV stopcock bacterial contamination during anesthesia which is aggravated by propofol anesthetic. Propofol anesthesia may increase risk for postoperative infection because of bacterial growth in IV stopcock dead spaces. (Anesth Analg 2015;120:861–7)

Propofol is widely used for both inpatient and outpatient anesthesia. Because propofol is highly hydrophobic, it is manufactured in a nutrient-rich emulsion called Intralipid that is white in appearance, containing soy bean oil, egg phospholipids, and glycerin. Shortly after propofol was introduced, investigators found its clinical use problematic because of microbial contamination. The Food and Drug Administration mandated addition of antimicrobial preservative, but the complication of infection persisted.[1,2] Investigators found that the improper handling of opened vials and reuse of syringes resulted in log-rhythmic growth at 6 hours, even in the presence of EDTA.[3,4] Thus, manufacturers' directions for use include discarding propofol after 6 hours of opening the vial or filling the syringe.[a] For continuous IV infusions, manufacturers recommend discarding tubing and any unused portion of propofol after 12 hours.[b]

Loftus et al.[5,6] found that microorganisms from anesthesia providers' hands and equipment commonly serve as significant sources for IV stopcock contamination associated with anesthesia delivery. However, these studies were limited to the intraoperative period only and did not investigate whether the use of nutrient-rich medications, such as propofol, increased contagion levels postoperatively.

Newly opened IV sets are sterile on removal from packaging, but quickly become at risk for bacterial contamination during anesthesia through repetitive interactions in the course of medication delivery with improper handling. The incidence of propofol syringe contamination in the operating room and intensive care unit (ICU) has been reported to be 4.8% to 6.0%.[7–9] Additional studies have shown contamination to be evident in 8% to 11% of syringes, even when propofol is drawn up according to the manufacturer's guidelines.[10,11] Despite these known acute care contamination rates, the longer term risk of IV stopcock bacterial contamination after routine propofol anesthesia remains unexamined.

Although IV tubing sets remain connected to patients after propofol anesthesia, dead spaces may harbor growing bacterial contaminants, even in the absence of visible residual propofol. We hypothesized bacterial growth occurring in these dead spaces could be detected by sampling the IV stopcock after propofol anesthesia and is a potential

From the *Department of Anesthesiology, University of Florida College of Medicine; and †University of Florida College of Medicine, Gainesville, Florida.

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Address correspondence to Nikolaus Gravenstein, MD, Department of Anesthesiology, University of Florida, PO Box 100254, Gainesville, Florida. Address e-mail to ngraven@anest.ufl.edu.

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[a]Novaplus. Propofol injectable emulsion, USP. 451192A/Revised: October 2009.

[b]AstraZeneca. Diprivan 1%, package insert 235003. Revised: August 2005.

indicator for contamination in the IV stopcock. Prior work in vitro by Fukada and Ozaki[12] showed that methicillin-resistant *Staphylococcus aureus* (MRSA) survived and grew in the dead space of IV stopcocks regardless of whether the propofol formulation contained EDTA or had a continuous acetate Ringer's solution flow rate of 50 mL/h for 24 hours after propofol anesthesia.

We sought to examine IV extension tubing stopcocks quantitatively for presence of aerobic bacteria after ambulatory procedures with or without propofol anesthesia. The primary aim was to determine whether propofol increased the presence of bacterial contaminants at 48 hours. Our secondary aim was to examine whether after propofol anesthesia administration, bacterial contamination (colony forming units [CFU] per milliliter) in IV stopcock dead spaces increased, regardless of whether residual propofol was visible.

METHODS

This was a prospective cohort study of IV extension tubing stopcock dead space (see Fig. 1) culturing after propofol and nonpropofol anesthesia. The study was conducted with approval and waiver of informed patient consent from the University of Florida College of Medicine, IRB, application #48–2011. There is no linkable identification of IV extension sets to patient or provider. We reviewed the anesthetic record at time of extension tubing collection to confirm propofol administration and absence of other nutrient-rich infusions such as blood products, platelets, or total parenteral nutrition. The study was blinded to all anesthesia and nursing care providers and absent of all patient identifiers. There were at least 10 different blinded providers in each arm of the study (propofol and nonpropofol), respectively.

Over a 30 consecutive work-day period, IV stopcock extension sets were collected after propofol (same-day ambulatory surgery) and nonpropofol anesthesia (mainly methohexital, administered for cataract extraction and electroconvulsive therapy). Propofol used throughout this study contained preservative EDTA (63323-270-25, APP Pharmaceutical, Schaumburg, IL). All tubing sets in this study included stopcock extension (MX5996, Smith Medical, Dublin, OH). We collected the IV stopcock extension sets after they were removed from patients at the time when the IV sets are typically discarded.

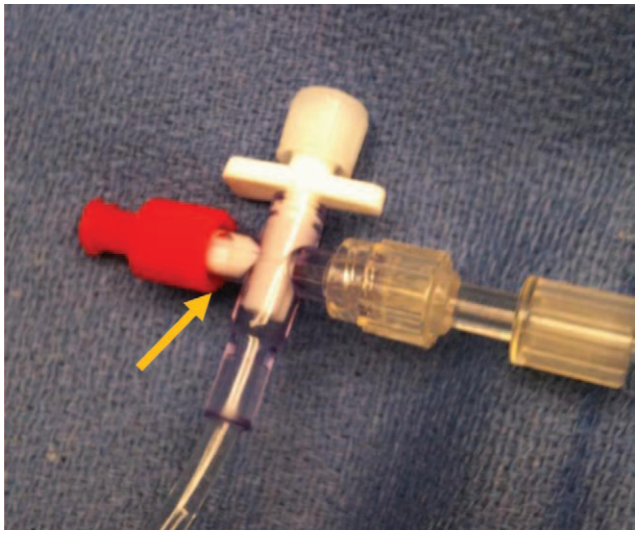

Figure 1. Visible white propofol (arrow) in IV extension set stopcock dead space after routine anesthesia care.

Collected IV tubing was stored at room temperature (20°C) with the roller clamp closed and all IV fluid remaining in the tubing. The tubing was coiled and protected in a biohazard bag for the duration of the holding time. The stopcock was covered with a sterile cap (R2000, B. Braun, Allentown, PA) and stored in a clean, room temperature environment with individual packaging.

The stopcock dead space from both propofol and nonpropofol IV extension sets was sampled at 6, 24, or 48 hours after surgery for a total of 50 samples at each interval. Individual extension sets recovered from propofol and nonpropofol anesthesia were randomized to different holding times. The study was designed to identify differences in bacterial contamination after anesthesia.

Because bacterial growth in propofol is slow at room temperature (beginning after a dormant period of 6 hours), we began our quantitative cultures at 6 hours for baseline values. Each IV extension set stopcock was sampled only once. We adhered to standard precautions for handling of all IV tubing, containers were clearly marked with biohazard labels, and no sharps were included in sample collections.

Bacteremia has been understood to result from catheter colonization at as few as 15 CFU/mL.[13] When blood drawn for quantitative culture from the catheter luminal hub or from peripheral venipuncture contains 4 to 10 times >15 CFU/mL, a catheter-related bloodstream infection is confirmed.[14] Thus, we considered any IV stopcock dead space bacterial counts >120 CFU/mL as a significant bacterial burden. Considering the dynamic nature of bacteria's natural system, we selected an effect size of 50 CFU/mL to ensure an adequate difference at lower counts. Our sample size calculations determined that we needed 50 samples in each group with a large SD of 200, along with type I error of 0.05 and type II error of 0.2.

All IV stopcock dead spaces were cultured in an aseptic environment by removal of the cap and using a sterile micropipette (02-707-135, Fisherbrand, Stephens City, VA) to aspirate the residual volume from the dead space. After tarring a sheep blood agar plate (R01198, Remel, Lenexa, KS) on a 3-digit scale (PE160, Mettler, Toledo, OH), each aspirate aliquot was spread on individual agar plates for culture (aspirates ranged from 25 to 200 μg). Weight in micrograms of aspirate aliquots was noted for quantitative culture calculation. Aspirated volumes were balanced equally with sterile buffer dilution (D699, Hardy Diagnostics, Santa Maria, CA) to a total of 250 μg for equal dispersion of all aliquots across the agar surface by 1-time use of sterile inoculating loop (R641820, Fisherbrand). Laboratory control blanks were also performed with each culture run by inoculating sterile blood agar with 250 μg sterile dilution buffer, and blanks were handled in the same fashion as study samples. Any sample runs with bacteria found on laboratory blanks were invalidated and not included in the study. A total of 320 samples were collected, but 20 samples were discarded due to contaminant colonies on laboratory blanks from that set, leaving a total of 300 samples with 150 in each group (propofol and nonpropofol), respectively.

We incubated all blood agar plates at 37°C for 48 hours (630D, Fisherbrand Isotemp, Stephens City, VA) with CFU per milliliter calculated by total colonies present (Fig. 2) divided by weight in micrograms multiplied by 1000 to get CFU per milliliter (correction factor 1000 µgmL approximately density of water) according to standard laboratory methods.[15] Colony morphology was noted, and pure isolates were submitted for speciation via bioMérieux (Vitek 2, Durham, NC). In the decade before mainstream propofol use, clinical studies indicated a low level of IV fluid contamination of 11% yielding microbial contaminants;[16] other studies identified contamination rates as high as 32%.[17]

We collected data using an Excel spreadsheet (version 2010, Microsoft, Redmond, WA) and analyzed them with SAS version 9.2 (SAS Institute, Cary, NC). We hypothesized that propofol increases the presence of bacterial contaminants at 48 hours. We modeled the number of bacteria using the administration of propofol anesthesia or nonpropofol anesthesia as the explanatory variable by negative binomial regression due to overdispersion, because the variance was greater than the mean.

Our secondary hypothesis required testing whether post–propofol anesthesia bacterial contamination (CFU per milliliter) in IV stopcock dead spaces increased over time compared with post–nonpropofol anesthesia; we wanted to discern whether there were any significant differences in positive bacteria counts regardless of whether residual propofol was visible. All positive bacteria counts were compared using negative binomial regression with grouping variable (visible propofol, nonvisible propofol, nonpropofol group) as the explanatory variable at each interval. Observed counts in average CFU per milliliter per group and holding times are listed in Table 1 and Figures 3 and 4. An additional log-linear mixed model with grouping variable with 3 levels, time variable with 3 levels (6, 24, and 48 hours), and time and group interaction were included in the model as fixed effects. Sample id was included as a random effect to account for correlation among measurements from the same sample at different intervals. Post hoc multiple comparisons were performed using Tukey–Kramer method. Diagnostic plots were reviewed to assure validity of the models. Kruskal–Wallis test was used to confirm the differences in counts among the 3 groups.

RESULTS

Positive bacterial cultures were recovered from 17.3% of propofol anesthesia stopcocks (26/150) and 18.6% of nonpropofol anesthesia stopcocks (28/150). Growth of all samples per respective holding times was averaged in CFU per milliliter plus 1 SD (1δ) with subset averages from only positive samples analyzed (Table 1). At 6 hours, we observed average values for visible propofol in the dead space at 44 CFU/mL and no visible propofol in the stopcock dead space from propofol-receiving patients and nonpropofol-receiving patients at 41 and 37 CFU/mL, respectively. At 24 and 48 hours, the incidence of positive bacterial cultures remained unchanged (Table 1), but differences in average bacterial counts were readily apparent (Figs. 3 and 4). When comparing all samples, average bacterial counts at 48 hours for propofol and nonpropofol groups were 472 and 4 CFU/mL, respectively. When comparing only positive samples at 48 hours, averages from the visible propofol group were 5066 CFU/mL, compared with the nonvisible propofol group at 831 CFU/mL and nonpropofol group at 30 CFU/mL. There was no evidence of significant differences among the 3 groups according to the negative binomial regression model or the Kruskal–Wallis test at 6 hours, although there were significant differences among the groups using both methods at 24 and 48 hours (Table 2).

Log-linear mixed-model analysis performed to compare visible propofol, nonvisible propofol, and nonpropofol groups showed that group and time were significant predictors of the number of bacteria (P values of 0.0005 and 0.006, respectively), although there was no strong evidence of significant interaction between group and time ($P = 0.09$). Multiple comparison tests using the Tukey–Kramer method showed that there were no significant differences among groups at 6 hours ($P = 0.99$), but number of bacteria was significantly higher for the visible propofol group than the nonvisible group ($P = 0.03$) and the nonpropofol group at 24 hours ($P = 0.0008$). Similarly, number of bacteria observed in the visible propofol group was significantly higher than in the nonvisible propofol and nonpropofol groups at 48 hours (P values of 0.01 and 0.0003, respectively). Table 3 shows P values for differences in bacteria count in visible propofol, nonvisible propofol, and nonpropofol groups at each time

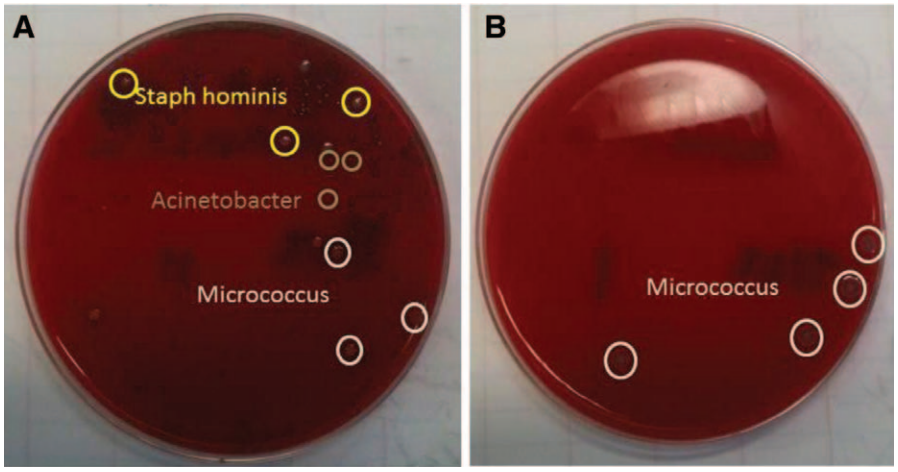

Figure 2. Cultures of IV extension set stopcock aspirates at 24 hours postoperatively. Plate (A) is from stopcock with visible residual propofol totaling 188 colonies (7230 CFU/mL). Plate (B) is from nonpropofol anesthesia stopcock totaling 4 colonies (60 CFU/mL). CFU = colony forming units. Staph = *Staphylococcus*.

Table 1. Average Colony Forming Units per Milliliter from IV Extension Set Stopcock Dead Spaces Held at Room Temperature After both Propofol and Nonpropofol Anesthesia

Hold times	Propofol		Nonpropofol	
6 h				
Samples (+) bacteria per total	8/50	(16%)	6/50	(12%)
Average (all samples) CFU/mL + 1δ	7 + 22	(*n* = 50)	4 + 14	(*n* = 50)
Average only (+) bacteria CFU/mL + 1δ	43 + 41	(*n* = 8)	37 + 21	(*n* = 6)
24 h				
Samples (+) bacteria per total	10/50	(20%)	16/50	(32%)
Average (all samples) CFU/mL + 1δ	278 + 1131	(*n* = 50)	31 + 96	(*n* = 50)
Average only (+) bacteria CFU/mL + 1δ	1526 + 2387	(*n* = 10)	94 + 154	(*n* = 16)
48 h				
Samples + bacteria per total	8/50	(16%)	6/50	(12%)
Average (all samples) CFU/mL + 1δ	472 + 2017	(*n* = 50)	4 + 11	(*n* = 50)
Average only (+) bacteria CFU/mL + 1δ	2949 + 4487	(*n* = 8)	30 + 12	(*n* = 6)

CFU = colony forming units; 1δ = 1 SD.

point obtained using mixed-model analysis along with estimates for differences and 95% confidence intervals on log scale. Median and 95% confidence intervals for the ratio of number of bacteria comparing pairs of groups are reported as well.

A representative set of colonies from each holding interval was submitted for speciation (Table 4). Review of microorganisms indicated that sources were most likely skin flora and environmental fomites. The bulk of bacteria recovered were Gram-positive cocci at varying levels of CFU per milliliter. Densities of slower growing bacteria, such as *Micrococcus* and *Kocuria*, had only moderate growth after propofol anesthesia compared with higher yields of *Staphylococcus*, *Acinetobacter*, and *Pseudomonas* after propofol anesthesia. The concentration of Intralipid varied widely and was not evaluated in this study; we noted presence or absence of visible propofol in the IV extension set stopcock dead space of patients known to have received propofol via those stopcocks.

DISCUSSION

In our study, we held IV stopcocks in isolation after removal from patients and measured bacterial contaminants up to 48 hours later. At our institution IV tubing sets are changed every 96 hours from time of initial use, except for propofol infusion sets (changed every 24 hours) and total parenteral nutrition sets (changed every 48 hours). In many hospitals, IV tubings are changed immediately after anesthesia in postoperative care units (PACUs), but this is not a patient safety standard. Considering the average patient who receives anesthesia, we wanted to determine whether IV stopcock contamination in the operative period posed subsequent risk if nutrient-rich medications were used during anesthesia. These data are most significant for patients who will continue to have their associated IV connections in place after anesthesia, especially those with longer term access at central lines and peripherally inserted central catheters. We isolated IV tubing sets after same-day surgery to limit possible contamination from subsequent hub interactions to

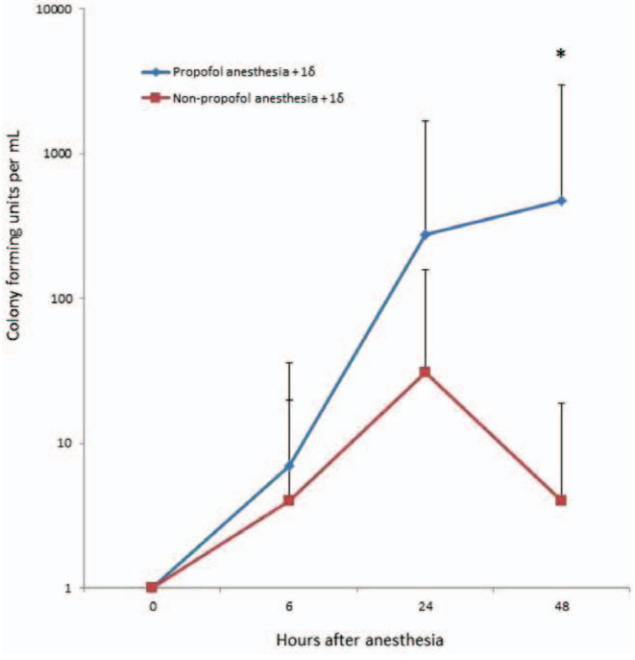

Figure 3. Growth of all samples in average colony forming units per milliliter at respective holding times plus 1 SD (1δ). **P* = 0.0008.

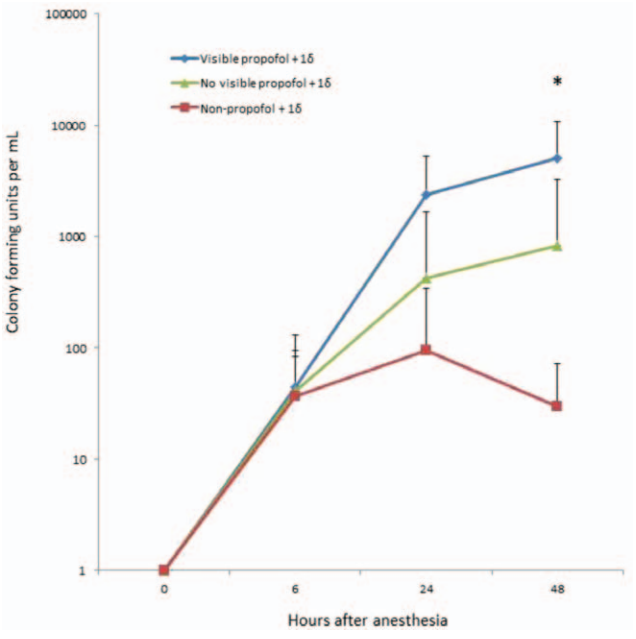

Figure 4. All samples with (+) bacterial growth in average colony forming units per milliliter at respective holding times plus 1 SD (1δ). **P* = 0.03 visible vs nonvisible vs non.

Table 2. Mean and Medians of Number of Bacteria Reported with Their 95% CIs Along with *P* Values Comparing Number of Bacteria Among Visible Propofol, Nonvisible Propofol, and Nonpropofol Groups at Each Time Point

	Mean/median (95% CI)				P values	
			Propofol			
Hold times	Nonpropofol	Propofol	Visible propofol	Nonvisible propofol	Kruskal–Wallis	Negative binomial regression
6 h					0.85	0.8
Mean (95% CI)	37 (14–59)	43 (9–77)	44 (0–106)	42 (0–118)		
Median (95% CI)	29 (14–65)	24 (17–114)	33 (11–100)	18 (17–114)		
24 h					**0.04**	**0.02**
Mean (95% CI)	95 (13–177)	1390 (0–3029)	2361 (0–6045)	418 (0–1418)		
Median (95% CI)	42 (32–74)	146 (38–2968)	1400 (42–7231)	53 (19–1857)		
48 h					**0.03**	**0.0002**
Mean (95% CI)	30 (18–43)	2949 (0–6700)	5066 (0–14,131)	831 (0–3374)		
Median (95% CI)	29 (15–45)	133 (24–10,000)	5091 (83–10,000)	45 (8–3228)		

CI = confidence interval.

specifically address contamination associated with anesthesia. It is local routine practice to have 1 IV stopcock extension used for all injections.

We measured positive bacterial cultures in 16% to 20% of IV stopcocks after propofol anesthesia, compared with 12% to 32% after nonpropofol anesthesia, which is consistent with previous studies that reported ranges of 11% to 32%.[16,17] Importantly, our study found a significant difference in bacterial density over time in the IV extension stopcocks after propofol anesthesia compared with nonpropofol anesthesia, as seen in the growth curve up to 48 hours (Fig. 3). It is unknown how many IV sets collected were from ambulatory patients remaining in the PACU beyond the average discharge time of <90 minutes (cursory review of PACU stays overall at these locations during the study period indicated this number to be <10%). This in vitro trial after routine anesthesia allowed comparison of bacterial growth over time after propofol and nonpropofol anesthesia without confounders from subsequent hub use for medication delivery. However, this study does not directly measure the actual bacterial burden experienced by patients in the context of an in-hospital setting.

Neither were the numbers of hub interactions recorded intraoperatively, nor were they noted postoperatively, because this study was blinded to all care providers in order not to detract from usual practices. Regardless of degree of acute care IV access handling and length of procedure, the incidence of contaminated stopcocks between propofol anesthesia and nonpropofol anesthesia was similar. Positive cultures were recovered from IV stopcocks at a rate of 17.3% after propofol anesthesia (26/150) and 18.6% after nonpropofol anesthesia (28/150). This may be biased due to an uninvestigated equivalent number of hub interactions during ambulatory anesthesia or directly observed vigilance of hand hygiene between anesthesia providers. It is expected that ambulatory anesthesia procedures require a much different degree of acute care IV access handling than main operating room procedures, and consequently have different (less) potential for contamination. Yet, baseline quantitative cultures at 6 hours yielded equivalent average bacterial counts from stopcocks with visible propofol (44 CFU/mL), compared with 41 CFU/mL in those stopcocks with nonvisible residual propofol, and 37 CFU/mL in stopcocks after nonpropofol anesthesia. The fact that there was no detected difference at time 6 hours may have been due to small sample size and skewness with corresponding large confidence intervals.

It is important to note that preservative-containing propofol was used throughout this study and could have reduced contamination within the first 6 hours. Surgery duration for ambulatory procedures in which propofol was used ranged from 1 to 2 hours, with >1 dozen hub interactions compared with less than half an hour for the nonpropofol group, where the total number of drugs administered ranged from 2 to 6 with less than a dozen hub interactions in total. This difference may render the former an inappropriate control group considering the varying degrees of acute care IV handling, but the incidence of contamination and average baseline counts were similar among all groups at 6 hours. The fact that the IV sets in this study had no other nutrient-rich infusions (i.e.,

Table 3. Differences in Bacteria Count on Log Scale Among Visible Propofol, Nonvisible Propofol, and Nonpropofol Groups at Each Time Point Obtained Using Mixed-Model Analysis

Hold times	Groups compared	Mean difference (log scale)	SE (log scale)	*P* value	95% CI for difference (log scale)	95% CI for ratio of medians (anti-log scale)
6	Visible propofol versus nonvisible propofol	0.16	1.02	0.87	(−1.9 to 2.2)	1.2 (0.2–9.1)
	Visible propofol versus nonpropofol	0.02	0.93	0.98	(−1.8 to 1.9)	1 (0.2–6.6)
	Nonvisible propofol versus nonpropofol	−0.14	0.93	0.88	(−2 to 1.7)	0.9 (0.1–5.6)
24	Visible propofol versus nonvisible propofol	2.02	0.91	**0.03**	(0.2–3.8)	7.5 (1.2–46.9)
	Visible propofol versus nonpropofol	2.65	0.74	**0.0008**	(1.2–4.1)	14.1 (3.2–62)
	Nonvisible propofol versus nonpropofol	0.63	0.74	0.40	(−0.9 to 2.1)	1.9 (0.4–8.2)
48	Visible propofol versus nonvisible propofol	2.64	1.02	**0.01**	(0.6–4.7)	14.1 (1.8–108.7)
	Visible propofol versus nonpropofol	3.67	0.93	**0.0003**	(1.8–5.5)	39.1 (6–253.2)
	Nonvisible propofol versus nonpropofol	1.02	0.93	0.28	(−0.8 to 2.9)	2.8 (0.4–18)

CI = confidence interval.

Table 4. Microorganism Concentrations Found in IV Extension Set Stopcock Dead Spaces After Propofol and Nonpropofol Anesthesia at Respective Holding Times

Propofol	CFU/mL	Nonpropofol	CFU/mL
6 h			
Staphylococcus epidermidis	18	*S warneri*	14
Acinetobacter	18	*S cohnii*	65
Micrococcus	46	*Micrococcus*	61
Kocuria	69	*Kocuria*	14
24 h			
S hominis	269	*Dermacoccus*	51
Micrococcus	115	*Micrococcus*	33
Acinetobacter	6846	*Kocuria*	79
S epidermidis	2968	*Streptococcus sanguinis*	41
48 h			
Pseudomonas oryzihabitans	>10,000	*S lentus*	31
Micrococcus	83	*Micrococcus*	45
Kocuria	182	*Kocuria*	15

CFU = colony forming units.

blood products, platelets, and total parenteral nutrition) supports the hypothesis that propofol alone can contribute to increased bacterial counts and to the risk of iatrogenic infection after propofol anesthesia.

Recent "Scrub the Hub" campaigns[18] encourage anesthesiologists to follow best-practice guidelines for disinfection of IV hubs with isopropyl alcohol before syringe or infusion tubing connection. A direct relationship between scrub duration and stopcock decontamination by residual fluorescent powder has been demonstrated.[19] Preventing stopcock contamination by improving hand hygiene compliance rates among anesthesia providers is also a clear goal. Real-time observations in the operating room by Loftus et al.[5] showed that contamination by anesthesia providers' hands persists and serves as a significant source of stopcock set contamination. We should continue to emphasize intraoperative hand hygiene both before and during patient care, but also consider postoperative decontamination strategies. With opportunities to use needleless hubs, this may require further investigation to determine efficacy of routine disinfection before handling every injection site in the operating room. Notwithstanding a 3- to 5-second swabbing of 70% alcohol pledget, Menyhay and Maki[20] found needleless Luer-activated connectors remained heavily contaminated by downstream quantitative cultures on the intraluminal side.

Our IV tubing sets also contained needle-free injection ports at various points. But to ensure no interference with usual practices, hub interactions were not monitored nor did we did trace whether the stopcock was the only possible access site for propofol delivery. There were, however, stopcocks with visible residual propofol, clearly identifying the propofol site of delivery. In comparison, Fukada and Ozaki[12] evaluated 3 venous access systems and growth of MRSA-contaminated propofol containing EDTA over 24 hours: 1 system with very little dead space (Planecta) versus a standard 3-way stopcock (TOP) and a 3-way stopcock plus needle-free adaptor (Interlink). They observed residual amounts of propofol in all 3 types of dead spaces and detected MRSA growth in all 3 systems at 6 hours, with logarithmic growth at 24 hours in the stopcocks.

Visible residual propofol in the stopcock was evident in multiple samples: 13 stopcocks with visible residual propofol had positive bacterial growth, and 14 had no detected growth. Considered alone, this observation yields an alarming 48% incidence of bacterial contamination when propofol remains visible in the IV stopcock dead space.

We acknowledge our study's approach is limited to the small sample volumes aspirated from the IV extension set's stopcock dead space. Yet, our results reinforce prior observations of bacterial transmission intraoperatively and, specifically, they identify the key role that propofol plays in enhancing bacterial amplification after IV extension set stopcock contamination after anesthesia. Our study is limited to only the IV stopcock dead space and does not allow us to assess total bacterial burden in IV tubing after propofol anesthesia.

Our high *Pseudomonas* count was also observed by Crichton[17] in a study of Intralipid with intentional bacterial seeding with *Serratia, Pseudomonas*, and *Klebsiella,* in which confluent growth at 48 hours was recorded. Considering this bacterial burden and the outcomes of critically ill patients, Haddad et al.[21] showed the use of preservative-free propofol as having an association with increased risk of ICU-acquired infection and with ICU-acquired severe sepsis and septic shock.

Other microbial analyses of Intralipid without preservative found that bacterial growth occurred as early as 6 hours after incubation and was at levels of clinical concern within the first 12 hours, about 103 to 104 CFU/mL.[22] It is possible that residual propofol in IV tubing after anesthesia may have diluted preservative and bacterial growth becomes easier. Interestingly, the spectrum of microorganisms recovered in our study is similar to that found by Loftus et al.,[6] whose perioperative surveillance found hand contaminants in 49% to 100% of anesthesia providers, including *Micrococcus*, *Staphylococcus,* and Gram-negative bacteria.

The fact that adherence to Surgical Care Improvement Project measures alone is not obviously associated with a significantly lower probability of postoperative infection[23] suggests there are other perioperative sources yet to be addressed. Many patients receive propofol via an IV stopcock access point during the course of an anesthetic. Previous work by Langevin et al.[3] showed deliberate infection of *S aureus* was recovered from rabbit kidneys regardless of whether bacterial suspensions were injected IV with Intralipid or followed after Intralipid with saline injection. These findings support our hypothesis that bacterial

contaminants in the IV stopcock and other dead space in the IV tubing may thrive after propofol anesthesia and suggest that inadvertent injection may become a significant stress to a vulnerable patient.

The incidence and quantity of IV tubing bacterial contamination after exposure to propofol with preservative is well known through in vitro studies. Microbial contamination in IV stopcock dead spaces after routine anesthesia has been studied previously, but not in regards to propofol compared with nonpropofol anesthesia. We hypothesized bacterial amplification occurs in IV stopcock dead spaces after propofol anesthesia even when there is no visible residual propofol. Identification of this risk suggests the need for a standard of care to remove (or replace) the IV tubing sets after propofol anesthesia. This in vitro study does not directly correlate to IV catheters remaining in situ for 48 hours postoperatively. However, this study is important from a patient safety standpoint because it indicates a continued need for improved hand hygiene skills in anesthesia providers; it also suggests, given the data on bacterial growth after 6 hours, that removal (or exchanging) of IV extension sets after propofol anesthesia may warrant a new standard of care. ■

DISCLOSURES

Name: Devon C. Cole, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Devon C. Cole has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Tezcan Ozrazgat Baslanti, PhD.
Contribution: This author helped with the statistical analysis of the data.
Attestation: Tezcan Ozrazgat Baslanti has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Nikolaus L. Gravenstein, BS.
Contribution: This author helped design and conduct the study.
Attestation: Nikolaus L. Gravenstein has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Nikolaus Gravenstein, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Nikolaus Gravenstein has seen the original study data, reviewed the analysis of the data, and approved the final manuscript. Dr. Gravenstein will be the archival author.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

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