Gonzalo Bearman
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Infection Prevention

New Perspectives and Controversies

Second Edition

Springer

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ISBN 978-3-030-98426-7 ISBN 978-3-030-98427-4 (eBook)
https://doi.org/10.1007/978-3-030-98427-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

We dedicate this book to our mentors and patients, and to the commitment, bravery, and sacrifice of our healthcare colleagues.

Foreword

The impact of healthcare-associated infections remains substantial: if there were a specific vital statistic, these infections would rank in the top 10 causes of death in the United States and many other countries. Morbidity, economic consequences, and lasting psychological stresses for affected patients are increasingly documented. At the same time, we face the global threat of rising antibiotic resistance, impairing effective prevention and therapy of these infections.

Recently, the advent of Covid-19 has added enormous stresses to the healthcare system, almost to the breaking point, with filled ICU beds, financial stresses, and increasing numbers of healthcare workers leaving the field with physical and emotional exhaustion. Moreover, resources and time to manage healthcare-associated infections have been diverted to the minute to minute demands related to Covid-19. At a societal level, there has been an erosion of trust in large institutions and medical and science expertise, limiting the extent to which infection control practitioners can engage patients, their families, and friends.

In the last 50 years of our young science, there has never been a more challenging time for infection control in the healthcare setting.

So, the timing is propitious for leaders in our field to articulate what we know, what we don't know, and what assumptions currently guide our policies. The editors of the second edition of *Infection Prevention: New Perspectives and Controversies* have done that with clearly written chapters by internationally recognized experts, summarizing the current state of knowledge. As Covid-19 recedes, this book will make a difference, guiding the pathway of reinvigorating infection control in the delivery of healthcare. It is a valuable resource for practitioners in our field.

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Preface

He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all. –Sir William Osler

Inspired by our patients, mentors, and colleagues to maximize safety in healthcare, and with the goal of highlighting key topics in the rapidly evolving science of infection prevention, we are proud to publish the second edition of *New Perspectives and Controversies in Infection Prevention*. We partnered with distinguished colleagues and collaborators in infectious diseases, epidemiology, infection prevention, and antimicrobial stewardship for an up-to-date summary in the field of healthcare epidemiology, with a focus on new and evolving perspectives and ongoing controversies. We hope that this text serves as a valuable point of reference along the continuous journey of growing knowledge in infection prevention and patient safety.

Contained herein are ongoing controversies such as the use contact precautions for endemic pathogens, decolonization strategies for multidrug-resistant organisms, the role of hand hygiene technologies in healthcare, and the role of antimicrobial textiles in infection prevention. New perspectives are explored in various topic areas including the evolving role of rapid diagnostics in infection prevention and the use of whole genome sequencing for outbreak investigations. Practical guidance is provided for animals in healthcare settings and testing water for Legionella prevention. With the COVID-19 pandemic, the importance of healthcare epidemiology, along with the role of the hospital epidemiologist, is summarized.

Although textbooks are limited by size, scope, and date of publication, we provide a digestible summary of current infection prevention knowledge for the practicing healthcare epidemiologist, infection preventionist, and trainee, both as a guide for day-to-day matters and as a point of departure for future research and inquiry.

As always, we welcome your thoughts, feedback, and novel perspectives on the ever-evolving field of healthcare epidemiology and patient safety.

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Acknowledgments

The authors would like to acknowledge Ms. Peggy Andrews-Depew for coordinating our editorial team meetings and Mr. Janakiraman Ganesan for keeping the collaboration on track.

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HAI Controversies: Contact Precautions

1

Elise Martin, Zachary Rubin, and Rekha K. Murthy

Introduction

Despite the widespread use of contact precautions in acute care hospitals, even after decades of experience, the use of contact precautions (CP) remains controversial [1]. This chapter aims to review the current controversies related to CP in acute care hospital settings, identify potential areas for future study, and provide updated information where available.

Current Guideline Recommendations for Contact Precautions in Acute Care Facilities

Current national guidelines from the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Centers for Disease Control and Prevention (CDC) broadly recommend that contact precautions (CP) be implemented routinely in "all patients infected with target MDROs and for patients that have been previously identified as being colonized with target MDROs" without identifying explicitly which multidrug-resistant organisms (MDROs) are to be included [2]. In addition, multiple guidelines address strategies for preventing cross-transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) in acute care settings that reference the use of CP. The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) jointly recommend that CP be used for MRSA-infected and MRSA-colonized patients in acute care settings for the control of MRSA in both endemic and outbreak settings [3]. A SHEA/IDSA joint guidance document also recommends that CP be used for patients with *C. difficile* infection for the duration of illness and notes that some authors recommend CP for up to 48 h after resolution of diarrhea [4]. Furthermore, the role of CP continues to be important for new and emerging pathogens such as *Candida auris*.

Despite these recommendations, recent publications have identified variations in policies among acute care facilities [1]. An increasing number of acute care hospitals surveyed do not apply CP for endemic MRSA and, in some cases, for endemic VRE in the setting of high compliance with hand hygiene, environmental cleaning, or other horizontal infection control strategies [1]. The COVID-19 pandemic also led many hospitals to conserve the PPE needed to care for COVID-19 patients, including gowns and gloves that would also be necessary for MRSA and VRE CP [5]. As many reevaluate the use of contact precautions for MRSA and VRE, some are even questioning it if it is actually something "we do for no reason," further highlighting the ongoing controversy [6].

In this chapter, we review the controversies associated with the use of CP for MRSA, VRE, multidrug-resistant gram-negative rods (MDR-GNR), *Clostridium difficile*, and *C. auris* in endemic or non-outbreak settings.

History of Isolation Precautions

In 1970, the CDC first sought to standardize the application of what are now called "transmission-based precautions" with the publication of the first edition of *Isolation Techniques for Use in Hospitals* [7]. The goal of this document was to prevent the spread of infectious pathogens within the hospital milieu and at the same time try to minimize what they saw

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_1

as the costs of isolation: added expense, inconvenience, decreased visits by providers, and psychological duress. In order to balance these sometimes competing goals, the CDC developed a graded isolation scheme based upon the mode of pathogen transmission. The categories were to be placed on colored cards on room doors and provide directions for incoming providers and visitors. The categories included the following categories, which would later become standard precautions and contact precautions: strict isolation, enteric precautions, wound and skin precautions, discharge precautions, which included excretion precautions, secretion precautions, and blood precautions [8]. Clinical staff determined which category patients best fit into based upon a combination of clinical syndromes and the isolation of specific pathogens. The second edition of *Isolation Techniques for Use in Hospitals* published in 1975 did not significantly alter the scheme [9].

In 1983, the CDC significantly revised isolation precautions schemes in the CDC Guideline for Isolation Precautions in Hospitals [10]. This document still included both category and disease-specific isolation systems and required end users to determine the best category. Soon after the 1983 document was published, however, the HIV epidemic led to the adoption of "universal precautions" for all blood and body fluids other than sweat in the mid-1980s [11, 12].

Ultimately, the 1996 Guidelines refined and simplified isolation precautions further and into its current form [8]. Instead of the complex and often subjective categories of previous guidelines, the categories of isolation practices were simplified into three transmission-based categories: contact, airborne, and droplet precautions. Additionally, "universal precautions" and body substance isolation were combined into the "standard precautions" in use today. The most recently published Guideline from 2007 essentially upheld this general simplified scheme intact with some minor updates [13].

Vertical Versus Horizontal Infection Control Strategies

Acute care hospitals employ a number of strategies to decrease healthcare-associated infections (HAIs) and the spread of resistant organisms between patients. In general, these infection prevention strategies can be grouped into two types of programs: vertical and horizontal strategies [14, 15]. Vertical approaches focus on specific pathogens and utilize targeted programs such as active surveillance testing (AST) to identify patients with specific organisms, followed by interventions to specifically prevent the spread of those organisms [14]. Horizontal programs are more broadly focused and aim to decrease the spread of any pathogen that could lead to an HAI through programs such as hand hygiene and standard precautions that are applied to all patients in the health system, not only those with resistant pathogens [14]. There are pros and cons to both strategies, and many hospitals use a combination of these interventions [16].

Vertical infection prevention programs are aimed at decreasing HAIs by focusing on high-risk pathogens that may be transmitted from patient to patient [14, 15, 17]. These programs are based on first identifying patients with a particular pathogen and then decreasing spread. Vertical programs have been used for a variety of high-risk pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Clostridium difficile*, multidrug-resistant gram-negative pathogens, and others [14]. Most of these programs are centered on the use of AST, in addition to identifying infected patients, to detect patients who are MDRO carriers as well. Infection prevention strategies are then employed to prevent the spread of these particular pathogens through interventions such as CP, isolation, and cohorting of patients. Decolonization strategies may also be applied for patients for a specific pathogen, such as MRSA, through the use of chlorhexidine gluconate (CHG) bathing or mupirocin [14]. While these strategies may decrease the spread of each of these specific organisms, each strategy only targets one specific pathogen, and not all important organisms, such as MRDO gram negatives and VRE, have options for decolonization.

Horizontal infection prevention strategies have a much broader focus. Instead of targeting a single high-risk pathogen, they focus on initiatives that reduce HAIs from any pathogen. One of the most well-known strategies is standard precautions, which include effective hand hygiene and the use of personal protective equipment when encountering body fluids [14]. Hospitals can also develop antimicrobial stewardship programs to decrease the development of resistant organisms, remove unnecessary medical devices to decrease the risk of device-associated infections, and improve environmental cleaning to decrease the risk of infection to subsequent patients [14]. Some of the interventions used for a specific organism, such as gloving, the use of other personal protective equipment, and decolonization with CHG, can be applied universally to all patients, not just those with a specific pathogen. These programs decrease the risk of infections from multiple organisms, including pathogens that have not yet been identified in the patient.

Groups have attempted to determine which of these is the optimal strategy to reduce HAIs [14, 15, 17]. Given that MRSA-focused interventions have become increasingly common, Wenzel, Bearman, and Edmond developed a model to assess the impact on mortality with a hospital intervention to reduce MRSA bloodstream infections (BSI) versus all causes of BSI [17]. Based on their calculations, even a 50% decrease in the rate of MRSA BSI would not impact mortal-

Table 1.1 Examples of vertical and horizontal infection prevention strategies

Vertical infection prevention strategies
Focus: specific pathogens (examples: MRSA, VRE, CRE)
Active surveillance testing to identify patients with specific pathogens
Contact precautions for specific pathogens
Spore precautions for specific pathogens
Targeted decolonization for specific pathogens
Horizontal infection prevention strategies
Focus: all pathogens, universal
Standard precautions (hand hygiene, barrier precautions when encountering fluids)
Universal gowning and gloving
Universal decolonization of all patients
Environmental cleaning and disinfection
Antimicrobial stewardship
Minimizing unnecessary medical devices

Modified from Septimus et al. [14] and Wenzel and Edmond [15]
MRSA methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant *Enterococcus*, *CRE* carbapenem-resistant Enterobacteriaceae

ity as much as can be achieved with just a 25% decrease in overall BSI [17]. The authors of this study argue that focusing on a single pathogen may be insufficient to reduce HAIs, and instead, hospitals should employ a variety of evidence-based interventions to optimally reduce the risk of HAIs to patients.

While there are two main categories of infection prevention strategies, they are not mutually exclusive and are often used in combination to decrease the spread of resistant organisms and HAIs (Table 1.1) [14].

MRSA and the Impact of Contact Precautions

The Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA) still recommend the use of CP to decrease the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in acute care hospitals, but the practice has become increasingly controversial [1, 3, 18]. Concerns include both the lack of evidence clearly showing benefit and data suggesting potential patient harm associated with CP. Despite the controversy, prior surveys have demonstrated that more than 90% of US acute care hospitals still use CP for MRSA, although data are needed on more recent practices [1, 16].

Although MRSA rates have been declining, MRSA remains a serious threat according to the CDC's 2019 Antimicrobial Resistance Threat report [19]. The CDC estimates that there were 323,700 cases of MRSA in hospitalized patients and 10,600 deaths in 2017 [19]. For this reason, efforts have been made to decrease the spread of MRSA in healthcare settings through various initiatives, including CP. According to published reports, up to 18% of patients are isolated for MRSA in acute care hospitals [20, 21].

Multiple studies have attempted to examine the benefit of CP for MRSA. The Veterans Affairs hospitals developed an "MRSA bundle," composed of universal surveillance, CP, improved hand hygiene, and an institutional culture change, that was associated with a decrease in transmissions of and infections with MRSA [20]. The study showed that MRSA infections in intensive care units (ICUs) decreased by 62% after the implementation of the bundle, from 1.64 to 0.62 infections per 1000 patient-days (PD) ($p < 0.001$). MRSA infections also decreased in non-ICUs by 45% from 0.47 to 0.26 per 1000 PD ($p < 0.001$). Another study by Huang et al. in 2006 utilized an interrupted time series to look at multiple interventions over a 9-year period and found that routine surveillance cultures and subsequent contact precautions lead to a 67% hospital-wide reduction in MRSA bacteremia ($p = 0.002$) [22]. French hospital found that MRSA acquisition decreased in their facilityContact precautionsisolation precautions from 7.0% to 2.8% after instituting weekly MRSA surveillance screening followed by CP [23]. A study evaluating universal gowning and gloving also found that MRSA acquisition decreased in ICU patients by 2.98 acquisitions per 1000 person-days ($p = 0.046$), although the primary outcome of MRSA/VRE acquisition was not met [24]. A large study from three hospitals found a reduction in MRSA disease during admission and 30 days after discharge with the introduction of universal surveillance and isolation for MRSA [25]. While these studies do show benefit with the use of CP, because these studies all used a combination of strategies, it is difficult to tease out whether it was the gowns and gloves specifically or if other factors drove the improvement. In addition, several of these studies were based in the ICU, and it is unknown if the results are generalizable to non-ICU settings.

Several other studies looking at the impact of CP for MRSA have not shown a benefit. A group from a Swiss teaching hospital performed a prospective, interventional cohort study with crossover on a surgical ward and found that MRSA nosocomial infection was not reduced with CP, AST, and targeted decolonization [26]. Another group performed a cluster randomized trial in 18 ICUs to evaluate the impact of enhanced surveillance for MRSA colonization and expanded use of CP and found no reduction in the transmission of MRSA, although the use of CP by providers was less than expected [27].

Given the conflicting data about the benefit of CP, multiple institutions have evaluated the impact of discontinuing CP for endemic MRSA [1]. One health system eliminated routine CP for MRSA in both their hospitals and started universal CHG bathing [28]. They found no increase in MRSA infections or colonization. The study also demonstrated a $643,776 cost savings in 1 year and significant savings in

healthcare worker time. Another study looked at the impact of discontinuing CP on device-associated infections and found no increase in these infections after they removed routine CP in both the ICUs and the wards [29]. A study from a surgical ICU compared the use of universal gloving to standard CP and found that universal gloving in their unit was associated with improved hand hygiene compliance and skin health and was not associated with a significant change in the rates of device-associated infection, *Clostridium difficile* infection, or multidrug-resistant organism acquisition [30]. While there has been limited data on the longer impacts of discontinuing routine MRSA CP, a recent interrupted time series from three hospitals found no significant increase in device-associated infections 4–13 years after CP were removed [31]. While these data are encouraging, limited data are available on the optimal hospital conditions necessary to make discontinuation of MRSA precautions successful, such as hospital size, HAI rates, and infection prevention practices.

A number of studies have evaluated the possible negative impacts of CP and the potential harms to those placed in isolation. Several studies have shown decreased contact with healthcare providers, including fewer bedside visits from healthcare providers, shorter contact time during those visits, fewer physical examinations by attending physicians, and fewer progress notes documenting their visits when compared to patients not on CP [32–37]. Patients on CP can also experience delays in transitions of care, including from the emergency room and discharge to skilled nursing facilities [37–40]. There is also evidence that patients on CP have higher rates of anxiety and depression during their hospitalization and lower satisfaction with their care [37, 41, 42]. The data on other adverse events have been conflicting. While some have found an association with increased preventable adverse events, such as pressure ulcers, falls, and medication administration errors, others have found a decrease in adverse events in patients on CP [37, 43, 44]. One hospital found that noninfectious adverse events decreased by 19% (12.3 to 10.0 per 1000 admissions, $p = .022$) after CP were discontinued for MRSA/VRE, with the largest reduction in the patients with known MRSA/VRE, who were no longer isolated in the post period (72% reduction; $p < 0.001$) [45].

Although the data on the efficacy of routine CP for endemic MRSA is controversial, it remains common practice [1, 16]. Currently, at least 30 US hospitals have discontinued routine CP for MRSA and are instead using other horizontal infection prevention strategies, such as improved hand hygiene, HAI bundles, decolonization, and syndromic indications for precautions (i.e., draining wounds) [1]. While the early data on discontinuing CP is encouraging, future research with larger trials is needed to conclusively determine whether or not CP are necessary for endemic MRSA. Further data are also needed on whether select populations may benefit from MRSA CP and the optimal strategies for discontinuing CP.

Vancomycin-Resistant *Enterococcus* (VRE)

In a recent survey of US-based physicians conducted by the Emerging Infections Network (EIN), 92% of 364 respondents reported routinely using CP for vancomycin-resistant *Enterococcus* [16]. As with MRSA, CP are commonly used for VRE, and although multiple publications have reported the benefits of CP in terminating VRE outbreaks, few published studies have actually examined the use of CP alone as an intervention to reduce VRE acquisition, particularly in non-outbreak settings [1].

Bearman et al. conducted two quasi-experimental studies where CP for patients with VRE was compared with universal glove use [30, 46]. The authors found no difference in VRE acquisition and found higher healthcare-associated infection rates with universal glove use in one of the studies. In a systematic review and meta-analysis of measures taken to control VRE in ICU settings, De Angelis et al. reported results from three studies in which application of CP was the only intervention. In these studies, CP did not significantly reduce the VRE acquisition rate (pooled relative risk, 1.08 [95% CI, 0.63–1.83]) [47]. Three other studies that examined the impact of CP on VRE acquisition in ICUs were cluster randomized trials [24, 27, 48]. Huskins et al. compared CP in the intervention group after active screening cultures (ASC) to standard precautions and found that the incidence of colonization or infection with VRE did not differ between the two groups ($p = .53$) [27]. In a cluster randomized trial among ICUs, Harris et al. evaluated intervention ICUs where HCP wore gowns and gloves for all patient contacts and room entries in comparison with control ICUs where CP were used only for patients with known antibiotic-resistant bacteria. No difference in VRE outcomes was found by investigators [24]. Similarly, a study in the setting of universal chlorhexidine body washes and hand hygiene improvement identified no benefit to ASC for addressing VRE or other MDROs [48].

Although the majority of US hospitals use CP for endemic VRE, Morgan et al. identified at least 30 hospitals that reported not using CP for VRE and instead employing horizontal infection control methods, with CP reserved only for syndromes correlated with greater contamination (e.g., diarrhea, wounds) [1, 16]. Several of these institutions focus on general horizontal approaches to limiting the transmission of VRE, such as hand hygiene, bathing patients with chlorhexidine, and environmental cleaning and disinfection. However, these hospitals continue to apply CP for *Clostridium difficile* and multidrug-resistant gram-negative rods. Martin et al.

assessed laboratory-identified culture rates of VRE before and after discontinuing CP for endemic MRSA and VRE and expansion of chlorhexidine bathing to all hospital units. The study found no significant change in the average rate of positive cultures for VRE before and after the intervention, these were 0.48 and 0.40 cultures/100 admissions for VRE ($p = .14$), respectively [28]. Furthermore, discontinuing routine CP for endemic VRE did not result in increased rates of VRE after 1 year. The authors concluded that with cost savings on materials, decreased healthcare worker time, and no concomitant increase in possible infections, elimination of routine CP may add substantial value to inpatient care delivery. A recent interrupted time series by Haessler et al. from three large academic hospitals found no significant increase in device-associated infections 4–13 years after CP for VRE were removed and horizontal infection prevention strategies were strengthened [31].

In conclusion, although CP are widely used for VRE based on current national guidelines, no clear evidence has been identified to substantiate a benefit to CP over standard precautions in acute care settings for controlling the transmission of VRE in non-outbreak settings. Unfortunately, no study has compared CP with standard precautions alone, and other studies are limited by likely positive publication bias and generally low study quality. Alternative approaches using horizontal infection control strategies have been employed at some acute care facilities without adverse impact on VRE acquisition rates, although confidence in the achievement and sustainment of successful horizontal infection control strategies has been a common factor among these institutions [28, 49, 50]. Given the lack of robust clinical data to establish clear evidence-based guidelines, the experience from hospitals using these alternate approaches suggests that individual institutions should assess local factors, needs, and resources (e.g., availability of single rooms, VRE acquisition and infection data, potential susceptibility of patient populations such as immunocompromised patients, etc.) to determine the risks and benefits of modifying current policies on the use CP for VRE. Finally, higher-quality research on the risks and benefits of CP in endemic VRE in acute care hospitals is needed to determine more definitive recommendations.

Contact Precautions for Gram-Negative Rods and *Clostridium difficile*

While we have previously discussed that a lack of evidence for the benefits of CP for endemic MRSA and VRE has led some institutions to abandon CP for these indications, many of these same institutions have continued CP for gram-negative rods (GNRs) and *Clostridium difficile* infection (CDI) [1].

Any discussion of CP for GNRs is hampered by the great diversity of these organisms and the different approaches taken by various institutions to each. For example, Ronald Reagan UCLA Medical Center does not isolate extended-spectrum beta-lactamase (ESBL) organisms but has isolated carbapenem-resistant GNRs, while Cedars-Sinai Medical Center, just a few miles away, applies CP to both. This anecdotal variability of CP practices is also reflected in larger, systematic surveys [51]. It is unclear whether CP and other interventions against GNRs can and should be generalized across different species and resistance phenotypes. Interestingly, the HICPAC's 2007 Guideline for Isolation Precautions and the 2006 Management of Multidrug-Resistant (MDR) Organisms in Healthcare Settings recommend CP for drug-resistant GNRs in general [13, 52]. Neither guideline explicitly differentiates between different classes of GNR organisms. The authors of the latter HICPAC document posit a general, though largely untested, rationale for the general use of CP for all GNRs. Because MDR-GNRs and *C. difficile* are thought to be correlated with environmental contamination, the reasoning goes in the 2007 document: CP should decrease the risk of indirect transmission of infectious agents. Though the strongest rationale supporting CP is not entirely borne out by medical research, hospitals persist in their use of CP for MDR-GNRs and CDI for a host of assumptions:

1. There is a greater perceived institutional threat from the rising incidence of these emerging pathogens compared to MRSA and VRE [53, 54].
2. MDR-GNRs and CDI are thought to be more highly correlated to indirect contact transmission than MRSA and VRE because of a higher environmental burden.
3. MDR-GNRs require extra control measures because they may be higher pathogenicity organisms than MRSA and VRE.
4. Because there is a lower incidence of MDR-GNRs currently compared to more widespread MRSA and VRE in the community, these organisms are more amenable to successful control with CP.
5. MDR-GNRs and CDI are likely controlled less effectively by horizontal infection prevention strategies than MRSA and VRE.

There are many difficulties in reviewing the literature regarding CP for MDR-GNRs not only owing to the lack of prospective, controlled data but also to the inherent diversity and complexity of the organisms themselves. As stated above, the definition of "MDR" may vary between institutions and public health entities, leading to significant variations in practice. Second, GNRs include a broad and diverse category of organisms, including organisms like *Pseudomonas aeruginosa*, *Acinetobacter*, and

Enterobacteriaceae, that may have very different colonization and transmission characteristics. They also differ in regard to susceptibilities to environmental cleaners. Not only does this diversity make it hard to extrapolate a study of a single organism to others, it also leads to confusion when trying to use data-driven practice in individual hospitals.

Adding to the confusion, as institutions and public health departments increasingly employ molecular testing methodologies, we are learning that the previously established correlation between phenotypic and genotypic resistance that has been used clinically to define MDR status can be tenuous and can change rapidly. Certain types of resistance, such as plasmid encoded genes, are transferred between organisms more readily, while chromosomal genes are not—even though the organisms may look similar phenotypically. Organisms can add or drop plasmids quickly, even in a single patient over time, so the same *Klebsiella* phenotype can look different from one culture to the next and can cause considerable confusion among clinical staff trying to monitor these organisms. Additionally, as MDR-GNRs increase in frequency in previously hospitalized patients, it is becoming clear that CP applied only to those who have positive clinical isolates of MDR-GNR will exclude many asymptomatic carriers. As a result, the CDC and other organizations have recommended active surveillance cultures, at least in the case of carbapenem-resistant Enterobacteriaceae (CRE), for some populations [55]. As with MRSA and VRE, it is doubtful that CP are as effective without active surveillance.

There is ample, though not entirely supportive, evidence that CP is successful when applied to outbreak situations due to MDR Enterobacteriaceae. As with all papers describing control of outbreaks, it is difficult to separate out any single intervention, given that CP was used in addition to other control measures. Additional measures used to control outbreaks include monitored hand hygiene programs, active surveillance testing, and cohorting. There is also lower-level evidence of a similar effect with regard to *Pseudomonas* outbreaks [56, 57]. However, robust evidence is lacking to support CP for endemic MDR-GNRs. Most work has been done with ESBLs, but these studies usually include only a single institution, often lack comparison groups and do not offer detailed information about their CP practices. The BUGG Cluster Randomized Trial, the largest high-quality randomized study to assess the efficacy of universal glove and gown use in the care of ICU patients, found a "non-statistically significant decrease in acquisition of antibiotic-resistant gram-negative bacteria" when contact precautions were used for all patients [58]. An interrupted time series analysis that monitored ESBL rates after discontinuation of CP demonstrated a transmission rate of 2.6% without CP, compared to 1.5% with CP in place at the same hospital [59–60]. This difference was deemed not clinically significant by the investigators. A study in Germany that performed ESBL surveillance after initiation of CP found a low overall transmission risk, but as there was no comparison group, it is difficult to make any conclusions [61]. Another study showed no changes in the incidence of nosocomial ESBL *E. coli* and *Klebsiella* organisms after active screening of urine isolates and CP for all positive cases [62]. One study of active surveillance and CP of ESBL *Klebsiella* in a neonatal ICU in Israel showed a significant decrease in carriage, from 24% to 11%, though the high baseline rate of transmission suggests an outbreak and not a normal, endemic carriage pattern [63]. Aside from significant methodologic concerns as discussed above, a significant confounder for all of these studies is that most were performed in hospitals with rooms that housed two to four patients. There is evidence from a number of studies that placing patients in private rooms decreases transmission of MDR-GNR organisms and furthermore reduces the overall infection rate, though many of these studies do not include control wards [64]. Complicating this assertion, a randomized study from the Netherlands published in 2019 did not find any difference in ESBL transmission in hospitals between patients in single or double rooms when CP was used, suggesting that CP may be protective in this setting [65]. While ESBL presents a confusing problem because of the lack of controlled data, the case for carbapenem-resistant Enterobacteriaceae (CRE) is even less clear. The majority of studies on CRE are in outbreak settings and used a bundle of interventions, making it difficult to extrapolate to endemic settings [66, 67].

Preventing CDI transmission in hospitals, like all the other organisms we have discussed in this chapter, is likely best done with a bundle of interventions. As in the other cases discussed, there are few studies that study only CP in isolation from other interventions for the control of CDI. The transmission characteristics of CDI, like GNR's, is not well worked understood. Because hospitals do not have the techniques to characterize CDI genotypes easily, we rely on relatively few studies that have looked at CDI at individual institutions. What these studies continue to demonstrate, is that there are often multiple distinct CDI organisms causing disease in hospitals at any given time, suggesting that community acquisition is common and that many patients may enter hospitals already colonized with the organisms that will ultimately cause their infections [68–71]. One Australian study found a strong correlation between hospital and community strains of both symptomatic CDI and asymptomatic carriage, suggesting that transmission may be common outside the healthcare setting [72]. In this model, patients' immune status and bowel flora disruption with antibiotics, and not direct transmission, may be the most common contributing factors to the development of CDI in the hospitals. In this model, CP may have only a limited role in decreasing hospital transmission. Interestingly, a prospective observational study of CDI rates in a hospital setting after keeping

CP only for CDI patients who were incontinent of stool found only a small rate (1.3%) of transmission between patients using genetic sequencing [73].

Contact Precautions for *Candida auris*

Candida auris is a multidrug-resistant yeast that is emerging as an important pathogen in hospitals in parts of the United States [74]. Unlike other *Candida* species, the organism predominantly colonizes skin and appears to be very transmissible in the environment, requiring specific environmental disinfectants. Studies assessing the efficacy of CP for *Candida auris* are not currently published, yet the CDC and other public health authorities recommend strict adherence to CP in managing this organism until more evidence is available [75]. An additional rationale for the use of CP for *Candida auris* at this time is that the organism is not currently endemic in most of the Unites States, so CP may be more effective in controlling spread in this setting, though no research currently published actually demonstrates the efficacy of CP for this organism.

We believe it is important to note that the lack of evidentiary support for CP for the management of endemic MDR-GNRs and CDI should not be taken to prove that CP are ineffective. Because most hospitals currently use CP to control CDI and MDR-GNRs and most epidemiologic studies have been unable to simultaneously compare transmission without CP, it is difficult to make a strong argument either way. It is very possible that CDI and MDR-GNR transmission within hospitals and the community would be more common without CP. Nevertheless, because CP has financial impact to hospitals and may have negative clinical impacts to patient care, it is clear that more prospective, controlled research in this area should be performed. In the meantime, while we await the final verdict on CP, it is important that hospitals not ignore the importance of basic elements of infection control that have been shown to be effective for over a century: hand hygiene, environmental disinfection, and the judicious use of antibiotics [76].

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Hand Hygiene Monitoring Technologies: Implementation and Outcomes

2

Michelle Doll and Jo Dee Armstrong-Novak

Introduction

Hand hygiene (HH) is considered to be the cornerstone of infection prevention and control [1], yet compliance rates among healthcare workers (HCW) are notoriously suboptimal. Average compliance rates are reported to be between 40% and 60% [2–4], though wide variation exists [5]. Reasons for noncompliance with hand hygiene in the healthcare setting are most often related to inconvenience for the healthcare worker, perceived lack of an indication for hand hygiene, skin irritation, and forgetfulness [6].

In 2005, the World Health Organization (WHO) introduced the First Global Patient Safety Challenge: Clean Care is Safe Care, a multimodal approach to improving HH compliance [7]. The initiative consists of five major elements. System change encourages continuous availability of HH resources including point-of-care access to alcohol-based hand rub. Education emphasizes training HCW as well as patients on the importance of HH and when and how to perform HH. Regular monitoring and feedback of HH raises awareness and facilitates compliance with best practices. The fourth and fifth elements are reminders in the workplace for HCW, patients, and visitors and an institutional climate of safety to foster accountability [7].

Building on that initiative, the WHO introduced the "5 moments of hand hygiene" in 2009, which calls for HH to be performed at key moments during patient care in order to effectively prevent microbial contamination and transmission of pathogens [8, 9]. The five moments are before patient contact, before performing an aseptic procedure, after exposure to body fluids, after patient contact, and after contact with the patient's surroundings [8].

Monitoring Hand Hygiene Compliance

Monitoring HH compliance is a critical component in optimization of HCW HH performance. There are several modalities for HH monitoring that are used in healthcare settings. Direct observation by a trained observer is widely considered the gold standard in HH monitoring [7]. Product usage data is also used to assess HH performance in aggregate. New technology has resulted in an expansion of options for monitoring of HH including electronic surveillance systems and video monitoring. These monitoring systems often provide real-time feedback that can assist the HCW in altering behavior at the point of care, and many attempt to capture compliance within the framework of the "5 moments" [10]. Regardless of the monitoring methods employed, data must be fed back to frontline providers and their leadership in order to promote behavioral change. The increased volume and detail of the data available from automated monitoring systems may be able to provide insights into specific opportunities for improvement by demonstrating the exact instance in which HH is missed.

Direct Observation

Direct observation remains the gold standard for HH monitoring despite technological advancement due to broad experience with this monitoring technique and the ability of observers to detect HH quality in addition to compliance. However, there are disadvantages to the direct observation method. Direct observation is labor intensive, and there is a limit to the volume of data that can be collected. Data from

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_2

nights and weekends in particular have been shown to be lacking [11]. While observers are trained for their HH monitoring role, they can miss HH events or misclassify opportunities due to fatigue, human errors, or inability to observe HCW practice when out of direct view. Finally, the Hawthorne effect can artificially inflate HH compliance data when HCW recognize the direct observer and perform differently in the observer's presence. Despite these limitations, there is good evidence that monitoring and feedback of HH performance data can improve compliance in healthcare workers, at least so long as these efforts are ongoing [12, 13].

Electronic Hand Hygiene Monitoring Systems (EHHMS)

There is intense interest in using new technologies to address the limitations of direct observer monitoring and further impact HH compliance. A variety of systems are available, from product usage monitors, to individual HCW HH behavior monitors, to video surveillance. High system costs, lack of acceptability to HCW, and accuracy concerns limit the widespread use of EHHMS in healthcare currently, but many organizations remain interested in a technological solution to the problem of stalled HH improvement with existing programs.

Meng et al. [14] performed a rapid review of literature discussing the acceptance of technological monitoring systems and their effect on hand hygiene compliance, focusing on technology that was both wearable and provided real-time feedback. Monitoring systems improved HH compliance by between 6% and 55%; sustainability of increased HH compliance was unclear [14]. The wide range of compliance improvements reported likely reflects the variability in available EHHMS products and the complexity of implementation of EHHMS in distinct healthcare systems.

Srigley et al. [15] conducted a systematic review of experimental and quasi-experimental studies that measured hand hygiene outcome and/or healthcare-associated infection (HAI) incidence. All seven studies evaluated in the review recorded an increase in "system-defined" HH compliance during the intervention period. However, the impacts on HAIs were not addressed, and there was a high risk of bias [15]. The authors lament a lack of comparison of EHHMS data to direct observation, as this observation is necessary to definitively link HH actions to patient care activities [15].

Accuracy is often not the focus of publications on EHHMS [16] despite being a primary concern of the end user. Reports that do focus on validating system accuracy show a wide range of results depending on the type of system evaluated [16, 17]. Recent publication of robust validation schemes using planned paths or simultaneous observation of clinical workflows will hopefully push the technology toward improved performance in the future [18].

Beyond improving HH performance, the ability of EHHMS to impact HAI rates is even more nebulous. Few studies have attempted to address this important question [19]. Exceptions include a multicenter stepped-wedge cluster randomized study in which implementation of an EHHMS measuring aggregate product usage was compared to incidence of HAIs [20]. Despite a significant improvement in HH compliance over the 2-year study, no significant improvement in HAIs was detected [20]. The same group published a separate report focusing on HAI outbreaks [21]. They were able to correlate HAI outbreaks with periods of lower-than-baseline HH compliance as measured with the same EHHMS [21]. An interrupted time series analysis of two time points post-implementation of EHHMS installation in four locations demonstrated decreased *Clostridium difficile* rates across the facility in the first 9 months, but not the second (months 10–18) [22]. No other HAI rates were impacted [22]. At a state level, New York State examined facility adoption of EHHMS against *C. difficile* rates, without the inclusion of other facility-level *C. difficile* risk stratification; no meaningful conclusion regarding EHHMS impact on *C. difficile* rates could be drawn [23].

Challenges of Implementing HH Monitoring Systems

Several challenges arise with the use and implementation of HH technologies. Challenges include both technological limitations and human factor or behavioral limitations. Several studies suggest assessing system accuracy prior to permanent adoption of the system and implementing behavior modification techniques in order to mitigate or minimize such pitfalls [17, 24].

Boyce et al. cite several challenges during a trial of an EHHMS [25]. Technological challenges include misplacement of sensors, sensors falling off, Wi-Fi interference, accuracy errors, and the necessity for modifications to the software to account for varying workflows. Human factor challenges include skepticism of system accuracy, line-of-sight communication issues with the badges, refusal to wear the badge, concerns regarding the data use being punitive, and inconsistent wearing of the badges [25].

An implementation study by Edmisten et al. documented both implementation challenges and ongoing challenges of an EHHMS [26]. Implementation challenges included lack of accuracy in capturing HH events, limitations of data collection and reporting, lack of flexibility for varying workflows, dissatisfaction with alcohol-based hand rub, skepticism

about the longevity of the program, privacy and tracking concerns, maintenance issues, the size of the monitoring badge, and safety concerns about the prolonged wearing of the badge device. Ongoing challenges were battery maintenance, sensor accuracy, false captures, lack of longitudinal data, and allergies to HH product [26].

Benudis et al. performed a quasi-experimental study on an EHHMS [27]. As part of the study, pre- and post-intervention surveys were given to staff. Survey responses indicated an overall negativity toward the system. The pre-intervention survey cited concerns regarding lack of privacy or "Big Brother" watching and concerns that the monitoring bracelet would be a nuisance to wear. Less than a third felt the technology would improve their HH practice. The post-intervention survey showed staff were uncomfortable wearing the technology and questioned the accuracy of data. User dissatisfaction hindered both data collection and analysis and resulted in the study ending earlier than planned [27].

Similarly, Levin et al. introduced an EHHMS and measured staff satisfaction using a questionnaire post-implementation [28]. Fifty-one percent of respondents rated their satisfaction with the system as low or very low. The two most common reasons for dissatisfaction were system inaccuracy and discomfort of wearing the monitoring bracelets [28].

Published EHHMS studies most frequently represent small pilots in a subset of hospital units. Large-scale facility implementations exist [20] but are rare [16]. The challenges of the implementation of EHHMS to scale across a facility remains a substantial barrier to widespread adoption.

Conclusion

HH is essential to infection prevention and control in healthcare settings. HH performance is suboptimal among members of the healthcare team due to multiple competing priorities. Improving HH performance requires both monitoring of current practice and feedback of data to team members. More meaningful data drives greater change in behavior [29]. Ongoing efforts to maintain attention and focus on issues of HH are necessary to sustain performance. While an EHHMS may represent a potentially powerful addition to HH programs, implementation to scale is a daunting challenge. Far from an easy solution, EHHMS actually requires significant human and financial resources to integrate into a comprehensive HH program that engages the healthcare team and consistently pushes toward improved HH practices.

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3 Universal Glove and Gown Use for the Prevention of Methicillin-Resistant *Staphylococcus aureus* (MRSA) or Vancomycin-Resistant *Enterococcus* (VRE)

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Background

Over one hundred thousand healthcare-associated infections (HAIs) occur in the United States annually [1]. Many are caused by multidrug-resistant organisms (MDROs) like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) [1, 2]. Infections with MRSA and VRE are associated with worse outcomes than antibiotic-sensitive counterparts [3, 4], and the estimated cost of antibiotic resistance in the United States is more than $4 billion per year [5].

Transmission of MRSA and VRE in healthcare settings is believed to occur from patient to patient through the hands or attire of healthcare workers (HCWs) and contamination of the environment [6]. Patients who are colonized with MRSA or VRE commonly contaminate the room environment, and HCWs leaving the rooms of these patients are contaminated 10–25% of the time [7–10].

The use of gloves and gowns as a barrier to contamination is a commonly employed method for preventing transmission of MRSA, VRE, and other pathogens [11]. Theoretically, this barrier will become contaminated during care but will be removed at room exit, reducing burden of HCW contamination. By reducing transient carriage of pathogens by the HCW, gloves and gowns should decrease the likelihood of contaminating subsequent patients. Gloves and gowns are recommended as a part of standard precautions for any patient with uncontrolled secretions and as a part of contact precautions for MDROs of importance, such as MRSA or VRE [11]. Evidence for effectiveness of contact precautions (gloves, gowns, and a private or cohorted room) is limited, leading to various interpretations of CDC guidance [12, 13]. Gloves and gowns can also be used in a universal fashion in which all HCWs use gloves and gowns for every patient contact or room entry regardless of colonization or infection with an MDRO. Universal glove and gown (UGG) use has been employed in relatively limited fashion in response to outbreaks or in specific hospital units with high risk of spread for MDROs [14–18]. A recent cluster randomized trial found that universal glove and gown use in intensive care units had no impact on the primary outcome of MRSA or VRE acquisition but appeared to decrease MRSA in secondary analysis [14].

Policies

Universal glove and gown use is not part of CDC recommendations [11]. SHEA recommendations for MRSA prevention include UGG as an option for "special approaches" where endemic MRSA rates are not effectively controlled despite compliance with basic practices [19]. "Special approaches include recommendations where the intervention is likely to reduce HAI risk but where there is concern about the risks for undesirable outcomes, where the quality of evidence is low, or where evidence supports the impact of the intervention in select settings." The evidence for using UGG for all patient contact and the patient care environment was rated moderate.

Controversies (Table 3.1)

Effectiveness of Universal Glove and Gown Use

Beyond the Benefits of Universal Glove and Gown (BUGG) cluster trial finding a decrease in MRSA as a secondary out-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_3

Table 3.1 Controversies related to universal glove and gown use

Controversial subject	Argument for	Argument against
Prevents endemic MRSA or VRE	Gloves and gowns are theoretically effective as a barrier to MRSA and VRE, which frequently contaminate HCWs. MRSA acquisition decreased in the BUGG randomized controlled trial (RCT)	The primary outcome of BUGG study was no effect on MRSA or VRE acquisition. Practice is laborious and expensive
Causes adverse events and other harm	UGG is similar to contact precautions which may cause adverse events	A cluster RCT found a trend toward fewer adverse events with UGG. Many non-randomized studies showing an increase in events have uncontrolled confounding from severity of illness
Improves hand hygiene	In BUGG RCT as well as observational studies of contact precautions, better hand hygiene compliance was noted	HCWs will believe hands are clean due to glove use and won't perform hand hygiene

come, follow-up of five BUGG sites compared UGG intervention-phase HCW clothing contamination to post-intervention usual care and found a 70% relative reduction in HCW clothing contamination with UGG (7.1% of HCW clothing contaminated during UGG; 23% during usual care) [20]. Secondary analyses reported no significant decrease in acquisition of antibiotic-resistant gram-negative bacteria (despite possible signal of a decrease) [21] and an additive effect of using chlorhexidine bathing in conjunction with universal gloving and gowning [22] and estimated that 56% of MRSA reduction with UGG was due to changes in hand hygiene or visit frequency and not the direct effect of gowns or gloves [23]. A single-center outbreak study that employed UGG for an outbreak of *Acinetobacter baumannii* found that UGG reduced VRE and MRSA acquisition over a 6-month period [18]. Likewise, a small individual-level patient trial from the 1980s found that children requiring mechanical ventilation and at least 3-day intensive care unit (ICU) stay randomized to either standard care or empiric gloving and gowning had a significant delay in median time to nosocomial colonization when gloving and gowning was used [17]. Likewise, in a burn unit, an MRSA outbreak was rapidly terminated after implementing UGG with all patients (rate ratio [R_tR] post-outbreak endemic rate vs. baseline, 0.48; 95% confidence interval [CI], 0.14–1.53; $p = 0.10$) [16]. The evidence for UGG in burn units remains mixed as a pre-post study of UGG found no effect on composite rate of carbapenem-resistant *Acinetobacter baumannii*, extended-spectrum beta-lactamase (ESBL)-producing *E. coli*, VRE, MRSA, and carbapenem-resistant *Pseudomonas aeruginosa* [24], although a meta-analysis of five studies using varied UGG interventions in this setting observed a reduction in HAI colonization and infection rate by almost half [25]. An intervention of universal glove use during respiratory syncytial virus (RSV) season versus standard care during non-RSV time periods was evaluated in a retrospective cohort of all patients in a tertiary care hospital's pediatric units from 2002 to 2010 [15]. They found that the overall risk of HAI was 25% lower during universal gloving versus non-glove time periods (relative risk [RR], 0.75; 95% CI, 0.69–0.93; $p = 0.01$). Universal gloving was also evaluated during a before-after study in a single ICU. This study found no difference in the rate of MDRO acquisition when emollient-impregnated universal gloving was used rather than contact precautions [26]. A meta-analysis of universal gloving found no significant reduction in either MRSA or VRE incidence, although surprisingly it did note a 23% reduction in incidence rate when universal gloving was the sole infection prevention intervention but this became non-statistically significant when implemented as part of an intervention bundle [27].

In nursing homes, patients at high risk of infection were assigned to UGG regardless of colonization status with MRSA or VRE in a bundled intervention [28]. Investigators found a decrease in both prevalence density of MDROs (R_tR, 0.77; 95% CI, 0.62–0.94) and MRSA acquisition in the intervention compared to control nursing homes (R_tR, 0.78; 95% CI, 0.64–0.96).

However, many studies have raised questions over the effectiveness of UGG. In the only cluster trial of UGG, no decrease was noted for the primary outcome of composite VRE or MRSA (1.71 fewer acquisitions per 1000 person-days with UGG but $p = 0.57$). There was also no decrease in the secondary outcome of VRE acquisition (0.89 fewer acquisitions per 1000 person-days with UGG compared to usual care, $p = 0.70$) and only a possible decrease in the secondary outcome of MRSA acquisition (2.98 fewer acquisitions per 1000 person-days with UGG, $p = 0.046$; acquisition of 40.2% in UGG and 15% in control) [14]. More recently, a pre-post study comparing three ICUs using UGG to three non-UGG ICUs over a 9-year period reported no effect of UGG on either composite rate of MRSA, VRE, or carbapenem-resistant *Klebsiella pneumoniae* or organism-specific rates [29]. Other studies have found a lack of effect with universal glove and gown or universal gloving. In a single ICU cohort study, no difference was noted among eight beds assigned to UGG (93 patients) and eight beds assigned to universal gloving (88 patients) [30]. Twenty-four patients (25.8%) in UGG acquired VRE, while 21 patients (23.9%) in glove-only acquired VRE ($p > 0.05$). In a medical

intensive care unit study comparing 3 months of CDC guideline contact precautions to 3 months of universal gloving, there was no difference in VRE acquisition (14% universal glove vs. 18% standard contact precautions; $p = 0.19$) or MRSA acquisition (5.0% universal glove vs. 5.7% standard contact precautions; $p = 0.92$) [31]. In addition, the rate of bloodstream infections was actually higher in the universal glove phase (14.1 vs. 6.2 per 1000 device days; $p < 0.001$). One difficulty in interpreting results of these studies is that the comparison of UGG to universal gloving would require gowns to add meaningful extra benefit beyond the contribution of glove use in order to show an effect.

The STAR*ICU Trial was a cluster randomized trial that investigated an intervention of placing all patients on universal gloving until discharge or admission surveillance cultures were reported negative. The study found no difference in MRSA or VRE colonization or infection rate [32].

A 2015 Cochrane systematic review of contact precautions (not UGG) found great heterogeneity in studies and comparison groups, potential sources of bias, low intervention effectiveness, etc., and concluded no recommendation for or against contact precautions (CP) effectiveness could be made [33].

Cost-Effectiveness of Universal Glove and Gown

The cost-effectiveness of UGG has been debated with some results suggesting it could be more cost-effective than other interventions. One systematic review of MRSA infection control interventions looked at cost-benefit analyses [34]. Contact precautions were implemented preemptively (until test results were known) in 12 studies, although all of the studies employed bundled interventions, making it difficult to assess how much of the effect (and cost) was due to UGG versus other aspects. In the review, the cost-benefit ratio varied wildly from 1.7 times higher cost than savings to 13.5 times savings with intervention employing preemptive gown and glove use. In contrast, Gidengil et al. used a hypothetical 10,000-person cohort to model the cost-effectiveness of various infection control approaches for MRSA and concluded that UGG was not cost-effective [35]. While UGG averted 387 cases of MRSA colonization and 107 infections, UGG as a lone intervention cost an estimated $8.15 million, while MRSA disease cost was $6.58 million.

Possible Unintended Consequences/Adverse Events from UGG

Only one study of adults has examined possible harms related to UGG. In the BUGG trial, fewer HCW visits per hour were noted among UGG units (4.28 visits vs. 5.24 visits per hour; $p = 0.02$) [14]. This study also found no statistical difference in adverse events and a trend toward fewer adverse events with UGG (58.7 adverse events per 1000 patient-days among UGG vs. 74.4 per 1000 patient-days with usual care; $p = 0.24$). Most studies of adverse events are with contact precautions. However, association between gloving and gowning and adverse events has not been identified for UGG. In the study of pediatric empiric gloving and gowning versus standard care, Klein et al. found that children in each group were touched and handled with the same frequency [17].

Studies of contact precautions have found more potential negative effects of gloves and gowns (although they also had more bias toward being applied to sicker patients) [36]. Forty-six (59%) physicians surveyed in one study reported they were less likely to examine isolated patients [37]. Likewise, greater depression, anxiety, and adverse events have been reported in some studies. In a retrospective cohort study, Stelfox et al. reported a doubling in the rate of adverse events and an almost sevenfold increase in preventable adverse events among patients placed on contact precautions compared to non-isolated [38]. Day et al. observed higher depression scores in veterans on contact precautions [39] as well as among patients placed on contact precautions at an academic medical center [40]. In addition, lower patient satisfaction has been noted with contact precautions, with isolated patients being twice as likely to report concerns with care [41]. Some have also argued that the use of contact precautions may interfere with a home-like environment in long-term care facilities (LTCFs) [42].

Hand hygiene has been generally noted to increase with universal glove and gown use, especially upon room exit [14, 43]. Some studies report increases in hand hygiene (HH) compliance with UGG as compared to traditional contact precautions or with usual care [14, 26]. Others report no change. While one quasi-experimental study of universal gloving compared to traditional contact precautions found a significant decrease in hand hygiene with universal gloving [31], a cluster trial found that hand hygiene compliance was higher with UGG (78.3% UGG vs. 62.9% control; $p = 0.02$) [14].

A possible effect of UGG relates to compliance. Requiring gloves and gowns for contact with all patients might result in lower compliance. The STAR*ICU Trial noted lower compliance with universal gloving than with contact precautions; the median compliance for contact precautions in intervention ICUs was 82% for gloves, 77% for gowns, and 69% for hand hygiene. However, for universal gloving in intervention ICUs, compliance was 72% for gloves and 62% for hand hygiene [32]. Issues with compliance may especially be the case outside of clinical studies with increased attention to compliance.

The simplicity of universal glove and gown has been proposed as a benefit. Instead of relying on active surveillance, which can be laborious and expensive, UGG could be implemented. Furthermore, this overcomes the weakness of active surveillance that colonized patients will not be isolated rapidly [44]. Active surveillance followed by usual contact precautions is not cost-effective. Modeling suggests universal MRSA screening followed by contact precautions for positives would be a net loss to a hospital of approximately $104,000 per 10,000 admissions (95% CI, $83,000–126,000) [45].

Practical Resolutions

Universal glove and gown use is one of the most rigorously tested interventions for infection control. Results of the BUGG study did not find strong evidence that it prevents MRSA and VRE, but UGG likely has some benefit on MRSA acquisition. MRSA acquisition under endemic settings is relatively rare, and only a portion of those patients develop actual infection with MRSA. The intervention of UGG is labor and resource intensive and not easily implemented.

Institution-specific decisions relating to UGG should be based on endemic MRSA rates after compliance with standard precautions and/or traditional contact precautions has been maximized or considered for use in higher-risk populations. UGG may have a favorable effort to effect ratio in situations such as outbreaks [16, 18] or for high-risk patient groups such as those with recent skin abscesses [46] or high-risk LTCF residents [28]. However, UGG is a labor-intensive intervention with extensive monitoring and education required.

Future Research

Given the strength of the BUGG RCT, it is unlikely there will be further trials for UGG. Observational or quasi-experimental studies could be helpful for examining the effect on specific pathogens or settings where UGG would be most useful. A cluster randomized trial of the related, and controversial, intervention of contact precautions versus standard precautions for endemic MRSA or VRE would advance the field of infection control approaches [19]. Additional insight regarding UGG is likely in the wake of the response to SARS-CoV-2. An initial pre-post study without control units observed an increase in carbapenem-resistant Enterobacteriaceae (from 6.7% to 50%) despite UGG for COVID unit patients [47]. Future studies will be needed to assess the complex interplay between the effectiveness of UGG, resource limitations, bandwidth for non-COVID infection prevention efforts, MDRO surveillance, and reported MDRO incidence during the pandemic.

Conclusions

Despite obvious theoretical benefits to UGG as a barrier to transmission, real-world effects on preventing infections are likely modest and limited to MRSA, and there are several possible unintended consequences. Given staff effort and resources, UGG is unlikely to be adopted in hospitals beyond outbreaks or in patients with high risk of infection.

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Isolation Precautions for Visitors to Healthcare Settings

4

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Introduction

Acquisition of healthcare-associated infections is an evolving concern, affecting the safety of patients, hospital staff, and visitors. Healthcare personnel typically receive training related to infection prevention protocols; however, based on the nature of hospital visitation, the applicability of such policies may not necessarily be appropriate for hospital visitors. Individuals who visit patients typically stay in the hospital rooms for more extended periods of time compared to the various healthcare providers [1]; however, in contrast to most healthcare personnel, their visitation is generally limited to a single patient. In light of limited data on this topic, in 2015, the Society for Healthcare Epidemiology of America (SHEA) issued guidance on the topic to assist healthcare institutions in addressing specific infection control concerns pertinent to visitors [2]. The objective of this chapter is to describe the various ways that visitors can potentially transmit specific organisms in healthcare facilities and outline the ways infection prevention protocols aim to reduce the spread of disease (Table 4.1). The importance of enhanced comprehension of the role that visitation plays in nosocomial infections has become increasingly apparent, in light of the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

Visitors and Transmission/Outbreaks

Reports in the medical literature linking visitors to infection transmission or nosocomial outbreaks in healthcare facilities have been infrequent, mainly due to the difficulty in producing evidence of infectious transmission from visitors to patients and/or healthcare personnel. As a result of scarce reporting, the frequency of visitor involvement is likely underestimated. It is more commonly suspected that visitors

Table 4.1 Summary of recommendations for visitors based on some common contagious organisms and the possible subsequent related challenges to consider [2, 21]

Organism	General recommendations for visitors	Comments or challenges
Measles virus	Airborne precautions	Difficulty in assessing immune status against measles. Fit testing for N95 respirators may be impractical. Visitor restriction should be considered
Varicella-zoster virus	Airborne and contact precautions recommended for non-immune persons in primary infection or disseminated disease	Difficulty to assess immunity status against varicella due to inability to obtain serology to document immunity. Visitor restriction should be considered for non-immune visitors
Mycobacterium tuberculosis	Airborne precautions	Fit testing for N95 respirators may be impractical. Difficult to impose to the patient to wear a surgical mask during the presence of visitors. Visitors who are close contacts may have already been infected
Influenza virus and other respiratory viruses	Droplet precautions	Recommend against visitation in case of outbreaks or if visitors are symptomatic (e.g., cough, fever, etc.)
Bordetella pertussis	Droplet precautions	Difficulty assessing vaccine history among visitors

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_4

Table 4.1 (continued)

Organism	General recommendations for visitors	Comments or challenges
Highly virulent or novel organisms (Ebola virus, MERS-CoV, SARS, SARS-CoV-2, etc.)	Visitor restriction/ limitation Guidance from local and national public health authorities should be sought	Video conferencing could be considered Consider exceptions based on end-of-life situations or when a visitor is essential for the patient's well-being and care
MRSA and VRE	Standard precautions may be acceptable. Contact precautions could be considered in outbreak situations, among immunocompromised visitors, visitors visiting multiple patients, or those unable to perform hand hygiene	Contact precautions might be of limited value for visitors. General high prevalence of these organisms in the community and family members may likely be colonized
Enteric pathogens (*Clostridioides difficile*, norovirus)	Contact precautions with visitor education promoting handwashing with soap and water	General low prevalence of these organisms in the general community. Visitors are susceptible to infections caused by these organisms which are associated with significant morbidity and mortality
CRE	Contact precautions should be considered	General low prevalence of these organisms in the community. Visitors are susceptible to infections caused by these organisms which are associated with limited therapeutic options
Scabies and head lice	Contact precautions	Individualized considerations should be undertaken for visitors spending extended time with their hospitalized child

MERS-CoV Middle East respiratory syndrome coronavirus, *SARS* Severe acute respiratory syndrome, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2

may contribute to existing healthcare-associated infectious outbreaks. For this reason, visitor restriction is one commonly utilized component of an outbreak response plan. Additionally, visitor restriction can provide consistency in control measures for healthcare personnel during outbreaks, which may include ensuring that visitors are compliant with infection prevention measures.

Nosocomial transmission of *Mycobacterium tuberculosis* has been clearly linked to hospital visitation. Adults are more likely than children to be infectious with tuberculosis; therefore, it is crucial to recognize symptomatic disease in visitors accompanying suspected pediatric tuberculosis patients. This urgency was made apparent when a paper published in 1995 described an incident of 24 children hospitalized at a pediatric hospital who developed active tuberculosis after exposure to a patient's mother with active, cavitary pulmonary tubercular disease [3]. Another report documented the development of latent tuberculosis infection in 2 hospital contacts of a visitor with active pulmonary disease spending time on a pediatric ward [4]. As a result of these revelations, subsequent data has suggested that the parents or guardians are commonly the origin of infection in pediatric patients with active tuberculosis [5]. For example, investigators at a children's hospital in Texas prospectively screened adults accompanying children with suspected tuberculosis over a 6-year period to determine the frequency of undiagnosed disease in visitors. Sixteen (15%) of 105 adults screened had previously undetected pulmonary tuberculosis. This was associated with 14 (24%) of the 59 children admitted to the hospital with suspected tuberculosis during the study period. As a result, the US Centers for Disease Control and Prevention (CDC) recommends screening the caregivers of pediatric tuberculosis patients for active disease [6]. Infection control practitioners should be cognizant of the strong association between pediatric tuberculosis and active disease in close adult contacts, recognize the risk of transmission of these visitors to other patients and staff, develop protocols for visitor screening when tuberculosis is suspected in a child, and facilitate prompt evaluation and/or reporting to local public health departments when indicated.

Influenza and other respiratory viruses are likely the most common organisms transmitted from visitors to patients due to their high seasonal prevalence, the potential for asymptomatic viral shedding, and the potential for indirect transmission from the environment. Following an outbreak of influenza A (H3N2) on a geriatric ward, genetic sequence analysis identified 3 distinct influenza clusters [7]. Two were linked to healthcare personnel, while the third was presumed to be introduced by a visitor to the facility. Similarly, studies on the molecular and genetic diversity of nosocomial respiratory syncytial virus (RSV) outbreaks suggest multiple strains tend to circulate during a hospital outbreak [8]. These data points support the possible role visitors can play as a source of healthcare-associated transmission of respiratory viruses, particularly when community prevalence is high. For example, during the 2009 influenza A virus pandemic, a hospital visitor was reported to be the source of an outbreak of six cases on a pediatric hematology-oncology ward [9]. Control measures included oseltamivir prophylaxis, isolation of cases, strict adherence to personal protective equip-

ment, and visitor restrictions. Visitor restriction has also been a key component in controlling RSV, human metapneumovirus, and parainfluenza outbreaks, especially among immunocompromised patient populations [10]. Because visitor restrictions typically occurs simultaneously with other control interventions, the incremental impact of this measure on reducing transmission is difficult to ascertain.

A hospital outbreak of *Bordetella pertussis* was linked to a hospital visitor in at least one instance, and nosocomial transmission from visitors has been suspected in other outbreaks [11–13]. The event was discovered following the delayed diagnosis in a mother of a confirmed neonatal patient with confirmed pertussis hospitalized in the pediatric intensive care unit, and it ultimately was the likely etiology of transmission to two other patients in the pediatric intensive care unit, as well as five healthcare personnel.

Visitor restrictions have often been employed to control healthcare-associated outbreaks of norovirus. Due to its low infectious dose and ability to persist in the environment, norovirus is capable of spreading rapidly through healthcare settings. A prospective analysis of 49 nursing homes in the Netherlands found that restricting symptomatic visitors was the only control measure to significantly reduce the odds of norovirus acquisition in multivariate analysis [14]. In a large US hospital outbreak affecting over 500 patients and staff, all hospital visitation was temporarily restricted after transmission continued to occur following symptom screening of visitors [15]. The CDC's guidelines for norovirus prevention in healthcare settings include a category 1B recommendation to restrict non-essential visitors from affected areas of the facility during outbreaks of norovirus gastroenteritis [16]. If this is not feasible or not deemed to be necessary, the CDC suggests screening and exclusion of visitors with symptoms concerning for norovirus, in conjunction with ensuring visitor compliance with hand hygiene and contact precautions.

The outbreak of severe acute respiratory syndrome (SARS) virus is a dramatic example that highlights the important role hospital visitors may play in the transmission and propagation of an infectious disease outbreak. Several reports documented visitors to healthcare settings acquiring SARS and becoming sources of transmission to patients, healthcare personnel, family members, and other community members [17, 18]. For instance, in Singapore, at least 21 SARS cases were reported resulting from transmission by hospital visitors to family and other community contacts [18]. Following recognition of the significance of visitors in SARS transmission dynamics, more stringent restrictions were placed on visitation. Visitors were tracked using logs, and exposed visitors were quarantined. Visitors initially were allowed to visit SARS wards with full personal protective equipment (PPE), but due to continued transmission, all visitation at some affected hospitals was prohibited [18]. In Toronto, hospitals implemented a visitor and healthcare personnel screening with a questionnaire and temperature assessment prior to hospital entrance [19]. Visitors with concerning symptoms were referred to the emergency room. In Taiwan, infrared thermography was used to screen 72,327 outpatients and visitors over a 2-month period with identification of three probable SARS cases [20]. The lessons learned from SARS regarding the pivotal role visitors may play in the transmission of a communicable disease have informed public health guidance about subsequent emerging infectious diseases such as Ebola and Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2.

Infection control committees and facility leadership carry the responsibility of ensuring that policies regarding screening visitors for communicable diseases are implemented and visitor entrance during outbreak scenarios is restricted. The procedures for visitor entry screening should be regularly reevaluated and adjusted, adapting to current hospital-wide clinical concerns and the health of the patient population and the level of respiratory virus transmission in the community. For example, in healthcare settings that are densely populated with vulnerable residents, such as neonates, senior citizens, or immunocompromised persons, more robust visitor screening initiatives may be beneficial, particularly during times of the year when there is a high prevalence of circulating respiratory viruses.

Standard Precautions

In 2007, the CDC outlined a two-pronged approach toward mitigation of transmissible pathogens in healthcare facilities describing standard precautions and transmission-based precautions [21]. Standard precautions are a group of infection control practices executed to limit the spread of potential diseases that can be transmitted by contacting body fluids, blood, and exposed mucous membranes. These measures include hand hygiene, respiratory hygiene (cough etiquette), the use of appropriate PPE depending on exposure risk, as well as safe injection practices. The majority of hospital visitors do not typically contact bodily fluids, secretions, or blood and rarely administer injections to patients; however, the practice of hand hygiene is an important infection prevention practice applicable to all visitors to healthcare facilities.

Hand Hygiene

Standard precautions are the mainstay of infection control in healthcare settings, and hand hygiene plays an integral role in any infection prevention system [21]. The World Health Organization (WHO) [22] and the CDC [23] have published evidence-based guidelines outlining essential components of hand hygiene in healthcare settings. These instructions focus on healthcare workers; however, many of these principles are applicable to any visitor who comes in contact with a patient and the patient's immediate surroundings. Adequate hand hygiene steps entail performance before and after all patient encounters, as well as coming into contact with a patient's bodily fluid or hospital environment. In most scenarios, using either an alcohol-based disinfectant or soap and water is an acceptable means of practicing hand hygiene in most healthcare settings. When interacting with an individual with suspected or proven infection with a spore-forming organism, such as *Clostridioides difficile*, soap and water, when available, are the preferred means of hand hygiene.

Increasing evidence has demonstrated that visitors' hands are frequently colonized with various microorganisms, including epidemiologically important pathogens, and that hand hygiene can reduce the microbial burden on the hands of visitors [24]. There is limited information about hand hygiene practices among visitors to healthcare settings, and most studies have been observational with significant heterogeneity in study design and setting. Generally, hand hygiene varied markedly between studies, usually lower than healthcare providers [25, 26], though a study in Japan showed high rates of adherence [27]. Increased hand hygiene rates have been identified among visitors to patients receiving care on contact precautions. Additionally, interventions have been shown to improve visitor adherence to hand hygiene practices [25, 26]. Such measures include easier access to sinks and alcohol-based hand hygiene stations, as well as posting handwashing reminder signs for before entering and after exiting a patient's room.

Contact Precautions

Transmission of organisms by direct and indirect contact has been historically the most commonly encountered mechanism of spread in the healthcare setting [28]. The mode of infection from such a microorganism can be divided into to separate phenomena: direct or indirect acquisition. Transmission via direct contact involves the spread of an organism between 2 people who physically touch skin to skin. Indirect spread results from an individual interacting with a contaminated surface in the patient's environment. Contact precautions are intended to block the transmission of epidemiologically important organisms within a given healthcare setting. The presence of copious bodily fluid excretion from a wound or fecal incontinence secondary to gastroenteritis has an increased likelihood of contaminating the environment. Consequently, such patients also warrant contact precautions regardless of microbiologic etiology. Patients should be placed in a single room, when possible. Hospital personnel caring for these persons wear standard barrier protection, including a protective gown and gloves while interacting with the patient or the surrounding patient care environment.

The literature outlining enforcement of barrier precautions use among visitors to healthcare facilities remains a topic of contention, as there is a paucity of evidence-based practices. Consequently, regulations focusing on barrier precautions among visitors are frequently handled at an institutional level and on a case-by-case basis, depending on organism type, the extent of organism antimicrobial resistance, as well as the degree of transmissibility to a visitor or another hospitalized patient [2]. Highly virulent and multidrug-resistant organisms that are only susceptible to 2 or less antibiotic classes, such as carbapenem-resistant Enterobacteriaceae (CRE), may warrant increased efforts to reduce spread, including the use of barrier precautions among visitors. Gastrointestinal pathogens, including norovirus and *Clostridioides difficile*, may infect and cause significant disease in normal hosts at a relatively high rate. Visitors to patients infected with these organisms may directly benefit from the use of barrier precautions in conjunction with standard precautions, especially hand hygiene, in order to lower the chances of contracting the infection. Conversely, the benefits achieved by implementing barrier precautions use among visitors to patients with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE), both endemic in many healthcare settings, have not been well established. Many household contacts of these patients may be likely to be colonized with these organisms themselves [29, 30]. Additionally, several studies, including a 2018 published retrospective analysis from the University of California, Los Angeles (UCLA), suggested that the discontinuation of routine contact precautions for MRSA and VRE did not increase nosocomial infections but could not definitively say that discontinuation reduced overall patient harms [28]. The study, however, found a decreased number of noninfectious adverse events, falls, pressure ulcers, and venous thromboembolisms after contact precaution removal [28]. In settings of suspected high rates of transmission of these organisms within a healthcare setting (outbreak or epidemic), the use of barrier precautions among visitors may be appropriate in order to maximize attempts to reduce transmission.

In 2016, the CDC described the emergence of *Candida auris*, a particularly virulent and often multidrug-resistant *Candida* species, as among the five bacterial and fungal pathogens posing an urgent threat to US public health [31]. One of the primary reasons for this concern is that it is frequently multidrug resistant, and some strains are known to lack susceptibility to all three available classes of antifungals. *C. auris* also has the ability to disseminate compared to other *Candida* species. As an epidemiologically important pathogen, *C. auris* infection warrants isolation using contact precautions, optimally in a single-bed room with single-patient use items (e.g., blood pressure cuffs), when available [31, 32]. Various public health organizations have published guidelines regarding infection control practices. According to the CDC, in addition to the aforementioned recommendations for both healthcare workers and visitors to use contact precautions while in the rooms of affected patients, the use of Environmental Protection Agency (EPA)-registered hospital-grade disinfectant effective against *Clostridioides difficile* spores is advised [32].

Sarcoptes scabiei (scabies) and *Pediculus humanus capitis* (head lice) are ectoparasites that have been described in hospital outbreaks where patients and visitors played a role in spreading the infection [33–35]. In order to reduce the chance of ectoparasitic spread throughout a healthcare facility, contact precautions should be implemented for all patient visitors with these patients until treatment completion because household members might not yet be infected or may be in the incubation period themselves. Symptomatic friends or family members should have restricted visitation rights until appropriate therapy has been initiated [21].

Survey data suggests that visitors have an understanding of contact precautions and their role in preventing organism transmission [36]. Ensuring visitor adherence to contact precautions, however, remains an ongoing challenge. Most institutions do not routinely enforce visitor adherence to barrier precautions in the healthcare setting [2]. Additionally, there is limited published data on this topic, and it is primarily observational in nature. Based on available reports, compliance with all components of contact precautions among visitors is low, particularly glove use and hand hygiene [37–39]. One study demonstrated higher rates of adherence to gown and glove use among visitors to patients in intensive care units compared to those on general medical floors [38]. Some studies included the use of gowns and gloves by visitors in the control of multidrug-resistant organisms but did not perform a separate analysis to determine whether their use by visitors had a measurable impact [40–42]. The overall risk of transmission associated with multidrug-resistant organisms via visitors as well as their optimal use of barrier precautions remains important areas of future study.

Droplet Precautions

Droplet transmission occurs when microorganisms contained in respiratory particles that are expectorated during the act of coughing, sneezing, talking, or singing are mobilized through the air. The structure of these particles enables travel less than 6 feet, and they are capable of infecting others if achieve contact with an open mucosal surface. Examples of infectious agents that are transmitted primarily through the droplet route include *Bordetella pertussis* [43], influenza virus [44], adenovirus [43], rhinovirus [45], *Mycoplasma pneumoniae* [46], SARS [47], *Streptococcus pyogenes* [48], and *Neisseria meningitidis* [49]. Although RSV may be transmitted by the droplet route, direct contact with infected respiratory secretions is the most important determinant of transmission, and consistent adherence to standard plus contact precautions is recommended to prevent transmission in healthcare settings [8]. When a patient has a suspected or confirmed case of an infection from a pathogen deemed to have been contracted via droplet transmission, the patient should be assigned a single-bed room. Associated recommended precautions include all healthcare personnel and visitors to wear surgical masks while in the patient's room and for such patients to wear surgical masks during transport events [8]. Visitors of pediatric patients could be considered an exception because of the interference with bonding and the potential adverse psychological impact. Both the CDC and SHEA guidance recommends restricting visitation by any ill individual or family member with active respiratory symptoms [2, 21]. However, during periods of increased prevalence of respiratory infections in the community, surgical masks should be offered to coughing patients and other symptomatic persons who accompany ill patients upon entry into the facility [48, 50], and these individuals should be encouraged to maintain a distance of at least 3 feet from others in common waiting areas [43, 44].

Visitors have been identified as a source of transmission of various respiratory viral infections in healthcare facilities [8, 51–53]. Therefore, it is the responsibility of the infection control practitioners of a hospital network to communicate with associated staff, patients, and family members in order to strategize effective ways of mitigating spread [11, 54, 55].

Influenza

The CDC recommends limiting visitors of patients in isolation for suspected or confirmed influenza to persons who play an active role in that patient's emotional well-being and care [21]. The CDC also recommends that visitors to patients in isolation for influenza should be screened for symptoms of acute respiratory illness before entering the hospital and

should be instructed on hand hygiene before entering patients' rooms, limiting surfaces touched and their movement within the facility, and the use of PPE according to current facility policy while in the patient's room [21, 56, 57]. Visitors should not be present during aerosol-generating procedures [3]. They also should be encouraged to receive influenza vaccination [21, 58]. Visitors who have been in contact with an infected patient before and during hospitalization are a possible source of influenza for other patients, visitors, and staff [7, 9, 59–64]. Tan et al. [65] surveyed the attitudes of ten visitors toward the 2009 H1N1 influenza virus response measures instituted within a tertiary hospital in Singapore with a high level of perceived inconvenience among respondents. Restriction of visitors who were symptomatic or who had contact with contagious patients has been a critical strategy for containing previous influenza virus outbreaks [9, 64, 66–70].

Bordetella pertussis

Bordetella pertussis, the bacterial cause of whooping cough, is another example of an infectious agent that is transmitted by the droplet route [21, 43]. Although classically recognized as a disease of infants and children, reported incidence in adolescents and adults has increased globally over the past decade [71]. Similarly, the rate of nosocomial transmission of pertussis has escalated [72, 73] due to asymptomatic infected patients serving as vectors to susceptible hosts, such as patients, healthcare personnel, as well as household contacts, resulting in substantial costs to the healthcare system [72]. Christie et al. [13] described the measures and procedures for visitors that were implemented in order to contain a pertussis outbreak in a Cincinnati pediatric facility. Those mandates involved wearing surgical masks and limiting visitation in the neonatal unit to parents, grandparents, and guardians while creating a temporary child care service [13].

Airborne Precautions

An infectious agent can be considered capable of airborne transmission if it is capable of remaining suspended in the air over prolonged distances and time – typically greater than 6 feet and several hours, respectively. Examples of such pathogens include *Mycobacterium tuberculosis* [74], rubeola virus (measles) [75], and varicella-zoster virus (chickenpox) [76]. Patients with such diseases should be designated a private airborne infection isolation room (AIIR), which should include negative air pressure, filtering the air with a minimum of 6 to 12 changes per hour before that air moves outside the room. The feasibility of a hospital system to accommodate all people who warrant these rooms can be trying during a global pandemic with a high inpatient census. Consequently, staff in charge of bed coordination should allocate the negative pressure rooms to those receiving continuous aerosol-generating procedures (e.g., high flow oxygen, noninvasive ventilation, mechanical ventilation, and those with a tracheostomy in place). According to the CDC, in scenarios where optimal air filtration conditions cannot be fully enforced due to lack of structural resources, such patients should be placed in a private room with a closed door and be moved to an AIIR if one becomes available [74]. Additionally, the CDC states that adequate PPE requires all individuals who enter these rooms to wear a respirator with a filtering capacity of 95%, allowing a tight seal over the nose and mouth (e.g., N95 or PAPR). In an attempt to reduce the chances of others inhaling airborne microscopic respiratory secretions and the challenges associated with implementing high-level respiratory protection among visitors, there should be a limited number of essential personnel at a given time, and visitors should never be present during aerosol-generating procedures. During global outbreaks of communicable diseases, healthcare systems should implement strict regulations prohibiting visitors to enter the rooms of these infected patients, with the exception of end-of-life situations.

Measles

Measles is a highly contagious rash illness that is transmitted via respiratory and airborne spread [21, 75]. Approximately nine out of ten susceptible persons with close contact to a measles patient will develop clinical measles [77]. Thus, the majority of people who are infected with measles are found to have either never been vaccinated or did not have a history of natural immunity against the virus for various reasons [77]. Immunocompetent individuals are considered communicable from 4 days before and then 4 days after rash onset [21]. In regard to those who have immunocompromised underlying conditions, the CDC published interim infection prevention recommendations for measles in healthcare settings in 2019, suggesting to maintain airborne precautions for the duration of illness due to potential prolonged shedding in this patient population. The SHEA guidance for visitors has no defined recommendation for the type of mask to be worn by visitors with probable measles immunity; however, the CDC discourages patient visitation without acceptable proof of probable immunity [2, 76]. Per the CDC, all hospital employees entering the room of a patient with a confirmed or suspected measles case should use barrier protection consistent with airborne precautions regardless of presumptive immunity status [21, 78]. Additionally, due to instances of the virus' ability to survive in the air for up to 2 h, that reported interval of time is the standard duration

recommended to maintain a non-AIIR's vacancy following the departure of a patient with measles [76]. This allows enough time for about 99.9% of airborne-contaminant removal [76].

Immunocompromised Visitors

Immunocompromised individuals may be at risk for opportunistic infections and severe infection from organisms that may cause mild disease in immunocompetent hosts. This group of people may include patients receiving immunosuppressing medications in the setting of organ transplantation or treatment of cancer or acquired or hereditary immunodeficiencies. The risks to hospital visitors with such underlying conditions likely varies by organism, mode of transmission, and other patient and environmental factors impacting infectivity. Specific guidelines for this special population of hospital visitors have not been issued by any professional societies or public health authorities. Among immunocompromised visitors, hand hygiene is a particularly important infection prevention strategy. Ideally, minimizing interaction with individuals with respiratory illness is recommended, and using a surgical mask is encouraged for the immunocompromised visitor if contact cannot be avoided. Utilizing other barrier precautions, particularly gowns and gloves, may be useful in the right setting in this unique visitor population. Additionally, these persons should strongly consider avoiding visiting patients who require airborne precautions, especially if he or she has not been fitted for an appropriate respirator [74].

Emerging Infections and Visitors to Healthcare Settings

Globalization and the ease of international travel pose new challenges for infection prevention and control of emerging infectious diseases. Outbreaks of communicable diseases in seemingly remote areas of the world have necessitated preparedness efforts for US healthcare facilities in the event of an imported case. The 2014 outbreaks of Ebola in West Africa and MERS-CoV in the Middle East are two such examples. The largest outbreak of MERS-CoV outside of the Middle East occurred in South Korea due to an imported case resulting in 186 secondary cases and 36 deaths. During this outbreak, hospital visitors were implicated in amplifying transmission in a similar fashion as was observed during the SARS outbreak [79–81]. Although imported cases of Ebola and MERS-CoV in the United States have been extremely rare, the high consequences of such events have led to greater recognition of the importance of hospital preparedness for emerging infectious diseases, such as SARS-CoV-2.

SARS-CoV-2

As of January 2021, SARS-CoV-2 has infected more than 90.6 million individuals worldwide and caused more than 1.9 million deaths [82]. The CDC has outlined interim guidance for managing visitors to healthcare facilities with hospitalized patients not infected with SARS-CoV-2 during the global pandemic [83]. Due to the highly contagious nature of this virus and its associated morbidity and mortality, healthcare systems have implemented strict rules and regulations about hospital visitation in an attempt to mitigate the spread of infection. Although those who are asymptomatic or presymptomatic may not be readily identified, screening visitors for symptoms typically associated with SARS-CoV-2 infection is a key strategy to help identify people who are at higher risk of exposing others to disease. Similarly, developing a system requiring all individuals coming into a facility to go through a designated entry point helps ensure that everyone abides by the aforementioned triage process. This method is also helpful when mandatory temperature checks are part of the screening criteria. Generally, entrance is only granted to people who are afebrile, lack symptoms of COVID-19, and have not carried a diagnosis of COVID-19 in the past 10 days, in addition denying exposure in the previous 14 days. If allowed inside of the building, providing visitors with face coverings and readily available access to supplies that promote appropriate respiratory hygiene, such as alcohol-based hand sanitizer and no-touch receptacle bins, facilitates higher rates of compliance [83].

In general, it is strongly encouraged that visitation should be limited to only persons who play a crucial role in a patient's physical or mental health. When the appropriate electronic technology is attainable, alternative modes of communication may be utilized, such as video conferencing. In the event that visitation is granted for a patient who tests positive for SARS-CoV-2, the interim CDC recommendations include the following: (1) screen visitors for both respiratory illnesses as well as mental capacity to comply with precautions; (2) educate visitors on hand hygiene, respiratory hygiene, cough etiquette, PPE, and limiting contact with environmental surfaces in the room; (3) restrict visitors from entering the room with consideration of exceptions for end-of life situations when the visitor is otherwise essential for the patient's well-being and care; (4) instruct visitors to limit their movement within the facility; (5) maintain physical distancing, ideally staying at least 6 feet away from other individuals [82]. In 2016, the CDC issued similar guidance for managing visitors of patients with suspected or confirmed MERS-CoV as well as Ebola [84, 85]. Taking into consideration the magnitude in volume of patients hospitalized with SARS-CoV-2 around the globe, it is not feasible to place every infected inpatient in AIIR. Consequently, such rooms should be reserved for those undergoing aerosolization pro-

cedures. When entering the room of a patient with suspected or confirmed SARS-CoV-2, there are generally accepted PPE practices that apply to hospital employees and visitors. Similar to the principles followed for patients infected with diseases capable of airborne transmission, it is strongly suggested to wear a respirator with a high filtering capacity, such as an N95, decreasing the wearer's risk of inhaling highly contagious particles. Eye protection, in the form of goggles or a face shield covering the front and sides of the face, is commonly worn in case of any bodily fluid exposures. Clean nonsterile gloves and barrier gowns provide protection similar to when contact precautions are warranted [83].

In circumstances where a novel or highly contagious pathogen is identified, implementation of the above recommendations for screening, monitoring, and educating visitors necessitates close collaboration between hospital infection control practitioners, local government, public health authorities, hospital leadership, and healthcare personnel. Given the evolving nature of the SARS-CoV-2 pandemic, frequent review of the WHO and CDC guidance and updating visitation policies and infection control guidelines accordingly are recommended.

Ethical Considerations in Isolation Precautions for Visitors to Healthcare Facilities

Visitor restriction policies raise important bioethical questions that merit consideration. In the context of an infectious disease outbreak, restriction of visitation can inflict emotional duress for patients and caregivers, interfering with the benefits gained from patient/family-centered care. Infection control practitioners must recognize the powerful psychosocial impact denying visitation rights may have on patients and families. Such restrictions, however, can be justified to protect public health on the basis of the epidemiological evidence demonstrating the role visitors can play in transmission of highly contagious infections such as SARS-CoV-2 [86]. Accounting for the disease-specific consequences of infection and transmission can inform the public health justifications for visitor restrictions. In the case of SARS, SARS-CoV-2, and MERS-CoV, the public health rationale for such stringent visitor precautions includes the lack of a safe and effective vaccine and chemoprophylaxis, the high rate of morbidity and mortality among infected patients, and incompletely defined modes of transmission [82]. Survey data from a Canadian hospital affected by the SARS outbreak demonstrated the majority of healthcare personnel (90%), patients (80%), and family members (76%) supported visitor restrictions [87]. Communication to patients and families explaining visitation restriction policies should be clear and sensitive. In some exceptional circumstances, the adverse psychosocial impact of visitor restriction and the patient's and family's emotional needs may necessitate flexibility in restricting visitation, particularly at the end of life. Understanding the short- and long-term psychosocial implications of visitor restriction and the impact of transmission-based precautions on visitation and relationships between patients and visitors, in settings of both endemic and epidemic disease, warrants further investigation.

Isolation precautions and implementation of visitor restrictions in pediatric populations pose unique ethical dilemmas, as such barriers can lead to downstream consequences, such as disrupting breastfeeding and other beneficial parent-child bonding experiences. It behooves healthcare employees to remember that the parents and guardians of the patients who warrant isolation precautions may likely have experienced substantial exposure to the infectious agent prior to the child's admission. SHEA guidance questions the practicality and effectiveness of using gowns and gloves and masks for such visitors and emphasizes the importance of standard precautions, good hand hygiene practices, and individualized considerations when evaluating visitation in these circumstances [2].

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5 Contamination in the Operating Room Environment: Patients, Providers, Surfaces, and Air

Srdjan Jelacic and Andrew Bowdle

Despite substantial progress in hospital infection control, healthcare-associated infections (HAIs) continue to pose a significant threat to patients. Healthcare workers are also at risk of becoming infected in the workplace. Although the incidence of some HAIs has decreased between 2009 and 2016, such as central line-associated bloodstream infections (CLABSI) and catheter-associated urinary tract infections, little progress has been made in preventing surgical site infections (SSIs) [1]. The issue of infection control in the healthcare environment was a major concern in the 1950s with the establishment of the first infection control programs and their refinement, leading in 1976 to the requirement by the Joint Commission for an infection surveillance and control program in order to receive hospital accreditation [2]. The collective interest in infection control in the healthcare environment decreased over the following decades, including interest in cleaning and disinfection. During the last couple of decades, we have experienced a resurgence of interest in addressing and preventing HAIs. More recently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has catapulted infection control in the healthcare environment to the forefront of our concerns.

The infection control efforts in the operating room were previously based on expert opinion and mainly focused on preventing SSI by optimizing patient risk factors, antimicrobial prophylaxis, ensuring proper surgical staff hand cleaning, maintaining sterility of the surgical field, and environmental surface cleaning and disinfection [3]. In an effort to introduce more evidence-based interventions, the updated SSI prevention guidelines published in 2017 have emphasized intraoperative glycemic control, normothermia, and increased oxygenation [4]. Adherence to these infection control measures in the operating room is important but only represents the tip of the iceberg of infection control issues that need to be addressed.

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The operating room represents a unique environment that is often incorrectly considered entirely sterile. Although the surgical field, which typically includes the draped patient, scrub table, and any draped equipment, is sterile, the remaining areas of the operating room are not sterile and likely contaminated despite environmental cleaning and disinfection [5]. The operating room is a busy, frequently noisy, and chaotic environment with multiple patient contacts involving all operating room staff and a high burden of soiled surfaces and, at times, airborne pathogens. Interestingly, pilot data suggest that surgical cases associated with SSI had higher levels of noise in the operating room, which may reflect a lack of discipline and breakdown in compliance with infection prevention measures [6, 7]. Unlike ward and intensive care unit rooms with single patient occupancy, multiple patients undergo procedures during a single day requiring environmental cleaning and disinfection between each procedure and a terminal clean at the end of the day. Given the frequency and complexity of environmental cleaning in the operating room due to the presence of multiple pieces of equipment along with constant pressure for faster room turnovers, it is nearly impossible to ensure a consistently clean operating room environment. During a procedure, anesthesia providers and nursing staff have hundreds of contacts with environmental and patient body surfaces. Particularly during intubation and extubation, the flow and frequency of these interactions make hand hygiene challenging, which can further increase the contamination of the operating room environment. Based on studies of the spread of multidrug-resistant organism (MDRO) in a hospital environment, a concept of "fecal patina" was developed and proposed as a model for pathogen spread in the operating room [8]. The proposed model involves an interplay among the triad of pathogen transmission that includes patient skin and body fluids, provider hands, and operating room surfaces. We would add a fourth element to the proposed model to include operating room air, which can contain airborne pathogens [9].

Traditionally, the SSI prevention measures were focused on the surgeon and the patient, but more recently, growing

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_5

evidence demonstrates that the anesthesia provider is an important vector in pathogen transmission and the anesthesia work area surfaces are an important reservoir of pathogens [10]. Several publications discussed in the next section have described the relevance of the hospital environment as a reservoir for various MDROs, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), *Clostridium difficile*, Enterobacteriaceae (e.g., *Klebsiella pneumoniae*, *Escherichia coli*), and other non-lactose fermenters such as *Acinetobacter baumannii*. Although the MDRO transmission has been described outside the operating rooms, their relevance in the operating room is not as well established.

This chapter will summarize the available evidence on the transmission of pathogens in the operating room with a particular focus on the anesthesia work area. The subsequent sections will discuss the role of patients and providers in pathogen transmission and environmental surfaces and air as sources of contamination. We will then discuss infection prevention measures, including patient decolonization, hand hygiene, gloving, surface cleaning and disinfection, and respiratory precautions, which were shown to decrease environmental contamination and, in some cases, HAIs and mortality.

Pathogen Transmission Outside of the Operating Room

First, we summarize the evidence for bacterial transmission outside of the operating room, which provides important insights for addressing infection control in the operating room and can guide future research efforts. MDROs such as MRSA and VRE are considered preeminent healthcare pathogens [11], which are known to contaminate the hospital environment. Although these organisms can survive in the environment for up to 2–3 months, routine cleaning and disinfection can easily eradicate them. For example, VRE strains were found to survive for 60 min on ungloved and gloved fingertips and up to 7 days on dry surfaces [12].

A study analyzed environmental cultures from MDRO contact precaution rooms that underwent routine and terminal cleaning [13]. The authors found that the mean MDRO burden, which was quantified as the number of colony-forming units (CFUs) per 100 cm^2 area, was higher in routine than that in terminal clean rooms and recovered these organisms in 34% of routine and 17% of terminal clean rooms. Similarly, a 2014 multicenter trial of rooms occupied by patients infected or colonized with MRSA or VRE found that 53% of rooms with colonized patients had at least one positive environmental culture [14]. Hota and colleagues showed in 2009 that 21% of environmental surfaces belonging to rooms occupied by VRE-positive patients were positive for VRE prior to cleaning [15]. A more recent paper published by Ford and colleagues showed that VRE was present on surfaces of 10% terminally cleaned rooms [7]. Most of the surfaces studied were nonporous surfaces that can be thoroughly cleaned. There is limited data on porous surfaces such as curtains, which are challenging to clean. Not surprisingly, Ohl and colleagues found 42% of cultured curtains to be positive for VRE [8].

The impact of environmental contamination on future room occupants has also been studied. Patients admitted to the rooms previously occupied by patients colonized with MRSA and VRE were at increased risk of acquiring MRSA and VRE and, in the case of VRE, even if the VRE-colonized patient was discharged from the room within the previous 2 weeks [16–18]. A landmark study of the relevance of VRE environmental contamination in rooms occupied by VRE-colonized patients showed that providers who touched both the patient and the room surfaces contaminated their hands in 70% of instances, while providers that touched only the environment contaminated their hands in 52% of instances [19]. Wearing gloves decreased the likelihood of hand contamination from 37% to 5%.

Among Gram-negative rods, *Acinetobacter* is probably one of the organisms with the highest level of environmental contamination, which seems related to its resistance to desiccation and ability to survive for months on dry surfaces [20]. Morgan et al. cultured healthcare workers after patient interactions and found that the organism most frequently transferred to gowns and gloves was *A. baumannii* [21]. The strongest independent risk factor for the transfer of *Acinetobacter* was the presence of environmental contamination with the same organism. Nutman and colleagues found that the environmental surfaces in rooms occupied by patients colonized with carbapenem-resistant *Acinetobacter baumannii* were contaminated by the same organism [22]. A subsequent study found that the risk of acquiring carbapenem-resistant *Acinetobacter baumannii* was 2.8 times greater if exposed to a known contaminated environment [23]. Given the evidence of environmental contamination outside of the operating room, it is not surprising that we would find similar organisms and levels of contamination in the operating room. The following sections will discuss the relative contribution of patients, providers, and operating room environment (surfaces and air) to pathogen transmission and strategies to minimize their contribution.

Patients

Patient colonization with healthcare-associated pathogens is a significant risk factor for developing SSIs and other HAIs; up to 80% of postoperative *S. aureus* HAIs originate from patients' own flora [24–26]. Published studies have mainly

focused on colonization with *S. aureus*, but other pathogens should be considered, especially the multidrug-resistant Gram-negative organisms. Targeted decolonization of patients who test positive requires significant resources to perform screening and excludes colonized patients with false-negative results. Some authors have proposed universal decolonization to avoid these issues associated with targeted decolonization [27].

The two most common strategies for the decolonization of *S. aureus*-positive patients are mupirocin ointment for nasal decolonization and chlorhexidine for skin decolonization [28]. In a multicenter study, *S. aureus*-positive patients were randomized to a decolonization strategy with both nasal mupirocin and 4% chlorhexidine gluconate shampoo versus placebo [29]. Decolonization with mupirocin and chlorhexidine reduced the risk of HAIs from 7.7% in the placebo group to 3.4% in the decolonization group (relative risk of infection 0.42). The decolonization was particularly effective for deep SSI (relative risk of infection 0.21). In a subsequent multicenter quasi-experimental study, a similar decolonization strategy for *S. aureus*-positive patients included mupirocin and chlorhexidine use for up to 5 days along with targeted antibiotic prophylaxis for methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA patients [30]. The mean rate of SSIs decreased from 36 per 10,000 procedures before the intervention to 21 per 10,000 procedures after the intervention, which was statistically significant. A meta-analysis by the World Health Organization (WHO) of six randomized controlled trials found that nasal mupirocin with or without chlorhexidine wash was effective in reducing the overall rate of HAI and SSI rates [31].

Based on the available evidence, patient decolonization appears to be effective in reducing postoperative infections in patients who are carriers of MSSA or MRSA. However, nasal mupirocin treatment is difficult to implement due to patient noncompliance with multiday treatment and growing concerns about mupirocin resistance. Alternative decolonization therapies that are easier to implement are needed. Due to concern for *S. aureus* resistance to mupirocin, compliance with multiday treatment, and allergic reactions to mupirocin, nasal povidone-iodine was identified as an effective alternative for patients undergoing orthopedic procedures [32]. Furthermore, a more individualized approach to perioperative decolonization and antimicrobial prophylaxis may also be needed. Targeting Gram-positive organisms by MRSA screening, nasal decolonization, and cefazolin-based antibiotic prophylaxis appears inadequate when examining the organisms causing SSI in spine fusions [33]. Gram-negative organisms with a high degree of cefazolin resistance were commonly found when the surgical field involved inferior regions of the spine, particularly the sacroiliac region. The study findings indicate that a patient- and procedure-specific approach to perioperative decolonization and antimicrobial prophylaxis is needed while matching the spectrum of antibiotic prophylactic activity to the microbiology of the patient's skin flora at the surgical site.

Providers

Hand Hygiene

Loftus and colleagues established the relevance of anesthesia providers' hands in intraoperative bacterial transmission [34]. In a study of 82 case pairs (first and second surgery cases on the same day), the authors found 12% of intravenous stopcocks to be contaminated and attributed 47% of stopcock contamination to the provider's hands. Similarly, 89% of the anesthesia environment (anesthesia machine adjustable pressure-limiting valve and agent dial) was found to be contaminated, and 12% was attributable to the provider's hands. Interestingly, 66% of the provider's hands were contaminated at the beginning of the first case, with 18% of cultures positive for *S. aureus* and 49% positive for Gram-negative rods. Four stopcocks belonging to the second case of the day were contaminated with the same organism found on the hands of anesthesia providers at the beginning of the first case.

Hand hygiene in the operating room that adheres to the WHO five moments for hand hygiene is difficult to perform, especially during busy times such as induction and emergence when there is a high frequency of activities. Low rates of hand hygiene by anesthesia providers were described in several studies. A Dutch study found that the frequency of hand hygiene by operating room staff was less than once per hour after 60 hours of observations [35]. Furthermore, the compliance with hand hygiene upon entry and exit of the operating rooms was only 2% and 8%, respectively. A different study identified that the most frequently touched objects were the anesthesia machines and keyboards, with only 13 hand hygiene events during the 8 hours of observation [36]. The intravenous stopcocks were only disinfected 15% of the time, and none of the procedures, such as bronchoscopies, line insertions, and blood exposures, were followed by hand hygiene. In an observational study, the frequency of anesthesia provider contacts with patients and the environment was significantly higher during induction than the maintenance of anesthesia (155 versus 60 contacts per hour, respectively) [37]. Despite numerous contacts, the average hand hygiene events during induction and maintenance were 1.8 and 1.2 events per hour. Evaluation of the WHO opportunities for hand hygiene among anesthesia providers found, on average, 34 to 41 opportunities per hour with peaks up to 54 opportunities per hour [38]. Compliance with hand hygiene based on these criteria was on average 18% with low hand hygiene compliance between patients, during preoperative nerve

block placements, keyboard use with soiled hands, during placement of intravenous lines, preparation of drugs and equipment with soiled hands, and use of soiled gloves after airway management.

Based on feedback by anesthesia providers on hand hygiene barriers in the operating room, a hand sanitizer mounted on the anesthesia machine was compared to that of a wall-mounted hand sanitizer [39]. The use of a hand sanitizer mounted on the anesthesia machine increased the frequency of hand hygiene from 0.5 to 0.8 events per hour, which was statistically significant but of limited clinical importance. Similarly, an infection prevention bundle, which resulted in a significant reduction in SSI, included a hand sanitizer mounted onto the pole used for administering intravenous fluids [40]. In another study, electronic visual reminders for anesthesia providers that stated "Please Sanitize Your Hands" for 1 minute every 15 minutes on the anesthesia computer monitor increased hand hygiene compliance from 0.2 events per hour in the anesthesia resident group without reminders to 2.1 events per hour in the anesthesia resident group with reminders [41].

In an effort to improve compliance with hand hygiene among anesthesia providers and further remove barriers to accessing hand sanitizers, Koff et al. evaluated the impact of a personal wearable hand hygiene device with an audible reminder [42]. When compared to that of traditional wall-mounted gel dispensers, the use of a personal hand hygiene device significantly increased the frequency of hand hygiene events from 0.2 to 7.1 events per hour among anesthesia attendings and from 0.4 to 8.7 events per hour among anesthesia residents. The use of a wearable hand hygiene device reduced the contamination of the stopcocks from 33% at baseline to 8% and decreased the contamination of the anesthesia machine by a mean of 77 CFUs per site. HAI rates were also significantly lower in the wearable hand hygiene device group. In a follow-up study involving both anesthesia providers and circulating nurses, the personal wearable hand hygiene device improved hand hygiene compliance when compared to that of a wall-mounted gel dispenser from 0.6 events per hour to 4.3 events per hour [43]. Unlike the previous study, the use of a wearable hand hygiene device was not associated with a reduction in HAIs. However, the use of the same hand hygiene device in the intensive care unit significantly reduced the incidence of ventilator-associated pneumonia per 1000 vent days but did not have a significant effect on CLABSI or mortality [44].

Based on the available evidence, the most effective strategy for improving anesthesia provider hand hygiene compliance is to provide immediate access to a hand gel via personal wearable hand hygiene devices. The Society for Healthcare Epidemiology of America (SHEA) expert guidance on infection prevention in the anesthesia work area included a similar recommendation on improving hand hygiene in the anesthesia work area [45]. Bowdle and colleagues reemphasized the same recommendations regarding hand hygiene in the context of the SARS-CoV-2 pandemic [46]. Although the wearable hand hygiene device used in studies by Koff and colleagues is no longer commercially available, there are other wearable hand hygiene devices that are currently commercially available (Fig. 5.1).

Fig. 5.1 A personal, wearable hand hygiene device clipped to scrub pants. (GelAuto, Blink DC, Seattle, WA)

Gloving

Indications for wearing nonsterile exam gloves remain a controversial issue despite the wide adoption of gloving as a part of "universal precautions" [47] (also known as "standard precautions" [48]) in response to the human immunodeficiency virus (HIV) epidemic. Research is needed to improve our understanding of when gloving should be used to protect the healthcare worker. Gloving may not protect patients beyond what is achievable by hand hygiene. Once soiled, hands should be washed with soap and water or cleaned with alcohol-based gel, while gloves should be replaced with a new pair (or gelled, see below). Anesthesia providers are often wearing nonsterile gloves given the frequency of interactions with the patient and the risk of contact with the patient's body fluids [49]. Kristensen et al. reported that

anesthesia providers come in contact with patient body fluids in 36% of common anesthesia procedures, blood and saliva being the most common body fluids. Another study using self-reporting incident forms during 270 anesthetics identified 46 incidents of blood exposure involving 65 operating room staff [50]. Three different surveys administered to anesthesiologists in New Zealand, United States, and the United Kingdom between 1995 and 2006 indicated that anywhere from 13% to 42% of respondents rarely wore gloves and 0.7% to 3% never wore gloves [51–53]. Furthermore, the survey of New Zealand anesthesiologists indicated that 3.4% of respondents rarely changed their gloves if they were contaminated, and 0.8% never changed contaminated gloves.

Standard precautions include wearing nonsterile gloves along with gowns and eye protection to prevent contact with a patient's body fluids that could contain bloodborne pathogens such as HIV and hepatitis B virus (HBV). Nonsterile gloves serve as a barrier that prevents bloodborne pathogen transmission via breaks in the skin of operating room staff hands. Although HIV transmission through non-needle stick exposure is rare, there are reports of healthcare workers becoming infected with HIV after non-needle stick exposures [54]. In the abovementioned study of blood contamination incidents of anesthesia and related staff, 5 out 65 (8%) staff reported having cuts on their hands [50].

Whether gloving protects patients is difficult to know, and the equivocal results of the meta-analysis of Chang et al. examining the effect of "universal gloving" on HAIs reflects this ambiguity [55]. Their meta-analysis included eight studies, most of which were conducted in intensive care units and showed a significant association between universal gloving and a decrease in HAIs when using pooled results. However, due to the small sample size and heterogeneity of included studies, the authors were concerned about the accuracy of their analysis. When only analyzing the four before-after quasi-experimental studies, the association remained statistically significant, while when limiting the analysis to randomized control trials, the association was no longer statistically significant. In a cluster-randomized multicenter study of 20 intensive care units, the use of gloves and gowns for all patient contact did not prevent the acquisition of MRSA and VRE when compared to that of usual care [56]. The risk to the patient may be similar if operating room staff touches the patient with hands cleaned with soap and water or alcohol-based gel versus while wearing nonsterile gloves.

Unlike hand hygiene, the role of nonsterile gloving in intraoperative pathogen transmission has not been extensively studied. The simulation-based studies by Birnbach and colleagues evaluated the impact on environmental contamination of wearing double gloves during airway management and discarding the outer layer of gloves following intubation or supraglottic airway placement [57, 58]. Wearing double gloves during intubation and immediately removing the outer gloves after airway management significantly reduced the number of environmental sites that had fluorescent dye detected by ultraviolet light [58]. In a similar study, the number of the manikin and environmental sites positive for fluorescent dye was further reduced by wearing double gloves, removing the outer gloves immediately after airway management, and inverting a discarded glove over the laryngoscope [57]. Although the evidence for the practice of double gloving is not strong and is lacking in a clinical setting, double gloving has minimal impact on anesthesia provider workflow and has the potential to impact intraoperative pathogen transmission. A recommendation for double gloving during airway management was included in the SHEA expert guidance for infection prevention during anesthesia and by Bowdle and colleagues [45, 46].

Applying an alcohol-based gel directly to gloves rather than doffing soiled gloves, applying the alcohol-based gel directly to the hands, and donning new gloves is controversial approaches to hand hygiene. Although the presence of bodily fluids on hands is an indication for hand hygiene with soap and water instead of alcohol-based gels, the only available sinks for the operating room staff are located outside of the operating room. Anesthesia providers are unable to leave the operating room while providing anesthesia care and, therefore, cannot wash their hands with soap and water during an anesthetic procedure. Anesthesia providers wear gloves to prevent contact of their hands with bodily fluids. The presence of bodily fluids on gloves is an indication for doffing gloves, performing hand hygiene with alcohol-based gel, and donning new gloves. However, anesthesia providers would be doffing soiled gloves nonstop during induction and emergence, given the frequency of contacts with patients and their bodily fluids. It seems reasonable to consider the application of an alcohol based-gel to gloves to help prevent intraoperative pathogen transmission. A review of available evidence for the efficacy of applying an alcohol-based gel to gloved hands was equal to applying an alcohol-based gel to bare hands even if gloves contained perforations [59]. The rate of perforations in gloves treated with an alcohol-based gel was similar to that of untreated gloves. These results were confirmed by Birnbach and colleagues, who evaluated the impact of alcohol-based gels on gloves [60]. The authors evaluated 50 new, unused nitrile exam gloves and found 1 new glove with a microperforation. Another set of 50 nitrile exam gloves was evaluated for microperforations after being worn for 2 hours with alcohol-based gel applications every 15 minutes. None of the gloves had microperforations. One of the major issues with wearing a single pair of gloves and gelling them is the inability of the anesthesia provider to determine when gloves are contaminated, and the false sense that wearing gloves equals clean hands. Additional research to further our understanding of the practice of gelling gloved hands is needed.

Another aspect of frequent hand hygiene to consider is the effect of the alcohol-based gel on providers' skin. When anesthesia providers cleaned their hands with an alcohol-based gel every 15 minutes for 8 hours for 5 days, there was a significant increase in the Hand Eczema Severity Index score and subjective complaints by anesthesia providers [61].

Surfaces

Evidence for environmental contamination in the operating room and, particularly, the anesthesia work area was contributed by several studies by Loftus and colleagues [62–66]. Their experimental model for studying intraoperative bacterial transmission revealed the extent of environmental contamination. In their initial study in 2008, cultures of the anesthesia machine adjustable pressure-limiting valve showed that the number of CFUs significantly increased by the end of surgery [62]. Similarly, 32% of intravenous stopcocks were found contaminated by the end of the case. Although most of the bacteria isolated were skin organisms, MRSA, VRE, and *Enterobacter cloacae* were also identified. In order to examine the relative contribution of the environment, providers, and patients to intravenous stopcock contamination, they studied the first and second cases in the same day (case pairs) and cultured providers' hands, intravenous stopcocks, anesthesia machine sites (adjustable pressure-limiting valve and agent dial), and patients' nasopharynx and axillae [63]. Stopcock contamination occurred in 23% of cases with 14 between-case transmissions in which the stopcock from the second case was contaminated with organisms isolated from the first case and 30 within-case transmission events. All three bacterial reservoirs contributed to between-case and within-case transmission, with the environment being a significantly more frequent source of contamination than that of providers' hands. Ten of the 14 between-case transmissions originated from the environment (including one *Pseudomonas* and one *Serratia* organism), two originated from the anesthesia provider in the first case, and two from the patients' axillae. With the exception of the abovementioned *Pseudomonas* and *Serratia* organisms, the majority of isolates were skin flora such as *S. aureus* and *Staphylococcus epidermidis*.

The subsequent multicenter study from the same group used the same experimental model to describe the transmission of *S. aureus* [65], enterococcus [64], and Gram-negative rods [66]. Two *S. aureus* phenotypes originating from patients and provider hands were identified across three academic centers. These highly transmissible phenotypes accounted for 65% of operating room transmission events. Similarly, two highly transmissible enterococcus phenotypes originating from providers' hands accounted for 84% of intraoperative transmission events involving enterococcus. Gram-negative rods were predominantly isolated from providers' hands but also from patients and the environmental surfaces (anesthesia machine adjustable pressure-limiting valve and agent dial).

Although often overlooked, contamination of the floor of the operating room should be evaluated in future studies. There is a limited amount of published data addressing the issue of floor contamination. Floor contamination due to dirty footwear of operating room staff can lead to significant floor contamination regardless of footwear used (street shoes, clean shoes, or shoe covers). Bacterial floor contamination due to staff walking on the floor was significantly higher than that of bacterial sedimentation from the air and areas of the operating room where walking was not allowed [67]. Studies have also shown that intravenous tubing, along with injection ports, monitoring cables, drapes, operating room bed safety belts, etc., are commonly in contact with the floor and placed back on the patients' body surfaces [5]. However, at this time, the relevance of the operating room's floor to cross-transmission is unclear.

Surface Cleaning and Disinfection

We have known for over a decade that our current cleaning and disinfecting practices in the hospital setting have not properly addressed the contamination of environmental surfaces [68]. There are significant knowledge gaps in understanding the role of environmental contamination in causing HAIs, which is partly due to our inability to routinely perform microbiological surveys of the hospital environment and correlate pathogens found in the environment with the ones isolated from patients. The most commonly used methods for evaluating the level of surface contamination (fluorescent markers and adenosine triphosphate bioluminescence assays) are crude techniques that lack the microbiological information such as the type and quantity of pathogens present [69, 70]. Novel microbiological surveillance techniques could provide this information and help us determine the significance of environmental contamination and ways to improve cleaning and disinfection techniques [71, 72]. Video recordings of surgeries have been used as a research tool to assess the compliance with infection prevention measures but could also be used for routine monitoring of compliance with operating room infection prevention measures, including cleaning and disinfection procedures during and between cases [73, 74].

The effectiveness of cleaning and disinfection procedures in the operating room has been shown to be inadequate, which is concerning given the frequent provider-patient contacts and patient's immunocompromised state as a result of surgery and anesthesia [75]. One of the early multicenter

studies evaluated ten standardized sites in the operating room by placing fluorescent markers and inspecting them with ultraviolet light after terminal cleaning was performed two to three times [76]. The study confirmed that despite terminal cleaning, 75% of operating room sites contained fluorescent markers, while 80% of anesthesia carts and 72% of anesthesia machines had a fluorescent marker. In another study, fluorescent markers were used to evaluate cleaning rates in the anesthesia area and the impact of feedback and education on the environmental services staff. The authors reported a significant improvement in objects appropriately cleaned over a 24-hour period and a significant decrease in Gram-negative rod contamination on surfaces [5]. An infection prevention bundle that was shown to significantly reduce postoperative HAIs included enhanced surface cleaning [40]. Anesthesia machines and monitors were wiped with a cloth soaked in quaternary ammonium compound before and after each surgical case. Anesthesia machines were also wiped with a cloth soaked in quaternary ammonium compound and isopropyl alcohol after induction of anesthesia.

Others have proposed redesigning the anesthesia machine to improve the cleaning and disinfection of the anesthesia machine. A simulation-based study did not find a significant difference in the number of cleaned sites between conventional and redesigned anesthesia machines [77]. Despite the lack of evidence that this specific anesthesia machine design improved cleaning, design improvements of anesthesia machines and other pieces of operating room equipment could facilitate frequent cleaning.

Disposable plastic covers over anesthesia machines, monitors, keyboards, and other equipment that is difficult to clean may enhance decontamination. There is evidence that the intraoperative use of an anesthesia machine cover significantly decreased CFUs on the anesthesia machine and significantly reduced the introduction of new bacterial species onto the anesthesia machine (Fig. 5.2) [78]. The use of anesthesia machine covers and improved cleaning and disinfection between cases and at the end of the day with particular focus on "high-touch" surfaces was recommended by the SHEA expert guidance and Bowdle et al. [45, 46, 79].

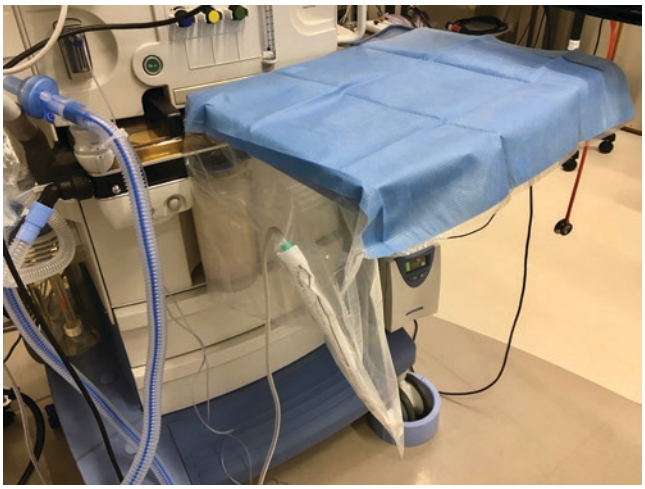

Fig. 5.2 A partial anesthesia machine cover with a pocket for Yankauer suction. (Anesthesia Hygiene, Los Angeles, CA)

Laryngoscopes

Reusable laryngoscopes used for airway management are semicritical devices that require high-level disinfection. Laryngoscope blades are easily processed, but laryngoscope handles typically require extensive disassembly prior to high-level disinfection or sterilization. Contaminated laryngoscopes have been associated with infectious outbreaks [80–83]. Despite the available evidence of infectious risks associated with low-level disinfection of laryngoscope handles, conventional laryngoscopes and videolaryngoscope handles often do not undergo proper high-level disinfection or sterilization. Furthermore, some videolaryngoscope handles cannot undergo high-level disinfection or sterilization per the manufacturer's recommendations (see supplemental digital content table in Bowdle et al. article [46]). Some authors have also recommended that videolaryngoscopes are preferred for the airway management of patients infected with SARS-CoV-2 [84], raising further concerns about proper disinfection. The use of single-use conventional and videolaryngoscopes may be a cost-effective alternative to high-level disinfection of reusable equipment [45].

Anesthesia Carts

One of the key challenges with anesthesia equipment care is the presence of drawers full of equipment and supplies. The drawer interior and its contents are difficult to clean. The anesthesia cart is probably the most challenging piece of operating room equipment to clean since it has multiple drawers containing supplies intended to serve multiple patients. Anesthesia providers are accessing anesthesia cart drawers repeatedly, often with contaminated hands or gloves, which can lead to contamination of the inside of the drawer and its contents. The contamination level of the anesthesia cart has not been studied, and its role in pathogen transmission is poorly understood. Proper cleaning and disinfection of the inside of the anesthesia cart would require enormous resources and time, even if it was performed only at the end of the day, similar to terminal operating room cleaning. A better strategy would be to prevent contamination of the anesthesia cart in the first place by requiring anesthesia providers to perform hand or glove hygiene prior to accessing the drawers. However, compliance with this practice is

difficult to achieve. A more transformative approach would be the development of single patient anesthesia case packs similar to the surgical case packs that would largely replace anesthesia carts. These packs would contain commonly used anesthesia supplies needed for a single case, unlike the anesthesia cart that contains commonly used supplies for multiple patients.

Implementation of a bundle of prevention measures in the anesthesia workplace to reduce infection of central venous catheters placed in the intensive care unit and then used during anesthesia care resulted in a highly significant reduction of CLABSI from 14.1 per thousand to 0 per thousand trips from the intensive care unit to procedural areas [85]. The infection prevention bundle consisted of a standardized intravenous line starting kits, a drug administration manifold attached to an intravenous pole, hand sanitizer on the anesthesia cart, anesthesia workspace divided into "dirty" and "clean" areas with the anesthesia cart included in the "clean" area, and a room turnover cleaning checklist.

Injection Ports

There is strong evidence that contaminated intravenous line injection ports are associated with intraoperative bacterial transmission [62, 86] and patient mortality [63]. One of the strategies to reduce injection port contamination is improved hand hygiene [42]. Another strategy is the use of closed injection ports, the surface of which can be decontaminated with relative ease. By contrast, conventional open-lumen stopcocks that are often used in anesthesia practice are difficult or impossible to disinfect with either alcohol wipes or alcohol-based scrub [87].

An ex vivo study of closed injection ports, which were disinfected by 70% alcohol, showed a significant reduction in the risk of bacterial injection when compared to that of the same injection ports without disinfection and conventional open-lumen stopcocks [88]. A follow-up study evaluating a catheter care bundle that included stopcocks with closed injection ports and alcohol-containing caps showed a significant reduction in stopcock lumen contamination, 30-day postoperative infections, and phlebitis when compared to that of stopcocks with standard caps [89]. These studies highlight the importance of using closed injection ports and disinfecting the port surface prior to drug administration via both central and peripheral venous catheters [45]. Because of the need to immediately inject drugs during anesthesia care, without having time to wipe or scrub the surface of closed injection ports, the use of alcohol-containing caps that remain on injection ports at all times would seem to be the approach most likely to gain compliance in the anesthesia setting. We suggest that open stopcocks should never be used during anesthesia care. Drugs should only be injected into closed ports. The surface of the closed port should be covered by an alcohol-containing cap at all times (Fig. 5.3).

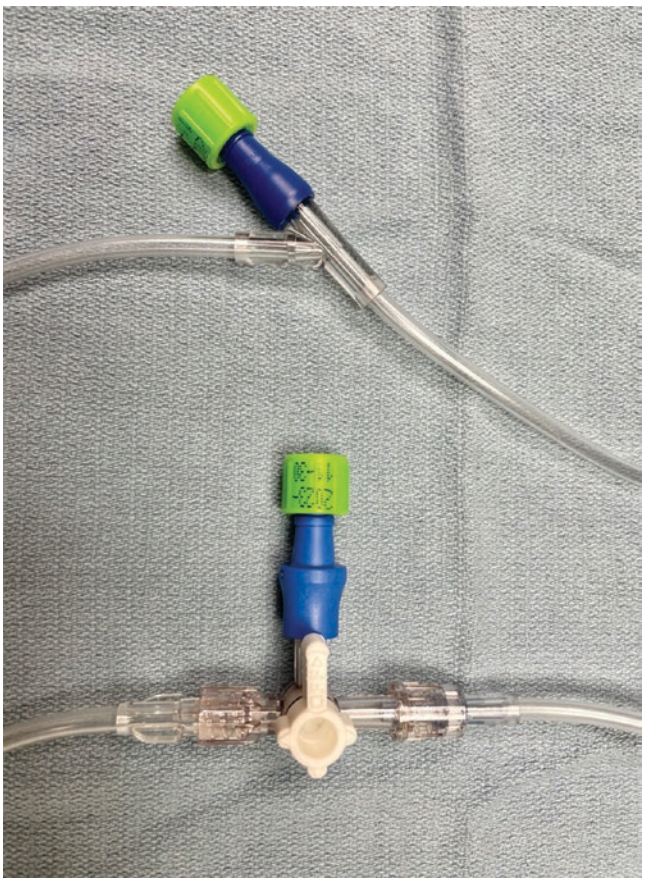

Fig. 5.3 A three-way stopcock with a closed injection port and alcohol-containing cap and an in-line closed injection port with an alcohol-containing cap

Other approaches have also been proposed. A device to discourage touching the injection port (described by the authors as a "shield") was evaluated in simulation-based pilot studies [90, 91]. Injecting drugs through a bacterial filter attached to the injection port is another interesting approach. Gargiulo et al. used 0.2-μm filter units attached to the injection port during anesthesia care and found that in 6% of cases, the filters contained bacterial pathogens; in 16% of cases, the residual contents of anesthetic drug syringes contained similar bacterial pathogens [92]. One drawback of using filters was that the common intravenous anesthetic propofol could not be injected through the filters because the filters were clogged by the lipid emulsion of the propofol vehicle.

Intravascular Catheters

Central venous catheters are a well-recognized source of bloodstream infection and therefore are managed with a

standardized set of infection prevention measures. Arterial catheters and peripheral venous catheters may also be important sources of bloodstream infection but generally have not received as much attention.

Peripheral intravenous catheters are a ubiquitous feature of perioperative care and are often considered to be relatively harmless from the standpoint of infection risk. However, the potential of peripheral intravenous catheters for producing bloodstream infections may be underestimated. A systematic review suggested that peripheral venous catheters accounted for 23% of catheter-related bloodstream infections [93]. In a study of 137 patients, peripheral intravenous catheter skin sites were swabbed and paired with the peripheral intravenous catheter tips [94]. The catheters had an average dwell time of 4 days. Prior to catheter insertion, the skin had been decontaminated with 1% chlorhexidine gluconate in 70% alcohol solution. Forty-five (33%) patients had colonized skin sites and/or catheter tips. Sixteen patients had paired colonization of both skin and catheter tips, and of these, 11 were colonized with the same bacterial species. There was one patient with *Pseudomonas aeruginosa* bloodstream infection that was genetically identical to the bacteria found on the skin and catheter tip. A retrospective, two-center study of *Staphylococcus aureus* bacteremia cases found that 137 of 583 (23%) cases were associated with peripheral intravenous catheters [95]. The average dwell time for the catheters was 3.5 days. In an effort to reduce the incidence of peripheral intravenous catheter-related bloodstream infections, an institution implemented a bundle of practice changes in 2003 and observed that the incidence of peripheral venous catheter-related bloodstream infections fell substantially during the ensuing 13 years [96]. Interestingly, one of the practice changes was the use of sterile gloves for peripheral intravenous catheter placement instead of nonsterile exam gloves.

A systematic review and meta-analysis of bloodstream infections related to arterial catheters suggested that infection rates were similar to central venous catheters. Published guidelines recommend using a placement bundle for arterial catheters similar to that for central venous catheters, including sterile gloves and a sterile drape [97].

Probably all intravascular catheters have a similar potential for producing bloodstream infection. The femoral site should be avoided whenever possible because of higher infection rates compared to that of other sites, and catheters should be placed with an aseptic technique following careful skin decontamination. In the opinion of the authors, consideration should be given to the use of sterile gloves for the placement of peripheral intravenous catheters. Catheters that are no longer needed or show any sign of infection should be promptly removed.

Intraoperative Bacterial Transmission and Mortality

Establishing an association between operating room environmental contamination and postoperative HAIs and mortality remains a challenge. One of the few studies evaluating this association in a single-center found that contaminated stopcocks during surgical procedures were not associated with HAIs [62]. However, patients with contaminated stopcocks were found to have higher mortality (0 out of 40 in the non-contaminated group vs. 2 of 20 in the contaminated group). The association between contaminated stopcocks and mortality was also observed in a multicenter study, therefore, reproducing the results of the single-center study [63]. Interventions such as the use of a wearable hand hygiene device significantly decreased the incidence of HAIs in one study [42]. None of the patients in the wearable hand hygiene device group died compared to 2 out of 58 in the control group. The same wearable hand hygiene device was shown to significantly reduce ventilator-associated pneumonia in the intensive care unit [44]. Finally, an infection prevention bundle including improvements in perioperative hand hygiene, vascular care, environmental cleaning, and patient decolonization efforts significantly reduced HAIs [40].

Air

Airborne Pathogen Transmission

Although most traditional infection prevention measures have addressed the role of patients, providers, and surfaces, recent influenza and coronavirus pandemics have reminded us that the air is sometimes an important route of disease transmission. Air can transmit bacterial or viral pathogens. Patients and healthcare workers alike may acquire infections through the air.

Operating rooms are unique airspaces. They have a high airflow, with a recommended minimal air exchange of 15 times per hour. Typically air is filtered by high-efficiency particulate air (HEPA) rated or similar filters and delivered at a rate that produces a slightly positive pressure inside the room when the doors are closed. Hypothetically, this reduces the particle count in the air and reduces the likelihood of bacterial contamination of surgical sites by bacteria suspended in the air. However, there are numerous sources of contamination of the operating room air, including aerosols from the airways of staff and patients, smoke from surgical cautery or lasers, and tissue aerosols from cutting tools such as saws. Operating room staff frequently work in very close proximity, sometimes literally within inches of each other, for prolonged periods of time, raising the concern for

transmission of respiratory infections between staff. While operating room staff typically wear surgical masks, these are primarily intended for splash protection and to reduce contamination of the surgical wound from respiratory droplets (coughs and sneezes). Surgical masks do not make a tight seal with the face and do not provide protection from aerosols; for protection from aerosols, filtering facepiece respirators (such as N95) are needed. A case report of a surgeon infected with SARS-CoV-2 believed to originate in a donor's lung during a lung transplant (confirmed by genetic sequencing) illustrates the potential hazard [98].

Although historically, the main concern in the operating room has been for protecting the surgical site from infection, there has been a periodic concern for infection of healthcare workers by airborne pathogens from patients, especially with seasonal influenza and tuberculosis. Concern for transmission of respiratory infections has increased in the setting of several recent influenza and coronavirus pandemics.

Initial experiments intended to study air contamination and airborne bacteria in the 1960s and 1970s were performed using "drop plates" (culture plates set on operating room surfaces), which were subsequently replaced by air sampling devices that could correlate colony counts to the volume of air sampled [99]. An experimental study in the 1980s using an operating room in which ventilation was turned off and all air leaks were sealed off found that less than 15% of airborne bacteria were redispersed from the floor intentionally contaminated by *S. aureus* [100]. Another study described a 2% rate of SSI (2 out 169 procedures) due to airborne *S. aureus* traced to operating room staff. The same isolate was found in 33% of procedures in the sterile surgical field, 25% of procedures on the floor, and 11% of procedures in air samples [101]. Several other studies established the association between foot traffic, door openings, and air contamination, but not the SSI [102, 103]. The strongest evidence for the association between airborne bacterial contamination and SSI came from a series of studies performed in the 1980s in the United Kingdom evaluating the impact of "ultraclean air" (arbitrarily defined as air containing less than 10 bacteria-carrying particles per m^3) on joint prosthesis infection rates [104–106]. The use of "ultraclean air" reduced the rate of prosthesis infections from 1.5% to 0.6%.

Smoke is a byproduct of energy-based instruments such as mono- and bipolar diathermy (electrocautery), ultrasonic scalpels, and lasers used in the operating room. A literature review in 2003 identified several anecdotal reports indicating human papilloma virus (HPV) transmission to operating room staff during the use of surgical lasers [107]. A more recent systematic review identified six studies that assessed surgical smoke for the presence of infective material, mostly HPV DNA generated by laser [108]. Out of six studies, one found HPV DNA present in the smoke generated by both laser and electrocoagulation [109], while another study found 38% of smoke cultures positive for coagulase-negative *Staphylococcus* [110]. HBV was also detected in surgical smoke from patients undergoing robotic or laparoscopic abdominal procedures [111]. To the best of our knowledge, the presence of the live virus in surgical smoke has not been demonstrated.

Airway management may generate aerosols and is thought to play a role in respiratory virus transmissions [112–114]. Growing evidence suggests that droplet and airborne transmission are not separate phenomena but rather represent a continuum of respiratory particle sizes [115–117].

Respiratory Precautions

Given the concern about respiratory pathogen transmission, the question arises whether operating room staff should adopt respiratory precautions in addition to standard precautions. Operating room staff may be at increased risk for infection by airborne pathogens given the performance of aerosol-generating procedures; the presence of aerosols produced by the surgical procedure, including smoke, and the presence of multiple providers in close contact for prolonged periods of time. We and others (including many professional societies) have suggested that operating room staff should routinely wear filtering facepiece respirators (such as disposable N95 respirators) at least during periods when community prevalence of transmissible respiratory pathogens is high (such as the SARS-CoV-2 pandemic) [46, 118]. The current design of the most commonly used N95 filtering facepiece respirators has some serious limitations, including frequent poor fit, resistance to breathing, discomfort, single use, and limited filtering efficacy of 95% [119]. There is a need for the innovative design of both disposable N95 and reusable filtering facepiece respirators (such as elastomeric and powered air-purifying respirators). An adhesive mask shown in Fig. 5.4 is just one example of an innovative design to improve respirator fit.

The Occupational Safety and Health Administration (OSHA) does not specifically mandate the use of surgical smoke evacuators. However, both the National Institute of Occupational Safety and Health (NIOSH) and the Association of periOperative Registered Nurses (AORN) recommend the use of surgical smoke evacuators.[1] A review concerning surgical smoke also strongly recommended the use of filtering facepiece respirators (such as N95) in addition to smoke evacuation systems (Fig. 5.5) [120].

[1]Occupational Safety and Health Administration recommendations can be found at https://www.osha.gov/laser-electrosurgery-plume. National Institute of Occupational Safety and Health recommendations can be found at https://www.cdc.gov/niosh/topics/healthcarehsps/smoke.html. Association of periOperative Registered Nurses recommendations are limited to members only.

Fig. 5.4 A strapless N95 filtering facepiece respirator attached to the face with adhesive to improve user fit of the author (SJ) who failed the fit test with a conventional N95 filtering facepiece respirator. (Avery Dennison, Glendale, CA)

Fig. 5.5 An example of a surgical smoke evacuator used at our institution. (PlumePen Pro, Buffalo Filter, Lancaster, NY)

Patients with transmissible respiratory infections are usually cared for in hospital rooms with negative pressure airflow, which is intended to prevent contaminated air from entering adjacent hallways and rooms. Since operating rooms have positive airflow, contaminated air may be forced into adjacent hallways and rooms. This becomes a concern in the presence of respiratory pathogens such as coronaviruses, influenza viruses, and tuberculosis. An approach to mitigating this problem is the use of portable HEPA purification units. The use of HEPA purification units was recommended by the Centers for Disease Control and Prevention (CDC) in 2003 guidelines when performing procedures on patients with tuberculosis, but only during intubation and extubation [121]. The CDC recommendations specified that the HEPA units should be turned off during the surgical procedure. The updated CDC guidelines in 2005 no longer specifically recommended the use of portable HEPA purification units [122]. These recommendations are consistent with the findings of a study comparing the portable HEPA purification units positioned inside the operating room versus the anteroom adjacent to the operating room [123]. The HEPA purification units positioned inside the operating room were found to be noisy and generated vertical air plumes that affected the breathing zone of the surgical team. In contrast, the HEPA purification units placed in anterooms evacuated air plumes away from the surgical field and toward the main entry door.

The use of negative pressure operating rooms for patients with transmissible respiratory diseases has been proposed. During the 2003 SARS outbreak, a hospital in Hong Kong temporarily converted one of its operating rooms to negative pressure to facilitate procedures in patients with SARS infections [124]. Subsequently, the hospital management decided to permanently convert one of its operating rooms to negative pressure in anticipation of future SARS-like or other novel airborne pathogen outbreaks. A hospital in South Korea took the same approach and temporarily converted two of its operating rooms to negative pressure during the MERS outbreak in 2015 [125]. The requirements for converting operating rooms to negative pressure vary depending upon the circumstances but could be accomplished by adding a temporary negative pressure anteroom and portable HEPA air purifier units directing the HEPA air purifier exhaust back into the operating room ventilation system [126]. Whether the use of negative pressure operating rooms would increase the risk of surgical wound infection is unknown.

Conclusions and Controversies

Infection prevention in the operating room should include patients, providers, surfaces, and air with the goal of protecting both the patients and healthcare workers. The notion that the operating room is not a source of HAIs because the surgical field is "sterile" is greatly oversimplified. Bacteria on patients' skin, providers' hands, and surfaces may cause infection. Air may also be a source of infection, particularly with airborne respiratory pathogens, which may be hazardous for patients and healthcare workers. Although many infection prevention measures have been recommended, the authors suggest that the following be given special attention:

1. Patient—utilize optimal decolonization procedures and antibiotic prophylaxis targeted to individual patients and procedures.
2. Providers—encourage frequent hand hygiene within the operating room through the use of an alcohol-based hand gel, which is optimally provided as wearable gel dispensers.
3. Surfaces—operating room surfaces should be subjected to more thorough decontamination, especially in the anesthesia work area. Anesthesia work area practices should be scrutinized with respect to infection prevention. Evidence-based practices such as the use of closed injection ports covered by alcohol-containing caps should be adopted. Consideration should be given to replacing traditional anesthesia carts containing supplies for multiple patients with individual patient case packs. Consideration should be given to covering equipment that is difficult to clean with disposable plastic covers.
4. Air—although high air exchange with filtered air provides some protection in the operating room, the presence of airway and surgical aerosols, surgical smoke, and constant close contact between providers for long periods of time introduces risks for airborne infection. Surgical smoke evacuation and the routine use of respiratory protection (such as disposable N95 respirators) should be considered. Selective use of negative pressure airflow in operating rooms should be considered, but more research is needed.

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Infection Control in the Outpatient Setting

6

Julie D. Boatman, Michael P. Stevens, and John Daniel Markley

Introduction

As healthcare continues to evolve, economic forces and technological innovations have facilitated the transition of healthcare delivery from acute care hospitals to a myriad of different outpatient care settings such as ambulatory surgery centers (ASCs), physician offices, urgent care centers, dialysis centers, home care, and other specialized settings [1]. The number of outpatient visits in the United States in 2016 was 883.7 million or 278 office-based physician visits per 100 persons [2]. Ambulatory surgical procedures increased by 25% from 2006 to 2017 costing Medicare $4.6 billion in 2017 alone [3]. Outpatient services as a proportion of hospital revenue has nearly doubled between 1995 and 2018 (Fig. 6.1).

Outpatient oncologic care is also on the rise in the United States as the prevalence of cancer continues to rise with over 15 million people living with cancer in 2017 [5] and an estimated 1.1 million cancer patients per year receiving outpatient chemotherapy or radiation [6]. The number of patients receiving home infusion therapy continues to grow as it provides multiple benefits including shorter hospital stays, fewer healthcare-associated infections (HAIs), and cost savings [7]. Between 2008 and 2015, the number of urgent care clinics increased by 119% and retail clinics by 214%, while Emergency Department visits decreased by 14% [8]. In the context of this rapid transition of healthcare delivery in the outpatient setting, implementation of evidence-based infection control processes and practices becomes increasingly relevant to ensure the safety of both patients and healthcare personnel (HCP).

It is estimated that HAIs occur in 1 out of every 25 hospital patients in the United States [9], corresponding to nearly two million patients per year, 99,000 deaths, and a cost of approximately $33 billion each year [10]. These estimates are primarily derived from infection surveillance in acute care settings including central line-associated bloodstream infections (CLABSI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), and surgical site infections (SSI). Indeed, since the Institute of Medicine (IOM) released the siren call, "To Err is Human: Building a Safer Health System," in 1999, hospital-based infection control and patient safety research have experienced a period of intense growth [11, 12]. Spurred by the IOM report, mandatory reporting and other requirements from the Joint Commission (formerly known as the Joint Commission on Accreditation of Hospitals and Healthcare Organizations [JCAHO]), the Department of Health and Human Services (DHHS), and the Centers for Medicare and Medicaid Services (CMS) have led to the development of systematic approaches to surveillance, isolation, outbreak investigation, environmental cleaning, and antimicrobial stewardship in the hospital setting.

These efforts have continued to be fruitful over the last decade. From 2015 to 2019, there was a 31% decrease in CLABSI, 26% in CAUTI, 42% decrease in *Clostridioides difficile* infections, 18% decrease in MRSA bacteremia, 3% decrease in VAP, 2% decrease in SSI from abdominal hysterectomy, and 15% decrease in SSI from colon surgeries [13]. Unfortunately, infection control in the outpatient setting has

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_6

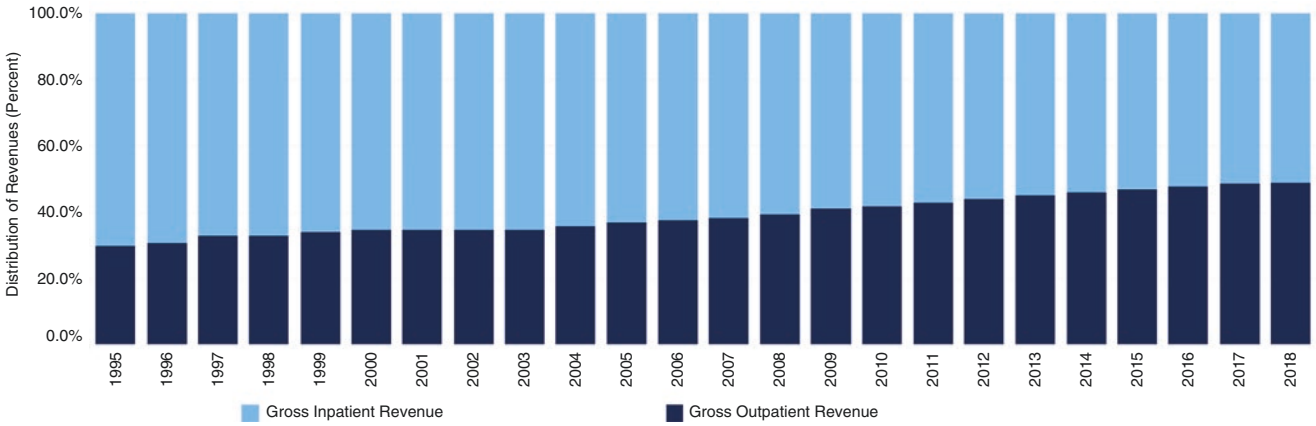

Fig. 6.1 Distribution of outpatient vs inpatient revenues, 1995–2018. (Source: American Hospital Association Trendwatch Chartbook 2020 [4])

Table 6.1 Infection control lapses in ambulatory surgery centers

Infection control category assessed	Number of facilities with lapses identified (%)
Hand hygiene and use of personal protective equipment	12/62 (19%)
Injection safety and medication handling	19/67 (28%)
Equipment reprocessing	19/67 (28%)
Environmental cleaning	12/64 (19%)
Handling of blood glucose monitoring equipment	25/54 (46%)

Adapted from: U.S. Department of Health and Human Services [16]

not experienced a parallel evolutionary trend and, when compared to hospital-based infection control, is largely in its nascency. Regulatory emphasis has primarily focused on acute care settings, though this emphasis is shifting to the outpatient setting as outlined in "Phase Two" of the DHHS *National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination* [14]. Historically, infection control in the outpatient setting has been managed by affiliated hospital programs. Private offices and freestanding ambulatory care centers have very little written infection control policies and lacked formal training procedures for their personnel [15]. This problem has been amplified by a lack of resources to support infection control and prevention in the outpatient setting.

To date, there is a paucity of data describing the rates and risks for HAIs in the outpatient setting, and much of what is known has been derived from outbreak investigations. Based on the few data available, it is likely that infection control lapses in the ambulatory setting are common. An enhanced inspection pilot, led by the CMS and supported by the Centers for Disease Control and Prevention (CDC) across three states, revealed that greater than 66% of ASCs had infection control lapses and half had not undergone a complete inspection in greater than 5 years (Table 6.1).

Numerous outbreaks of *Staphylococcus aureus*, hepatitis B and C, nontuberculous mycobacteria, *Clostridioides difficile*, and multidrug-resistant organisms (MDROs) have been described and have increased public awareness of the dire need for improvement in outpatient infection control and prevention practices. Outbreaks in ASCs have stemmed from lapses in basic infection control processes such as reusing syringes, mishandling of injectable medications from single-dose vials (SDVs) or multidose vials (MDVs), breaches in sterilization protocols of endoscopy equipment, and the breakdown in use of personal protective equipment (PPE), to name a few [17]. In 2012, one of the largest outbreaks in US history took place due to steroid injections with infected lots of methylprednisolone acetate from the New England Compounding Center (NECC). Out of the nearly 14,000 patients at risk, a total of 749 cases of fungal infections spanning 20 states culminated in 61 deaths and untold morbidity [18]. A congressional hearing concluded that greater oversight and standards for nontraditional compounding be implemented, and the Drug Quality and Security Act was passed by the Senate on November 27, 2013.

Several regulatory and expert bodies have begun outlining recommendations to guide infection control and prevention programs in the outpatient setting. In 2015, the CDC released a summary guide of infection prevention recommendations for outpatient (ambulatory care) settings that includes evidence-based guidelines produced by the CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). The guide focuses on the basic elements of standard precautions and proclaims itself to be "the minimum infection prevention expectations for safe care in ambulatory care settings" [19]. This document serves as a major step forward to assist infection control and prevention professionals to develop more robust outpatient programs.

While significant progress has been made, there remains an urgent need for addressing HAI prevention across the healthcare continuum, including the outpatient setting. Infection control in the outpatient setting is largely undeveloped compared to the inpatient setting. Currently there is a paucity of data on national estimates of HAIs originating in the outpatient setting [16]. Basic infection control practices including surveillance of infection rates, isolation, environmental cleaning, sterilization of devices/tools, outbreak investigation, personnel training, education, antimicrobial stewardship, and mandatory reporting and monitoring should be applied to the outpatient setting.

Definitions

For the purposes of consistency, this chapter will employ the following definitions as outlined by the recent recommendations from the CDC's "Guide to Infection Prevention for Outpatient Settings: Minimum Expectations for Safe Care" [19].

- *Outpatient care*: care provided in facilities where patients do not remain overnight (e.g., hospital-based outpatient clinics, nonhospital-based clinics and physician offices, urgent care centers, ASCs, public health clinics, imaging centers, oncology clinics, behavioral health clinics, and physical therapy and rehabilitation centers) [19].
- *Healthcare personnel* (HCP): all persons, paid and unpaid, working in outpatient settings who have the potential for exposure to patients and/or to infectious materials, including body substances, contaminated medical supplies and devices, contaminated environmental surfaces, or contaminated air. This includes persons not directly involved in patient care (e.g., clerical, housekeeping, and volunteers) but potentially exposed to infectious agents that can be transmitted to and from HCP and patients [19].

In this chapter, we aim to outline the basic principles of infection control and prevention in the outpatient setting, as well as emphasize common scenarios that represent the highest infectious risk to patients and HCP. It is beyond the scope of this chapter to discuss every particular outpatient setting currently in use; however, we will review major concepts that can be applied to all outpatient settings and highlight a few particularly high-risk scenarios. For an exhaustive review of practices and protocols, we refer you to our references. We will not discuss home healthcare and dental offices; for guidance on these topics, the reader is referred to recent reviews [20–23].

Applying the Principles of Hospital Infection Control to Outpatient Infection Control

Across the vast spectrum of outpatient care settings, there are many unique patient care environments, some of which are quite unique compared to the hospital settings. However, the principles of infection control and prevention remain constant regardless of the patient care location. Generally speaking, there are two basic epidemiologic approaches to infection control and prevention: (1) broad programs which attempt to reduce the rates of all infections due to all pathogens, so-called horizontal activities, and (2) narrow programs focusing on a single pathogen or single anatomic site, so-called vertical activities [24]. When conceptualizing the approach to outpatient infection control, it is helpful to evoke this concept. Horizontal activities span both the inpatient and outpatient settings. While there will always be exceptional infection control situations, one need not think of outpatient infection control as a field within a field. But rather, it is the application of core principles of infection control across the entire continuum of care. With that said, the outpatient setting does pose distinct challenges when compared to inpatient settings that should not be overlooked. In general, outpatient facilities lack the infrastructure and resources to conduct thorough infection prevention and control or intensive antibiotic stewardship activities compared to inpatient settings. Herein we aim to expound on the key principles of outpatient infection control and how they compare to inpatient practices.

Infrastructure

Infection prevention and control (IPC) programs are tasked with coordinating and directing a large number of activities that are vital to patient safety and quality care. Implementing the most current and credible scientific evidence and guidelines, detecting and investigating outbreaks, surveillance of HAIs, educating HCP, and intervening to prevent infections are but a few functions of any robust program. Antimicrobial stewardship programs (ASPs) aim to maximize the benefit of antibiotic treatment while reducing harm related to antibiotic use. By doing so, ASPs can also serve the goal of infection prevention by limiting the spread of antimicrobial resistance [25]. A program must be outfitted with sufficient equipment, supplies, and trained personnel to carry out these tasks. In the hospital setting, mandatory compliance with state and federal regulations has led to significant resources being funneled to infection control programs; however, the same cannot be said of outpatient settings.

Unfortunately, as the CDC indicated in its summary document, *Guide to Infection Prevention for Outpatient Settings: Minimum Expectation for Safe Care*, compared to inpatient acute care settings, outpatient settings have traditionally lacked infrastructure and resources to support infection prevention and surveillance activities [19]. Because many outpatient care settings are not certified by the CMS or licensed by states, they do not invest appropriate funding to develop robust infection prevention and control programs. However, as the number of patients undergoing increasingly complex medical treatment in the ambulatory setting continues to grow, a parallel increase in risk of iatrogenic infection can be anticipated [15]. One must conclude that outpatients deserve care that is at least as effective and safe as that received by inpatients.

Regulations, Mandatory Reporting, and Monitoring

Unlike acute care settings which are highly regulated and where accreditation is the standard, outpatient care settings are not held to the same regulatory standard and are operating more under the auspices of trust. For example, despite ASCs being subject to the same regulatory requirements for Medicare participation as inpatient facilities for similar services provided, the majority of monitoring of regulatory compliance has been left to individual states, and direct observation has not been required [26]. Healthcare organizations that desire to receive payment from Medicare or Medicaid must be certified as complying with the Conditions of Participation (CoPs), outlined in federal regulations. This certification is voluntary and based on a survey conducted by a state agency or other accreditation organization on behalf of the CMS (see Table 6.2). Most facilities only undergo a state agency survey to demonstrate that they meet these requirements and are considered "nondeemed." If accredited by a Medicare-approved accreditor, the facility receives "deemed" status. Nondeemed facilities do not receive the same level of the CMS oversight as deemed facilities. The CMS has attempted to strengthen this monitoring by creating requirements that each state must survey at least 25% of nondeemed ASCs each year and that no more than 6 years elapse between surveys for each of ASC. A 2017 Office of Inspector General (OIG) report analyzing Medicare's oversight of ASCs revealed that 11 states did not meet either requirement [27]. States cited 77% of nondeemed ASCs with at least one deficiency, with infection control deficiencies the most frequent, making up one-fifth. The report concluded that the CMS needs further strengthening of its oversight and a focus on ASCs' recurring challenges in meeting health and safety requirements, especially for infection control [27]. Only a minority, 20–25% of ASCs, are accredited by one of the official accreditation organizations deemed by the CMS (see Table 6.2) [16].

Table 6.2 Accrediting organization deemed by the CMS

Accrediting organization deemed by the CMS	The Joint Commission (TJC)
	Healthcare Facilities Accreditation Program (HFAP)
	Accreditation Association for Ambulatory Health Care (AAAHC)
	American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF)
	American Osteopathic Association (AOA)

Several high-profile cases of HAIs in ASCs revealing significant lapses in infection control practices have also created a sense of urgency for increased oversight and monitoring. One such example involved approximately 40,000 patients in Nevada that were potentially exposed to hepatitis C, HIV, and other blood-borne pathogens over a 4-year period [28]. Cases such as this prompted an investigation of ASCs by the Government Accountability Organization (GAO) in 2009. The report emphasized the unacceptable absence of health outcomes and process measure data available for ASCs. They concluded:

> The increasing volume of procedures and evidence of infection control lapses in ASCs create a compelling need for current and nationally representative data on HAIs in ASCs in order to reduce their risk. Because HAIs generally only occur after a patient has left an ASC, data on the occurrence of these infections—outcome data—are difficult to collect. But data on the implementation of CDC-recommended infection control practices—process data—in ASCs can be collected more easily and can provide critical information on why HAIs are occurring and what can be done to help prevent them. [29]

The GAO went on to recommend that the Acting Secretary of DHHS develop and implement a written plan to use a data collection instrument and methodology to conduct recurring periodic surveys of randomly selected ASCs in order to collect data on infection control practices and target ICP strategies [29]. In 2008 the U.S. Department of Health and Human Services (DHHS) established the Federal Steering Committee for the Prevention of Health Care-Associated Infections and in 2009 developed the *National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination*. As part of Phase Two of the action plan, ASCs' end-stage renal disease (ESRD) facilities were selected as focus areas (Fig. 6.2). Among numerous recommendations, the DHHS recommended enhanced oversight, monitoring, collaboration, and the need to develop meaningful HAI surveillance and reporting procedures in ASCs and other ambulatory settings [30]. The Road Map, coordinated by the Office of Disease Prevention and Health Promotion (ODPHP), has been instrumental in coordinating the work of various health-

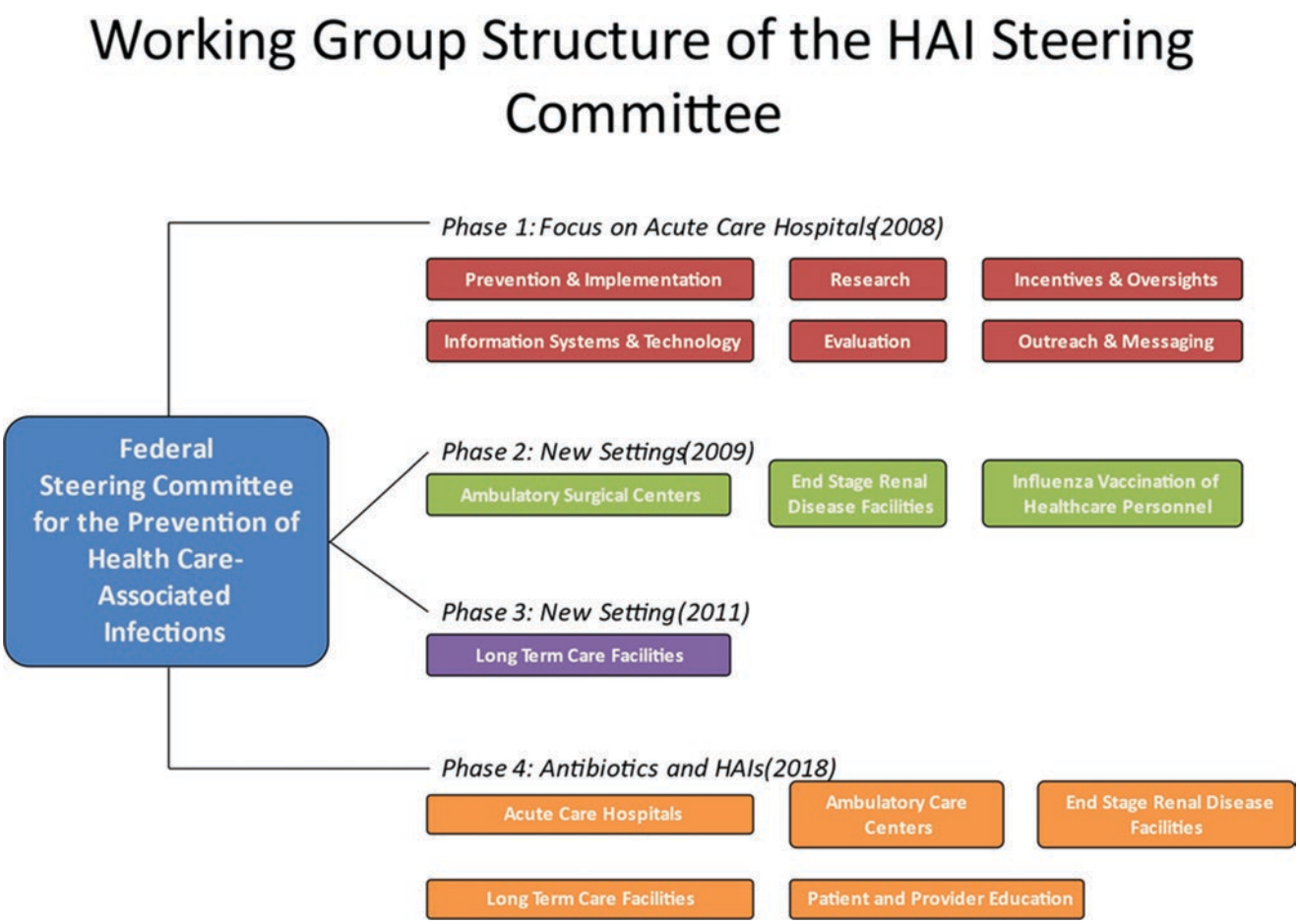

Fig. 6.2 Working Group Structure of the HAI Steering Committee. (Source: Adapted from the Office of Disease Prevention and Health Promotion (ODPHP) [30])

care agencies and transforming the regulatory structure underpinning HAIs and antimicrobial stewardship across the healthcare continuum.

Surveillance

Surveillance is defined as the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health [19]. Conducting outcomes-based infection surveillance in the outpatient setting is inherently challenging. In contrast to the hospital setting where a patient is under close observation, outpatient encounters are sporadic and short lived. Patients that develop outpatient HAIs do not become symptomatic until returning home and subsequently might not report to the same facility where the HAI developed. Therefore, surveillance in the outpatient setting typically requires retrospective reviews of medical records or prospective audits. Cross talk and data extraction between electronic medical record (EMR) systems is lacking or nonexistent, further complicating the process of data procurement. Novel methods to track infections across the continuum of care are needed to capture the true rates of outpatient HAIs. Research in this area is underway, for example, researchers at Duke developed an automated system for prospective surveillance for post-ERCP bacteremia in order to establish an institutional baseline rate of post-ERCP bloodstream infections [31]. Further developments in technology are needed so that outpatient HAIs can be promptly identified.

Generally speaking, surveillance data in outpatient care facilities are largely absent [29]. For example, a mere 20 ASCs reported data to the National Healthcare Safety Network (NHSN) between 2006 and 2008, compared with data reported by 1545 hospitals [32]. The majority of surveillance data related to HAIs comes from hospitals, which, in contrast to outpatient settings, have established infrastructure with dedicated infection control personnel to carry out HAI surveillance. Furthermore, regulations requiring surveillance and reporting of HAIs in the outpatient setting are far less robust than their inpatient counterparts [16]. However,

due to several unprecedented outbreaks in the outpatient setting, public awareness has been significantly heightened in the past decade and more oversight is forthcoming.

Currently, the CDC recommends that at a minimum outpatient care settings adhere to local, state, and federal regulations regarding reportable diseases, as well as performing regular audits and competency evaluations of HCP adherence to infection prevention practices (see Table 6.3 below) [19]. As opposed to outcomes data (e.g., rates of CLABSI at hemodialysis centers), performing surveillance on process measures such as HCP compliance with existing infection prevention guidelines may also serve to enhance surveillance in the outpatient setting.

More stringent federal regulations regarding surveillance in the outpatient setting are forthcoming as outlined in the DHHS National *Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination* [16]. Based on previous trends, without government-mandated surveillance and reporting, the likelihood of outpatient care settings investing in infection control programs to carry out high-quality surveillance is low (see section below for further discussion of this topic) (see Table 6.3).

Standard Precautions

Standard precautions include a bundle of practices that apply to all patients and HCWs across the entire spectrum of healthcare (see Table 6.4). As outlined in the HICPAC 2007 Guideline for Isolation Precautions, the "implementation of Standard Precautions constitutes the primary strategy for the prevention of healthcare-associated transmission of infectious agents among patients and healthcare personnel" [33]. These practices should be employed wherever healthcare is delivered, including outpatient settings, regardless of whether the patient is suspected of having an infection. True rates of compliance with standard precautions across the spectrum of outpatient settings are currently unknown but are likely below expectations owing to the relative absence of surveillance when compared to the inpatient setting.

The individual components of standard precautions as they pertain to outpatient settings will be expanded upon below. We refer the reader to the CDC website and current guidelines for a detailed review of standard precautions in the outpatient setting [33, 34].

Table 6.3 Recommendations

Key recommendations for HAI surveillance and reporting in outpatient settings	Educate patients who have undergone procedures at the facility regarding signs and symptoms of infection that may be associated with the procedure and instruct them to notify the facility if such signs and symptoms occur.
	Adhere to local, state, and federal requirements regarding HAI surveillance, reportable diseases, and outbreak reporting.
	Perform regular audits of HCP adherence to infection prevention practices.

Adapted from: Centers for Disease Control and Prevention [19]

Table 6.4 Essential standard precautions

Standard precautions	Hand hygiene
	Use of personal protective equipment (e.g., gloves, gowns, masks)
	Safe injection practices
	Safe handling of potentially contaminated equipment or surfaces in the patient environment
	Respiratory hygiene/cough etiquette

Adapted from: Centers for Disease Control and Prevention [19]

Hand Hygiene

In terms of overall impact on infection rates, it is difficult to overstate the vital importance of proper hand hygiene. The hands of HCWs are the most common vectors by which microorganisms are transmitted to patients [35]. Beginning with the establishment of the germ theory by Ignaz Semmelweis in the 1840s, the association between hand hygiene and reduction of HAIs has been demonstrated in various settings, and hand hygiene is now widely regarded as one of the most important of all infection control practices [36, 37]. It serves as the backbone of any effective infection control program. Despite a strong consensus of its effectiveness among infection control professionals and the widespread dissemination of convenient access to alcohol-based hand sanitizers, hand hygiene compliance rates remain far below expectations, perhaps as low as 40% in inpatient settings [36, 38]. The reasons for this are many, including an overestimation of self-compliance, inconvenient location of sinks, understaffing or busy work setting, skin irritation, and poor attention to guidelines [36, 38]. To date, there is no comprehensive analysis of surveillance data for hand hygiene compliance across the wide spectrum of outpatient care settings; however, individual settings have been studied and rates of compliance seem to be below expectations (as low as 18% among HCPs) [39, 40].

Why Is Hand Hygiene Compliance So Poor in the Outpatient Setting?

In contrast to inpatient settings, the physical layout of outpatient settings is more variable. Often times, there is no alcohol-based hand rub (ABHR) outside of examination rooms. Sinks and/or ABHR is often inside the examination

room. The examination room door is closed when an HCW is seeing a patient, essentially eliminating the ability to covertly observe the process [41]. Furthermore, hand hygiene compliance monitoring is performed less often than in the inpatient setting due to the absence of infection control staff, dedicated resources, and regulations mandating that monitoring be performed. More research is needed to further elucidate these factors and likely many more effect compliance rates.

Recommendations for Hand Hygiene in the Outpatient Setting

In the outpatient setting, the CDC and WHO recommend ABHR due to its broad antimicrobial activity, superior compliance rates, expediency, and convenience when compared to soap and water [19, 42]. When hands are visibly soiled or after caring for patients with infectious diarrhea (e.g., *Clostridioides difficile*, norovirus, etc.), soap and water is preferred [19, 43] (see Table 6.5).

For comprehensive guidance on how and when hand hygiene should be performed, we refer you to the *Guideline for Hand Hygiene in Health-Care Settings Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force* [43].

Transmission-Based Precautions

Transmission-based precautions are intended to serve as an adjunct to standard precautions in patients with known or suspected colonization or infection of highly transmissible or epidemiologically important pathogens. Transmission-based precautions encompass three categories: contact precautions, droplet precautions, and airborne precautions.

Table 6.5 Key recommendations for hand hygiene in ambulatory care settings

Key situations where hand hygiene should be performed	Before touching a patient, even if gloves will be worn
	Before exiting the patient's care area after touching the patient or the patient's immediate environment
	After contact with blood, body fluids or excretions, or wound dressings
	Prior to performing an aseptic task (e.g., placing an IV, preparing an injection)
	If hands will be moving from a contaminated body site to a clean body site during patient care
	After glove removal

Adapted from: Centers for Disease Control and Prevention [19]

Transmission of MDROs such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenemase-producing *Enterobacteriaceae* (CRE), and *Clostridioides difficile* is not confined to the inpatient setting. These organisms have the potential to be acquired in the outpatient setting as well. With the rise of community-associated MRSA and *C. difficile*, some experts have hypothesized that outpatient care settings may be serving as silent reservoirs for these organisms. Indeed, environmental contamination and patient colonization with vancomycin-resistant *Enterococcus* (VRE) and MRSA have been reported in the outpatient setting [44, 45]. Although research is limited, the risk of infection transmission in the outpatient setting is thought to be lower than in the hospital owing to shorter contact time, fewer encounters, and exposure to lower inoculums of bacteria [46]. Consequently, the traditional approach to isolation in the outpatient setting has not been as aggressive as its inpatient counterpart. However, as more and more high-risk populations such as bone marrow and solid organ transplant recipients and patients with febrile neutropenia are managed in the outpatient setting, traditional paradigms will need to be reevaluated. The risk of transmission of infectious pathogens will vary between outpatient settings depending on the patient population, facility design, and services provided.

In general, the CDC recommends that *each outpatient facility should evaluate the services they provide to determine specific needs and to assure that sufficient and appropriate personal protective equipment (PPE) is available for adherence to standard precautions* [19]. All HCWs at outpatient facilities should be educated regarding proper use of and selection of PPE. Comprehensive guidance on the selection and proper use of PPE is available in the CDC's *HICPAC 2007 Guideline for Isolation Precautions* [33].

The CDC has issued specific guidance for special settings. In 2011, they released recommendations pertaining to infection control and prevention in outpatient oncology settings [34]. Identifying potentially infected patients prior to arrival is recommended (see Table 6.6).

Table 6.6 Identifying potentially infectious patients in the outpatient setting

Identifying potentially infectious patients in the outpatient setting	Patients with symptoms of active infection (e.g., diarrhea, rash, respiratory symptoms, draining wounds, skin lesions) come at a time when the facility is less crowded
	Alert registration staff to place potentially infected patients in a private exam room upon arrival and if available and follow the procedures pertinent to the route of transmission
	If the purpose of the visit is nonurgent, patients are encouraged to reschedule the appointment until symptoms have resolved

Adapted from the Centers for Disease Control and Prevention [34]

Table 6.7 Contact precautions

Apply to patients with the following conditions:	Presence of stool incontinence (may include patients with norovirus, rotavirus, *C. diff*), draining wounds, uncontrolled secretions, pressure ulcers, presence of ostomy tubes and/or bags draining body fluids.
	Presence of generalized rash or exanthems.
Isolation	Stool incontinence, draining wounds and/or skin lesions that cannot be covered, or uncontrolled secretions.
Hand hygiene	Perform hand hygiene before touching patient and prior to wearing gloves.
	Perform hand hygiene after removal of PPE; note: use soap and water when hands are visibly soiled (e.g., blood, body fluids) or after caring for patients with known or suspected infectious diarrhea (e.g., *Clostridium difficile*, norovirus).
PPE use	Wear gloves when touching the patient and the patient's immediate environment or belongings.
	Wear a gown if substantial contact with the patient or their environment is anticipated.
Environmental cleaning	Clean/disinfect the exam room.
Bathroom use	Instruct patients with known or suspected infectious diarrhea to use a separate bathroom, if available; clean/disinfect the bathroom before it can be used again (refer to section "Environmental Cleaning" for bathroom cleaning/disinfection).

Adapted from the Centers for Disease Control and Prevention [34]

The CDC has also provided specific recommendations pertaining to contact precautions, droplet precautions, and airborne precautions in the outpatient oncology setting (see Table 6.7). These recommendations may serve as a general guide for transmission-based precautions in the outpatient setting, though more recommendations tailored to the myriad of unique outpatient settings are needed.

Respiratory Hygiene and Cough Etiquette

Patients awaiting care in the outpatient setting often sit for long periods in common areas such as waiting rooms, which complicates the application of transmission-based precautions. Often, patients with transmissible respiratory illnesses are awaiting a diagnosis and are not recognized immediately. This is especially risky for immunocompromised patients such as bone marrow or solid organ transplant recipients that may be sitting next to a patient with influenza, respiratory syncytial virus (RSV), measles, or herpes zoster. Transmission of *Mycobacterium tuberculosis* and measles has been reported in the outpatient setting [47, 48]. To minimize transmission of airborne and droplet infectious agents, patients must be screened for these infections at the outset of the patient encounter [33]. This is especially important for patients with clinical signs including cough, rhinorrhea, and other respiratory secretions. The CDC's *2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings* outlines the most important elements of cough etiquette, which should be implemented in outpatient settings [33] (see Table 6.8).

Table 6.8 Respiratory etiquette

Key components of respiratory etiquette	Education of healthcare facility staff, patients, and visitors
	Posted signs, in language(s) appropriate to the population served, with instructions to patients and accompanying family members or friends
	Source control measures (e.g., covering the mouth/nose with a tissue when coughing and prompt disposal of used tissues, using surgical masks on the coughing person when tolerated and appropriate)
	Hand hygiene after contact with respiratory secretions
	Spatial separation, ideally >3 ft, of persons with respiratory infections in common waiting areas when possible

Adapted from the Siegel et al. [33]

Patients with potentially transmissible airborne or droplet infectious diseases should be quickly separated, and appropriate transmission-based infection control measure should be implemented as outlined in the 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings [33] (see Tables 6.9 and 6.10).

Of note, implementation of contact precautions in the United States is undergoing a period of significant paradigm shift. Recently, the utility of isolating carriers of MRSA and resistant *Enterococcus* in the hospital setting has been called into question [49]. Many hospitals have changed long-standing infection prevention practices accordingly. As new evidence and protocols are deployed for inpatient infection control, these data and practices should be extrapolated to the outpatient setting, as well, when appropriate. In the context of the COVID-19 pandemic and PPE shortages, the CDC developed a tiered strategy (based on PPE capacity and the transmission risk of the activity) to optimize the supply of PPE. Contingency capacity strategies advise, "Facilities can consider suspending use of gowns for endemic multidrug resistant organisms (e.g., methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), extended spectrum B-lactamases (ESBL)-producing organisms)" [50]. Robust data on the impact of these recommendations are lacking at this time.

Table 6.9 Droplet precautions

Apply to patients with known or suspected:	Respiratory viruses (e.g., influenza, parainfluenza virus, adenovirus, respiratory syncytial virus, human metapneumovirus)
	For first 24 h of antibiotic therapy: *Neisseria meningitidis*, group A streptococcus
	Bordetella pertussis
Isolation	Place the patient in an exam room with a closed door as soon as possible.
	Prioritize patients who have excessive cough and sputum production.
	If an exam room is not available, the patient is provided a face mask and placed in a separate area as far from other patients as possible while awaiting care.
PPE	Wear a face mask, such as a procedure or surgical mask, for close contact with the patient; the face mask should be donned upon entering the exam room.
	If substantial spraying of respiratory fluids is anticipated, gloves and gown as well as goggles (or face shield in place of goggles) should be worn.
	Instruct patient to wear a face mask when exiting the exam room, avoid coming into close contact with other patients, and practice respiratory hygiene and cough etiquette.
Hand hygiene	Perform hand hygiene before and after touching the patient and after contact with respiratory secretions and contaminated objects/materials; note: use soap and water when hands are visibly soiled (e.g., blood, body fluids).
Environmental cleaning	Clean and disinfect the exam room.

Adapted from the Centers for Disease Control and Prevention [34]

Table 6.10 Airborne precautions

Apply to patient with known or suspected:	Active tuberculosis
	Measles
	Chickenpox (until lesions crusted over)
	Localized (in immunocompromised patient) or disseminated herpes (until lesions are crusted over)
Isolation	Have patient enter through a separate entrance to the facility (e.g., dedicated isolation entrance), if available, to avoid the reception and registration area.
	Place the patient immediately in an airborne infection isolation room (AIIR).
	If an AIIR is not available:
	Provide a face mask (e.g., procedure or surgical mask) to the patient and place the patient immediately in an exam room with a closed door.
	Instruct the patient to keep the face mask on while in the exam room, if possible, and to change the mask if it becomes wet.
	Initiate protocol to transfer patient to a healthcare facility that has the recommended infection control capacity to properly manage the patient.
PPE	Wear a fit-tested N95 or higher-level disposable respirator, if available, when caring for the patient; the respirator should be donned prior to room entry and removed after exiting room.
	If substantial spraying of respiratory fluids is anticipated, gloves and gown as well as goggles or face shield should be worn.
Hand hygiene	Perform hand hygiene before and after touching the patient and after contact with respiratory secretions and/or body fluids and contaminated objects/materials; note: use soap and water when hands are visibly soiled (e.g., blood, body fluids).
Patient instructions	Instruct patient to wear a face mask when exiting the exam room, avoid coming into close contact with other patients, and practice respiratory hygiene and cough etiquette.
Environmental cleaning	Once the patient leaves, the exam room should remain vacant for generally 1 h before anyone enters; however, adequate wait time may vary depending on the ventilation rate of the room and should be determined accordingly.
	If staff must enter the room during the wait time, they are required to use respiratory protection.

Adapted from the Centers for Disease Control and Prevention [34]

Injection Practices

Safe injection practices are part of standard precautions. The CDC defines injection safety as "practices intended to prevent transmission of infectious diseases between one patient and another, or between a patient and healthcare provider during preparation and administration of parenteral medications" [19]. Injections are invasive procedures, and, as with any invasive procedure, they pose a risk of infection to the patient and the HCW. Consequently, the Occupational Safety and Health Administration (OSHA) has developed the "Bloodborne Pathogens Standard" which can be found in the Code of Federal Regulations. The standard OSHA has set forth outlines what employers must do to protect workers who are occupationally exposed to blood or other potentially infectious materials (OPIM), as defined in the standard. However, despite having clear guidelines to maximize injection safety, major safety breeches continue to plague the outpatient care setting. There have been many significant outbreaks linked to ambulatory care procedures reported in the last 20 years. Outbreaks have been tied to common source exposures such as single- and multidose medication vials, intravenous solutions, vaccine administration, insulin needles, and, in 2012–2013, a multistate fungal meningitis outbreak linked to glucocorticoid injections originating from compounding pharmacies [18, 51–54].

Much progress is needed in ensuring safe injections practices in the United States. Traditionally, problems with injection practices were thought to be a problem of low- and middle-income countries. In the year 2000, the estimated global incidence of infections related to unsafe injection practices included a total of >20 million hepatitis B virus infections, >two million hepatitis C virus infection, and >250,000 HIV infections [55]. However, the United States is not exempted from this alarming trend. A comprehensive review of patient notification of blood-borne pathogen exposure occurring between 2001 and 2011 identified 35 patient notification events related to unsafe injection practices in at least 17 states, resulting in an estimated total of 130,198 patients notified. Eighty-three percent involved outpatient care settings and 74% occurred since 2007. The most common breach identified (≥16 events; 44%) was syringe reuse to access shared medications (e.g., single-dose or multidose vials). Most notification events were linked to viral hepatitis transmission (22 events; 63%), and 13 (37%) notification events were prompted by the discovery of unsafe injection practices [54]. Another review evaluating outpatient viral hepatitis outbreaks in the United States between 1998 and 2008 identified a total of 33 outbreaks that occurred in non-hospital settings (outpatient clinics [$N = 12$], dialysis centers [$N = 6$], and long-term care facilities [$N = 15$]), resulting in 448 cases of HBV or HCV infection [56].

Breaches in safe injection practices have led to catastrophic consequences. In 2008, an endoscopy clinic in Las Vegas was linked to the largest hepatitis C outbreak in US history. Investigation of the outbreak uncovered that transmission of hepatitis C stemmed from the routine reuse of single-dose vials of propofol from one patient to another. Ultimately, 114 cases of hepatitis C acquisition were linked to the clinic and over 40,000 patients required notification of potential exposure to blood-borne diseases [28]. In 2002, unsafe practices at an outpatient pain clinic in Oklahoma led to 71 patients acquiring hepatitis C and 31 patients acquiring hepatitis B. A total of 908 people required notification of potential exposure [57]. Investigation of the outbreak determined that the Certified Registered Nurse Anesthetist (CRNA) responsibly routinely prepared three needles and syringes per day (one for each medication) and reused them on multiple patients during each clinic session.

Misconceptions about injection safety are common. A survey among nurse anesthetists in the United States revealed that nearly 4% have administered medications from the same syringe to multiple patients, 18% had reused a needle on the same patient, and 82% had refilled used syringes [58]. Furthermore, the study found that 22% had reused a syringe or needle to withdraw medication from a multidose vial, and nearly 50% had reentered a single-use medication vial to prepare doses for multiple patients [58]. After analyzing four major outbreaks of hepatitis B and C in four unique outpatient settings (a pain clinic, private medical practice, endoscopy clinic, and hematology-oncology clinic), HICPAC concluded that the primary breaches in infection control practices were the following:

1. Reinsertion of used needles into a multiple-dose vial or solution container (e.g., saline bag)
2. Use of a single needle/syringe to administer intravenous medication to multiple patients [33]

Other common lapses include the preparation of medications in close proximity to contaminated supplies or equipment and the failure to wear a face mask (e.g., surgical mask) when placing a catheter or injecting material into the epidural or subdural space [19]. There are many more examples of injection safety breeches, though the reported events are likely only the tip of the iceberg. The true prevalence of unsafe injection practices is unknown.

Injection safety is a complex public health problem requiring coordination on multiple levels within healthcare organizations as well as enforcement and oversight on the state and federal level. Safe injection practices are a key element of standard precautions. Definitive guidance on safe injection practices can be accessed via the 2007 Guideline for Isolation Precautions [19]. The numerous outbreaks stemming from breaches in injection safety should serve as a beacon to encourage heightened infection control attention in this area. Recently, the CDC has partnered with the Safe Injection Practices Coalition (SIPC) to develop a public health campaign called the "One & Only Campaign" to raise awareness among patients and healthcare providers about safe injection practices and to promote said practices. The CDC website on injection safety also provides numerous resources including an injection safety toolkit for infection control programs (see Table 6.11) [19, 59].

Environmental Cleaning

All outpatient healthcare facilities should develop protocols and procedures for the systematic cleaning and disinfection of environmental surfaces. High-contact patient care surfaces should be prioritized, including bedrails, doorknobs, bedside tables, commodes, sinks, surfaces, and any other surfaces in close proximity to the patient [33]. Facilities should be utilizing EPA-registered disinfectants and cleaning supplies best suited for their particular needs. Strict adherence to the manufacturer's recommendations regarding the usage of cleaning products should be followed. Particular infectious agents such as *C. difficile*, norovirus, rotavirus, and prions may be resistant to disinfectants and require spe-

Table 6.11 Safe injection practices

Key recommendations for safe injection practices in outpatient settings	Use aseptic technique when preparing and administering medications.
	Cleanse the access diaphragms of medication vials with alcohol before inserting a device into the vial.
	Never administer medications from the same syringe to multiple patients, even if the needle is changed or the injection is administered through an intervening length of intravenous tubing.
	Do not reuse a syringe to enter a medication vial or solution.
	Do not administer medications from single-dose or single-use vials, ampoules, or bags or bottles of intravenous solution to more than one patient.
	Do not use fluid infusion or administration sets (e.g., intravenous tubing) for more than one patient.
	Dedicate multidose vials to a single patient whenever possible. If multidose vials will be used for more than one patient, they should be restricted to a centralized medication area and should not enter the immediate patient treatment area (e.g., operating room, patient room/cubicle).
	Dispose of used sharps at the point of use in a sharps container that is closable, puncture resistant, and leak-proof.
	Wear a face mask (e.g., surgical mask) when placing a catheter or injecting material into the epidural or subdural space (e.g., during myelogram, epidural, or spinal anesthesia).

Adapted from: Centers for Disease Control and Prevention [19]

Table 6.12 Cleaning and disinfection of environmental surfaces in outpatient settings

Establish policies and procedures for routine cleaning and disinfection of environmental surfaces in the facility.
Policies and procedures should also address prompt and appropriate cleaning and decontamination of spills of blood or other potentially infectious materials.
Select EPA-registered disinfectants or detergents/disinfectants with label claims for use in healthcare.
Follow manufacturer's recommendations for use of cleaners and EPA-registered disinfectants (e.g., amount, dilution, contact time, safe use, and disposal).

Adapted from: Centers for Disease Control and Prevention [19]

cialized disinfectants. For detailed recommendations regarding the disinfection of surfaces, outpatient infection control programs should adhere to the Guidelines for Environmental Infection Control in Healthcare Facilities [60]. Adherence to environmental cleaning procedures and protocols should be monitored and reinforced (see Table 6.12).

Medical Devices

Manufacturers classify medical devices as either single use or multiuse. Single-use devices (SUDs) should never be reused, with the exception of those entities that have received special authorization from the Food and Drug Administration (FDA) [61]. In such cases, reprocessing of SUDs can only be performed by third-party or hospital reprocessors that have explicit clearance from the FDA and are registered with FDA as reprocessing facilities [62]. Transmission of infection can occur through medical devices that are inadequately cleaned between patients before disinfection or sterilization (e.g., endoscopes, bronchoscopes, surgical instruments) or that have manufacturing defects that interfere with the effectiveness of reprocessing [33]. In the ambulatory care setting, the field of endoscopy makes up a significant proportion of the medical devices pertinent to this discussion. Over the past decade, the rate of gastroenterology procedures being performed varies on the specific procedure. For example, numbers of colonoscopies and upper endoscopies have been slightly decreasing since 2002. However, the number of upper endoscopic ultrasounds performed since 2002 have increased [63]. Regardless, there is still a high volume of procedures being performed with an estimated 17.7 million endoscopic procedures performed annually. In 2015, there were estimated 11 million lower endoscopies, 6.1 million upper endoscopies, and almost 170,000 biliary endoscopies performed [63].

The estimated incidence of infections transmitted by GI endoscopic procedures is 1 in 1.8 million procedures [64]. Bronchoscopy also makes up a significant number of ambulatory procedures, estimated at nearly 500,000 per year [65]. The field of endoscopy continues to rapidly expand into urology, ENT, cardiology, and more. The true rate of infection associated with these procedures is unknown given the absence of robust surveillance systems in the outpatient setting. Consequently, infections are typically identified in outbreak scenarios. Most pathogen transmission occurs due to a failure to adhere to established cleaning, disinfection, and sterilization guidelines. A study evaluating the infection control procedures across a random sample of 68 ambulatory care centers in three states identified reprocessing of reusable medical devices as one of the most common lapses in infection control, with nearly 30% of facilities failing to adhere to recommended practices regarding reprocessing of equipment [66]. Inappropriate reprocessing and reuse of single-use devices (e.g., bite blocks and syringes used to flush the endoscope during endoscopy procedures) was also discovered in 6% of all ambulatory facilities in the study [66]. Reprocessing of medical devices is highly complex. For example, contamination of bronchoscopes has been linked to a myriad of causes including ineffective cleaning, contamination of instilled solutions, disinfectants (inadequate activ-

ity, incorrect disinfectant, or contaminated disinfectant), recontamination after disinfection (e.g., rinsing with tap water, contaminated tap water filters), contaminated reprocessing equipment, and many other sources [67]. Biofilm production further inhibits the disinfection process [68]. Finally, the burden of contaminating infectious organisms can be massive. After a routine bronchoscopy, the instrument is contaminated with about 6.4×10^4 cfu/ml of bacteria [69].

When lapses in reprocessing of SUD or reusable medical devices occur, the consequences are not insignificant. In a review of infectious complications of endoscopy between 1966 and 2002, the authors identified 281 cases of transmission due to GI procedures and 96 cases due to bronchoscopy. Various pathogens were implicated in GI endoscopy including *Pseudomonas aeruginosa, Salmonella* spp., *Helicobacter pylori, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Clostridium difficile, Strongyloides stercoralis*, HBV, and HCV [70]. In a review of flexible bronchoscopy-associated infections occurring between 1977 and 2003, only 18 publications reporting true infection were identified with the most common pathogens being *M. tuberculosis*, *Serratia* spp., atypical mycobacterium, and *P. aeruginosa* [71]. Creutzfeldt-Jakob disease (CJD) and HIV have not been reported to be transmitted via endoscopy [70]. All cases were linked to breaches in reprocessing recommendations.

However, it must be noted that outbreaks have been reported even when all reprocessing recommendations have been followed. After an outbreak of New Delhi metallo-β-lactamase-producing carbapenem-resistant *Escherichia coli* (CRE) associated with exposure to duodenoscopes was investigated, no breaches in the six-step reprocessing procedure were identified [72]. To control the outbreak, the facility changed its reprocessing procedure from automated high-level disinfection with ortho-phthalaldehyde to gas sterilization with ethylene oxide. Subsequently, there were no cases of CRE identified. These findings suggest that sterilization, rather than high-level disinfection, was needed to fully mitigate the risk of transmission. The authors suggested that conducting testing for residual contamination after reprocessing might be warranted. In response to the outbreak, the US Food and Drug Administration, Centers for Disease Control and Prevention, and American Society of Microbiology collaborated in 2018 to create voluntary standardized protocol for duodenoscope surveillance culturing following reprocessing [73]. Preliminary results from a post-market surveillance study in 2019 indicated a contamination rate of 3.6% for low- to moderate-concern organisms with >100 CFU and a contamination rate of 5.4% for high-concern organisms such as *Escherichia coli* and *Pseudomonas aeruginosa* even after appropriate reprocessing [74]. Since the creation of these new recommendations, reports of outbreaks associated with duodenoscope use have decreased. However, the FDA continues to encourage manufacturers to further innovate device designs to facilitate more effective reprocessing and evaluate current standards of reprocessing in healthcare facilities [75].

The reprocessing of reusable medical devices is complicated and requires highly trained personnel. Flexible endoscopes used in procedures such as duodenoscopy, bronchoscopy, and colonoscopy are challenging to clean and disinfect owing to the long, thin internal channels and their inability to be steam sterilized [76]. Proper reprocessing requires an understanding of the internal structure of the device and attention to detail. Because endoscopes are expensive, they are often reused at a high frequency that increases the risk of breaches in cleaning and disinfection protocol. Furthermore, each model must be reprocessed by the unique specifications outlined by the manufacturer, and this is incompatible with a "one-size-fits-all" approach. Traditionally, the Spaulding Classification has defined the reprocessing of medical equipment (see Table 6.13) [78]. This approach is based on categorizing medical instruments as critical, semicritical, and noncritical according to the degree of risk for infection involved in their use. Each category has a different degree of disinfection required. The goal of the highest level of disinfection is total sterility of the instrument. High-level disinfection is traditionally defined as the complete elimination of all microorganisms in or on an instrument, except for small numbers of bacterial spores [77].

More recently, the Spaulding Classification has come under scrutiny due to oversimplification of certain complexities among medical devices and fastidious organisms. For example, the method does not account for challenges of reprocessing the complicated mechanical hardware within new endoscopes or inactivating certain types of infectious agents such as Creutzfeldt-Jakob disease (CJD). There is no universal agreement among professional organizations as to the optimal contact time for high-level disinfection [77].

Healthcare personnel involved in reprocessing of reusable medical devices should be properly trained, and their competency in carrying out their duties should be evaluated regularly [19]. This is especially important when new devices enter the medical environment, as well as new methods of reprocessing. Individual healthcare organizations should create policies and procedures that guide the proper handling and reprocessing of contaminated reusable medical devices pertinent to their facility, as outlined by the manufacturer's instructions. Infection control personnel should also be versed in the most up-to-date recommendations and guidelines regarding the cleaning and disinfection process of medical devices (see Table 6.14) [19, 33, 61, 68, 77, 79].

Table 6.13 The Spaulding Classification

Category	Examples of instruments	Level of disinfection
Critical	Surgical instruments	Highest level of disinfection, must be sterile prior to use
	Cardiac and urinary catheters	
	Implants	
	Probes used in sterile body cavities	
	Objects that enter sterile tissue or the vascular system	
Semicritical	Endoscopes used for upper endoscopy and colonoscopy	At minimum, high-level disinfection prior to use
	Respiratory therapy and anesthesia equipment	
	Laryngoscope blades	
	Esophageal manometry probes	
	Cystoscopes	
	Anorectal manometry catheters	
	Diaphragm fitting rings	
	Contact mucous membranes or non-intact skin	
Noncritical	Blood pressure cuffs	Low- or intermediate-level disinfection depending on the nature of contamination
	Bedpans	
	Crutches	
	Computers	
	May come in contact with intact skin but not mucous membranes	
Environmental surfaces	Floors, walls (surfaces typically not in direct contact with patients during delivery of care)	Simple cleaning or low-level disinfection

Adapted from the Rutala and Weber [77]

Table 6.14 Cleaning and disinfection or sterilization of medical devices in outpatient settings

Key recommendations	Facilities should ensure that reusable medical devices (e.g., blood glucose meters and other point-of-care devices, surgical instruments, endoscopes) are cleaned and reprocessed appropriately prior to use on another patient.
	Reusable medical devices should be cleaned and reprocessed (disinfection or sterilization) and maintained according to the manufacturer's instructions. If the manufacturer does not provide such instructions, the device may not be suitable for multi-patient use.
	Assign responsibilities for reprocessing of medical devices to HCP with appropriate training:
	Maintain copies of the manufacturer's instructions for reprocessing of devices in use at the facility; post instructions at locations where reprocessing is performed.
	Hands-on training on proper selection and use of PPE and recommended steps for reprocessing assigned devices should be provided upon hire (prior to being allowed to reprocess devices), annually, and when new devices are introduced or policies/procedures change.
	HCP should be required to demonstrate competency with reprocessing procedures (i.e., correct technique is observed by trainer) following each training.
	Assure HCP has access to and wears appropriate PPE when handling and reprocessing contaminated medical devices.

Adapted from: Centers for Disease Control and Prevention [19]

Medical Waste

Some medical waste poses a public health risk and requires special processing with autoclaves or incinerators. Many ambulatory care facilities may not have an expert in infectious waste management at their facility. Ambulatory care facilities must comply with medical waste processing requirements pertaining to their particular city, county, and state, as well as federal regulations. A full discussion of this topic is beyond the scope of this chapter, but has been expounded upon in other texts [80]. A review by Herwaldt et al. [76] advised that outpatient facilities must:

- Define which items are noninfectious waste and which are infectious
- Develop protocols and procedures for separating infectious waste from noninfectious waste, labeling the infectious waste properly and transporting, storing, and disposing of infectious wastes safely
- Develop contingency plans for managing waste spills and inadvertent exposures of patients, visitors, or healthcare workers
- Develop programs to teach staff to handle infectious waste
- Identify ways to minimize infectious waste, e.g.:
  - Stop discarding noninfectious waste, such as wrappers and newspapers in infectious waste
  - Substitute products that do not require special modes of disposal (e.g., needleless intravenous systems) for those that must be discarded in the infectious waste (e.g., needles)
  - Substitute reusable items for the single-use items

Clostridium difficile in the Outpatient Setting

Clostridium difficile infection (CDI) is the major cause of infectious diarrhea with over 500,000 annual cases, 223,000 hospitalizations, with acute inpatient care costs exceeding over $4.8 billion dollars [81–83]. The consequence of this infection is deadly with estimated 12,800 deaths in the United States in 2017 [82]. In addition to the threat of *C. difficile* infection in inpatients, community-associated CDI (CA-CDI) is on the rise [84, 85]. *C. difficile* infection is defined as community acquired if symptom onset occurs in the community or within 48 h of admission to a hospital, after no hospitalization in the past 12 weeks [86]. It is estimated that CA-CDI actually represents one-third of all *C. difficile* cases. Traditional risk factors such as age and prior antibiotic exposure may be absent; indeed CA-CDI may affect low-risk hosts such as healthy peripartum women; antibiotic-naïve, young adults or children; and those lacking recent healthcare exposure [84]. One recent study of 984 patients found that 35.9% did not receive preceding antibiotics, 18% had no outpatient healthcare exposure, and 40.7% had low-level outpatient healthcare exposure [87]. While the primary means of transmission has traditionally been presumed to be person to person or environment to person via the fecal-oral route, recent studies utilizing whole-genome sequencing of isolates from the community setting demonstrated that 45% of all isolates were genetically unique [88].

In addition to the overuse of antibiotics, one possible explanation for the increasing burden of CA-CDI is the rising burden of spores in the outpatient healthcare environment. Patients that are successfully treated for hospital-acquired CDI (HA-CDI) have been found to exhibit skin contamination and environmental shedding of *C. difficile* spores 1–4 weeks after therapy [89]. Furthermore, 80% of patients with HA-CDI are seen in the outpatient setting within 12 weeks of discharge [90]. Therefore, patients recovering from a recent CDI could pose a significant risk for transmission of spores during outpatient visits and the outpatient setting may be an underappreciated source of CA-CDI cases [90]. However, current guidelines do not recommend contact precautions for patients in whose diarrhea has resolved for >48 h [91].

At this time, the best infection control approach to active or suspected CDI in the outpatient setting is unknown. Some experts suggest that patients at highest risk for transmission (i.e., patients on CDI therapy for ≤2 weeks, recent treatment for CDI in the past 2–12 weeks but not on current therapy) should be managed with enhanced precautions including wearing gloves when examining patients and cleaning high-touch surfaces with sporicidal disinfectants after visits [91]. Infection prevention programs should stay up to date with the most current recommendations to prevent *C. difficile* transmission in the outpatients setting, as this topic has changed with newest guidelines from IDSA and SHEA in 2017 [91].

Epidemic Keratoconjunctivitis

Epidemic keratoconjunctivitis (EKC) is a severe, acute infection of the eye caused by multiple serotypes of adenovirus. Patients may be contagious even before symptoms arise and remain contagious for up to 2 weeks after symptoms resolve [92]. Viral particles are hardy and may remain viable on surfaces for up to 3 months [93]. For these reasons, EKC is highly contagious and is a frequent cause of epidemics worldwide [92, 94–97]. Outbreaks may last weeks to months, and transmission has occurred in both healthcare- and community-associated settings. Transmission may occur directly via contact with eye secretions or indirectly when an uninfected person is exposed to contaminated surfaces, hands, eye drops, or instruments. In the United States, outpatient ophthalmology clinics have been linked to numerous outbreak reports [98–101]. From 2008 to 2010, there were six healthcare-associated outbreaks reported to the CDC across four states, resulting in 411 cases of EKC. Transmission was linked to ophthalmologic examination [101]. Outbreaks have been linked to numerous ophthalmologic procedures such as slit-lamp examinations, contact lens placement, multiple patient visit, tonometry, contaminated solutions, and contact with HCWs that continue to work despite having active EKC [99–101].

Implementation of a formal infection control policy has been shown to reduce and control EKC outbreaks [95, 100]. To minimize the risk of EKC outbreaks, several key recommendations have been made in an article by Herwaldt et al. [76] including:

- HCP should wash hands before and after examining patients.
- HCP should wear gloves for possible contact with the conjunctiva.
- Equipment, including tonometers, should be cleaned and disinfected according to the manufacturer's recommendations and consensus guidelines.
- If a healthcare-associated outbreak is identified, all open ophthalmic solutions should be discarded, and the equipment and environment should be cleaned and disinfected thoroughly.
- During an outbreak, unit doses of ophthalmic solutions should be used.
- During an outbreak, patients with conjunctivitis should be examined in a separate room with designated equipment, supplies, and ophthalmic solutions.

- During an outbreak, elective procedures such as tonometry should be postponed.
- HCP who work in any outpatient area and who have adenovirus conjunctivitis should not work until the inflammation has resolved, which may take 14 or more days.

Ambulatory Surgery Centers (ASCs)

ASCs are defined by the CMS as distinct entities that exclusively provide surgical services to patients who do not require hospitalization or stay overnight [3]. In 2017, 7% of surgical procedures paid for by Medicare occurred in ASCs [3]. The number of facilities of this type has experienced a meteoric rise in the past few decades, increasing by 54% between 2001 and 2010 with over 5600 Medicare-certified facilities by 2017 [3, 14]. There is a tremendous volume of care being provided in ASCs. In 2007, over six million procedures were performed in ASCs and at a cost of nearly three billion dollars to Medicare [14]. Greater than three-quarters of all surgical procedures in the United States are performed in ASCs, and the spectrum of procedures is vast, including endoscopy, injections to treat chronic pain, cosmetic surgery, and dental surgery [26]. Numerous outbreaks have been linked to ASCs, indicating that infection control efforts need to be enhanced. From 2001 through 2011, there were 18 known outbreaks in ASCs in which two or more patients became infected with viral hepatitis associated with unsafe injection practices. Of these known outbreaks, approximately 100,000 patients were notified to seek testing for possible exposure to blood-borne pathogens, and a total of 358 of them were infected with viral hepatitis [102]. One such outbreak in 2007 occurring in an endoscopy clinic in Las Vegas, Nevada, resulted in the notification of >60,000 patients of possible exposure to blood-borne pathogens [28, 102]. A joint investigation by the CDC, Southern Nevada Health District (SNHD), and Nevada State Health Division (NSHD) concluded that hepatitis C transmission likely resulted from reuse of syringes and single-dose vials of propofol on multiple patients. It was also discovered that this Las Vegas clinic had not undergone a full state inspection to evaluate ASC compliance with Medicare health and safety standards in 7 years [66].

As alluded to earlier (see section on "Surveillance"), historically infection control in these facilities has not been well regulated, and little is known about actual infection rates and adherence to basic infection control practices. In order to gain insight into the infection control practices within ASCs, the CMS piloted an infection control audit tool in 68 ASCs across three states (Maryland, Oklahoma, and North Carolina), to assess facility adherence to recommended practices [66]. Nearly 68% of facilities were found to have at least one lapse in infection control. The most common lapses included mishandling of blood glucose monitoring equipment (25/54; 46.3%), using single-dose medication vials on more than one patient (18/64; 28.1%), and failing to adhere to recommended practices regarding reprocessing of equipment (19/67; 28.4%) and environmental cleaning (12/64; 19%) [66].

Table 6.15 Action plan to prevent HAIs in ASCs [66]

The CMS is now requiring all states to use the infection control audit tool and case tracer method for ASC inspections [103].
ASCs cited for deficient practices are required to correct them; ASCs that fail to correct serious deficiencies risk termination of their participation in Medicare.
The CMS and CDC have provided in-depth infection control training sessions for surveyors, making the CMS regional office physicians available to accompany surveyors on inspections and arranging consultations with experienced personnel when questions arise.
The CMS updated several ASC health and safety standards, effective May 2009.
The CMS committed to inspect one-third of all ASCs nationwide this year, including a nationally representative subsample for an updated analysis of infection control practices, as recommended by the GAO.

Adapted from Schaefer et al. [66]

In response to this disparity, the DHHS convened a task force in 2007 to develop an action plan to prevent HAIs in ASCs. The CDC has subsequently summarized the current action plan as follows (see Table 6.15):

Ambulatory surgery centers should take a proactive role in enhancing their infection control practices. In addition to tighter regulatory control and surveillance at the federal and state level, ASCs must stay up to date with the most current evidence-based guidelines to inform their local infection control programs. Self-audits should be performed on a regular basis using the infection control audit tool designed by the CMS [103].

Dialysis Centers

While there was a significant increase in the incidence of dialysis initiation, it peaked in the early 2000s and has been stable since then [104]. While incidence has stabilized, the financial burden of dialysis and associated infection continue to be costly. In 2017, Medicare spent over $36 billion for end-stage renal disease with almost 90% of patients receiving outpatient dialysis at over 6800 dialysis facilities [105, 106].This large volume of patients receiving HD in the outpatient setting poses a formidable challenge for infection control programs. The principal infection control problem in dialysis centers is the transmission of blood-borne patho-

gens. Several factors predispose HD patients to infections with blood-borne pathogens, including the following [107]:

- Frequent contact with other patients and HCWs at dialysis centers increasing the risk of person-to-person transmission of infectious agents
- Repeated contact with medical devices, equipment, and environmental surfaces in the healthcare setting
- Frequent vascular access for prolonged time periods via various modalities (arteriovenous or "AV" fistula, AV graft, catheters – tunneled and non-tunneled)
- Immunosuppression secondary to uremia, DM, and other comorbidities

Infection is particularly devastating in ESRD patients, conferring a higher risk of mortality than that of the general population. For example, a diagnosis of septicemia bears a cumulative mortality rate of 43% at 1 year, compared to 20% for the general population [108]. The type of HD access is an important factor when considering infection risk. In a systematic review in 2013, Ravani et al. concluded that central venous catheters were associated with the highest risk of fatal infection when compared to other types of vascular access (AV fistulas and grafts). AV fistulas were associated with the lowest risk of infection, followed by AV grafts [109]. In 2017, 80% of patients were using a catheter at the initiation of hemodialysis but the rate of AV fistula use at initiation increased from 12% to 17% from 2005 to 2017 [105]. Consequently, practice guidelines recommend that AV fistulas be the preferred access for HD [107, 110, 111]. With that said, placement of a viable AV fistula is difficult or impossible in some cases and not necessarily the best option for all patients [112]. The most current data suggest that AV fistulas are the most common type of vascular access overall, achieving 63% prevalence [105].

Patients receiving HD at dialysis centers are at risk for transmission of viral hepatitis and HIV. Since the implementation of the first recommendations for the control of hepatitis B in dialysis centers in 1977 and the recommendations for hepatitis B vaccination for all HD patients and staff members in 1982 [113], overall rates of hepatitis B infection have decreased. From the period of 1976 to 1997, the incidence of HBV infection decreased from 3.0% to 0.05% among patients and from 2.6% to 0.05% among staff members [114]. More recently, the prevalence of hepatitis B surface antigen (HBsAg) positivity among US dialysis patients has improved and is estimated to be around 1%.Overall, the prevalence of chronic hepatitis C in the United States has been slowly decreasing from 1.8% between 1988 and 1994 to 0.8% from 2009 to 2016 [1, 115]. Despite significant gains being made, outbreaks of viral hepatitis continue to plague dialysis centers in the United States. Recently, the CDC has been receiving an increasing number of reports of acute HCV infection among patients undergoing HD. From 2014 to 2015, the CDC was made aware of 36 cases of acute HCV infection in 19 different hemodialysis clinics in eight states. To date, there have been no reported cases of person-to-person transmission of HIV at dialysis centers in the United States [107]. Investigation of the outbreaks revealed breaches in infection control practices including injection safety, environmental disinfection, and hand hygiene. This prompted the CDC to release an official health advisory alert (see Table 6.16).

Table 6.16 The CDC health advisory recommendations to improve infection control practices to stop hepatitis C virus transmission in patients undergoing hemodialysis [116]

Evaluate infection control practices in each facility and ensure adherence to infection control standards.
CDC has checklists and audit tools (http://www.cdc.gov/dialysis/prevention-tools/index.html) that providers can use to assess their practices, identify gaps, and improve infection control practices to protect patients.
If gaps are identified, promptly address any issues to protect patients' health and safety (http://www.cdc.gov/dialysis/).
Take action to improve injection safety (http://www.cdc.gov/injectionsafety/), hand hygiene (http://www.cdc.gov/handhygiene/), and routine environmental disinfection procedures, as appropriate.
Ensure staff are aware of and trained to implement infection control guidelines (http://www.cdc.gov/dialysis/guidelines/index.html) for hemodialysis settings. Facilities should provide regular (e.g., annual) training (http://www.cdc.gov/dialysis/clinician/index.html) of staff to ensure adherence to infection control recommendations.
Follow CDC recommendations for HCV screening of hemodialysis patients and management of patients who test positive.
Immediately report any case of new HCV infection among patients undergoing hemodialysis to the state or local health department.
Inform patients if HCV transmission is suspected to have occurred within the facility, and explain steps being taken to address the problem.

Infections are the second leading cause of mortality in dialysis patients. The incidence of sepsis in patients with ESRD can be up to 100 times as high compared to the general population [117]. Bacteremia accounts for the majority of severe infections in this population and is most often associated with vascular access [107]. Infection caused by bacterial pathogens in HD patients can be classified as either exogenous (acquired from contaminated dialysis fluids or equipment) or endogenous (caused by invasion of bacteria present in or on the patient) [107]. Exogenous infections have been linked to inadequate dialyzer reprocessing procedures and inadequate treatment of municipal water used in dialysis [118, 119]. Facility staff reported pooling and regurgitation of waste fluid at recessed wall boxes that house connections for dialysate components and the effluent drain within dialysis treatment stations [119]. Most recently, there was multicenter outbreak of gram-negative bacteremia with *Serratia marcescens* and *Pseudomonas aeruginosa* was linked to a recessed wall box that housed connection for

dialysate components and effluent drain within dialysis treatment stations [120].

Updated federal infection control requirements for dialysis centers in the United States were developed in 2008 when the CMS published the final rule on Conditions for Coverage for End-Stage Renal Disease in the Federal Register that integrated the CDC's Recommendations for Preventing Transmission of Infections among Chronic Hemodialysis Patients [107, 121]. In order for dialysis centers to remain certified and receive payments under Medicare, they must comply with the infection control requirements outlined by the CMS. The DHHS recently spearheaded the National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination campaign, Phase Two, which focuses on end-stage renal disease facilities [122]. The Steering Committee emphasized the need to maintain the HAI action plan as a "living document," aimed at "developing successor plans in collaboration with public and private stakeholders to incorporate advances in science and technology, shifts in the ways health care is delivered, changes in health care system processes and cultural norms, and other factors" [30]. Infection control programs must remain up to date on the most current infection control guidelines for dialysis centers. A compendium of the most current guidelines and recommendations along with additional resources can be found at the CDC's webpage devoted to dialysis safety [19, 110, 111, 116].

Oncology Centers

As the US population grows and chemotherapy advancement continues to thrive, the number of persons living with cancer will continue to increase [123]. A majority of these treatments are conducted in outpatient settings with more than a million cancer patients receiving chemotherapy or radiation each year [6]. Patients receiving cancer treatment are at increased risk for infection given immunosuppression, healthcare exposure, and often indwelling vascular access. Infectious complications from chemotherapy-induced neutropenia are life-threatening with mortality rate of febrile neutropenia ranging from 2% to 21% [124]. It is estimated that bacteremia occurs in 10%–25% of all cancer patients, regardless of neutropenia [125]. As such, the CDC's Division of Cancer Prevention and Control has developed the PreventCancerInfections.org for both patients and healthcare personnel to help decrease the rates of infections in cancer patients. As described above, standard precautions recommended for all ambulatory facilities of hand hygiene, respiratory hygiene and cough etiquette, and injection safety certainly apply to oncology settings as well. Droplet precautions, especially for those with known neutropenia are of utmost importance. In addition, proper education and training of staff personnel regarding central venous catheters is vital to decreasing the number of associated infections. The CDC has created a Basic Infection Control and Prevention Plan for Outpatient Oncology Settings in 2011which provides more detailed recommendations regarding maintenance and access procedures of central venous catheters [34].

Education of Healthcare Personnel (HCP)

The education of HCP regarding infection control policies and procedures is vital to optimize patient safety. The frequent updates to guidelines and recommendations require that educational programs be longitudinal and that they incorporate regular competency evaluations. Individual healthcare organizations should develop programs that are tailored to the specific needs of the HCP. The CDC recommends that training should be provided upon orientation and anytime policies and procedures are updated or revised [19].

Risk Assessment

To assist with performing a self-assessment of outpatient infection prevention programs, the CDC has developed a checklist tool. This basic checklist can aid in ensuring that ambulatory facilities have appropriate infection prevention policies and procedures in place, as well as supplies to enable healthcare personnel (HCP) to provide safe care. The tool also provides a systematic approach to assessing HCP adherence to correct infection prevention practices [19].

Antimicrobial Stewardship

Antibiotic use is thought to be the most important modifiable cause of antibiotic resistance [82]. Outpatient antimicrobial stewardship promotes the appropriate prescribing of antibiotics for nonhospitalized patients in clinics, offices, and emergency rooms [25]. The primary objective of ASPs is to promote compliance with clinical practice guidelines in order to optimize patient care and minimize the spread of antibiotic-resistant bacteria. Early on, AS focus was on the inpatient setting; however, a tremendous amount of antibiotic prescribing occurs in the outpatient setting. In 2018, there were over 249.8 million outpatient antibiotics prescribed which equates to 763 per 1000 persons [126]. A study conducted to evaluate trends in antibiotic prescribing for adults in the United States from 1995 to 2002 revealed that 15.3%–17.9% of all outpatient office visits resulted in an antibiotic prescription [127]. Outpatient healthcare providers often feel pressured by patients to prescribe antibiot-

Table 6.17 Core elements of outpatient antibiotic stewardship

Core element	Goal
Commitment	Demonstrate dedication to and accountability for optimizing antibiotic prescribing and patient safety.
Action for policy and practice	Implement at least one policy or practice to improve antibiotic prescribing, assess whether it is working, and modify as needed.
Tracking and reporting	Monitor antibiotic prescribing practices and offer regular feedback to clinicians or have clinicians assess their own antibiotic prescribing practices themselves.
Education and expertise	Provide educational resources to clinicians and patients on antibiotic prescribing, and ensure access to needed expertise on optimizing antibiotic prescribing.

Adapted from: Sanchez [25]

ics for conditions that are most likely viral in etiology. A study evaluating antibiotic prescribing for adults in ambulatory care in the United States from 2007 to 2009 concluded that of the roughly 985 million outpatient office visits per year, >100 million visits resulted in an antibiotic prescription and over half of all antibiotic prescribing was unnecessary. The most common conditions associated with inappropriate treatment were acute respiratory infections like sinusitis and bronchitis [126].

Shifting more attention to the outpatient setting, the CDC released "The Core Elements of Outpatient Antibiotic Stewardship" to provide a framework for improving antibiotic prescribing in the outpatient setting (Table 6.17 [25]).

Reducing inappropriate prescribing could have a significant impact on HAIs. It is estimated that a 10% decrease in inappropriate antibiotic prescribing in the outpatient setting could produce a 17% decrease in rates of *Clostridium difficile* infection [128]. In an effort to decrease inappropriate antibiotic prescribing at the local level, the CDC has increased from 2016 to 2019 to health departments with >300 million dollars given to create ASPs and decrease rates of multidrug-resistant organisms [129, 130]. Additionally, the US National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) was recreated in 2015 to address the rising antimicrobial resistance across the healthcare continuum. The plan's primary goals are to (1) slow the emergence and spread of resistant infections, (2) strengthen the national surveillance efforts, (3) advance the development and use of diagnostic tests, (4) accelerate research related to MDRO, and (5) improve international collaboration [131].

In terms of education, in 2003, the CDC created the "Get Smart: Know How Antibiotics Work" to educate the general public on appropriate antibiotic use. As patients can influence the increase of antibiotic prescription, patient education is vital to appropriate antibiotic use [132]. The Get Smart program has since been rebranded in 2017 to "Be Antibiotics Aware" to target both patients and clinician. The CDC and World Health Organization have also started the Antibiotic Awareness Week to raise awareness [133, 134]. New and innovative approaches to healthcare delivery such as telemedicine, telehealth, urgent care and retail clinics, infusion centers, and OPAT will require creative antimicrobial stewardship strategies. Further investigation is needed to determine the most effective interventions to optimize antimicrobial prescribing in the outpatient setting. As of January 1, 2020, the Joint Commission enacted new antimicrobial stewardship requirements in the outpatient setting, applicable to ambulatory healthcare organizations that routinely prescribe antimicrobial medications. Currently the requirement is not applicable to ASCs or the office-based surgery programs, but does extend to organizations providing medical or dental services, episodic care, occupational/worksite health, urgent/immediate care, or convenient care [135]. New accreditation requirements will stimulate further growth of AS in the outpatient setting.

Pandemic Planning in the Context of COVID-19

It is difficult to overstate the monumental impact the global pandemic of COVID-19, caused by the SARS-CoV-2 virus, has had on society and medicine at large. As of February 28, 2021, over 110 million cases and 2.5 million deaths have occurred worldwide. Responding to this crisis has stressed healthcare systems to their limits. In terms of outpatient infection prevention practices, COVID-19 has revolutionized the approach to care. Early on in the pandemic, it became clear that long-term care facilities could become local epicenters of outbreaks. For example, the first major site of COVID-19 transmission identified in the United States occurred in a long-term care nursing facility in Washington State. Major vulnerabilities in infection control practices were identified as contributing factors in the outbreak including deficiencies in case identification, isolation surveillance, reporting, staffing, PPE use, and communication [136, 137]. Transmission in the outpatient setting, including among asymptomatic patients, has forced facilities to transform their typical approach to delivering healthcare in order to reduce patient to patient contact and in-person visits. Strategies such as universal source control via face coverings, optimization of telehealth, symptom screening at points of entry, and intensified diagnostic testing have been required to enhance infection prevention during the pandemic. More than ever, there is a heightened awareness of the fundamental and critical importance of transmission-based precautions, hand hygiene, environmental controls, and respiratory etiquette. Prior to the COVID-19 pandemic, pandemic planning in the outpatient setting had not been a high priority for infection prevention programs. In addition

to the basic infection prevention strategies outlined above, the COVID-19 pandemic has required unique and intensified infection prevention practices, outlined by the CDC and summarized in Table 6.18.

Moving forward, pandemic planning in the outpatient setting will become a standard requirement with a high degree of oversight. New Joint Commission ambulatory care standards indicate that effective January 1, 2021, emergency plans must be tested at least annually, and a full-scale, community-based exercise or a functional exercise must occur at least biannually. The biannual exercise must include one of the following: a second full-scale community exercise, a second facility-based functional exercise, mock disaster drill, or a tabletop exercise or workshop [139].While ideally these plans are developed by individuals with training in infectious disease or infectious prevention, there is currently a significant shortage of infectious disease specialists. During the 2020 National Resident Matching Program, 21% of infectious disease fellowship positions remained unfilled [140]. In 2017, almost 80% of counties in the United States did not have an infectious disease physician [141]. This will force of the utilization of telehealth for improved outreach to rural communities and education of other qualified staff members in infection prevention to ensure more robust pandemic plans for outpatient facilities.

Table 6.18 Specific practices for targeting infection control objectives

Infection control strategy	Specific practices
Implement telehealth and nurse-directed triage protocols.	Triaging patient for timing and appropriateness of in-person appointments while increasing utilization of telehealth.
Screen and triage everyone entering a healthcare facility for signs and symptoms of COVID-19.	Screening patients and visitors for symptoms, optionally with temperature checks or electronic monitoring systems.
Implement universal source control measures.	Refers to use of well-fitting cloth masks, face masks, or respirators to cover a person's mouth and nose to prevent the spread of respiratory secretions when they are breathing, talking, sneezing, or coughing.
Encourage physical distancing.	Encouraging social distancing of 6 ft when possible, including in waiting rooms, break rooms, and other staffing areas.
Implement universal use of personal protective equipment.	Enforcing PPE use for even asymptomatic or presymptomatic patients in areas with moderate to substantial community transmission. Current PPE recommendations include face mask (preferably surgical if available), eye protection, and N95 or equivalent for aerosol-generating procedures.
Perform targeted SARS-CoV-2 testing of patients without signs or symptoms of COVID-19.	Implementing preadmission or pre-procedure screening testing based on guidance from local and state health departments.
Consider postponing elective procedures, surgeries, and nonurgent outpatient services in certain circumstances.	Triaging elective procedures and surgeries, especially aerosol-generating procedures to limit exposure.
Optimize the use of engineering controls and indoor air quality.	Consulting with facility engineers to optimize indoor air-handling systems and airborne isolation rooms
Create a process to respond to SARS-CoV-2 exposures among HCP and others.	Establishing a plan for contact tracing and creating policies in the event of HCW or patient exposures.
Manage visitor access and movement within the facility.	Limiting the number of entrances to facilitate screening, reducing the number of visitors to prevent exposures.

Adapted from: Centers for Disease Control and Prevention [138]

Additional infection prevention interventions such as masking during the pandemic have raised several questions with the potential to fundamentally transform the approach to infection prevention in the outpatient setting. For example, the rates of influenza and respiratory syncytial virus infection have been historically low during the pandemic which may be attributed to masking practices. Thus far during the 2020–2021 influenza season, the percentage of outpatient visits for influenza-like illness in the United States have ranged from 1% to 1.6%. Over the past 10 years, the average has been significantly higher at 2.6%, which also includes the H1N1 influenza pandemic in 2009 [142]. Should HCP universally mask with all encounters during the influenza season in the future? Or just with special populations? Beyond the COVID-19 pandemic recovery, novel strategies implemented to reduce transmission may become standard of care. As the pandemic continues to evolve, we instruct the reader to refer the reader to the CDC for the most current recommendations [138].

Conclusions

As healthcare delivery in the United States continues to become ever more complex and we see more transition from the inpatient to the outpatient setting, strengthening of outpatient infection prevention and control practices becomes increasingly relevant. Historically, infection prevention and control in the outpatient setting has not received the attention or resources afforded to inpatient programs. However, high-profile infection control lapses have led to greater awareness of the need for robust outpatient infection prevention programs. Major progress from state and federal agencies has led to a wave of new regulatory requirements in the outpatient setting that will hopefully translate into significant

gains in patient and HCP safety. A heightened and sustained focus on the development of outpatient infection control infrastructure, surveillance, reporting, oversight, and monitoring is urgently needed. Beyond regulation, a culture of safety that embraces a proactive approach to healthcare-associated infection prevention, engaging a variety of stakeholders, is essential to facilitate collaboration and advancement. Finally, pandemic planning in the outpatient setting is critical and will stimulate further growth and development of infection prevention across the healthcare continuum.

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New Technologies for Infection Prevention

7

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Introduction

Interest in technologies to assist infection prevention efforts is increasing. The basic science literature contains an abundance of novel ideas at varying stages of development. A few of these technologies have been developed beyond preclinical testing and have been used in the healthcare setting with the goal of reducing bioburden and interrupting the transmission paths of healthcare-associated organisms. New technologies are assisting in cleaning of surfaces and devices. Other technologies endeavor to insert bactericidal materials into healthcare center furnishings and garments. Additional technologies capable of tracking and monitoring have been developed to assess hand hygiene of healthcare workers. These products are attractive to infection prevention departments and hospital administrators given the difficulties inherent in achieving and maintaining desired staff behaviors; they promise to bypass the human element and deliver automated infection prevention. Yet clinical and cost-effectiveness of these often expensive interventions are uncertain, and incremental benefit over traditional infection prevention best practices may be scant. Nevertheless, as infection prevention programs are tasked with more activities than ever [1], they will continue to look for innovative strategies to improve the effectiveness of existing efforts.

Ultraviolet (UV) and Hydrogen Peroxide (HP) Room Disinfection Systems

Contamination of the inanimate hospital environment is an area of ongoing concern for the accumulation of bioburden and increased potential for transmission of organisms between patients. Variations in the effectiveness of the cleaning provided by environmental services staff has led to the development of technologies designed to complement human efforts and provide a more consistent and complete level of cleaning for patient rooms and other hospital areas. Extensive research has been done on the efficacy of these devices using various methodologies. However, true clinical benefit currently remains dubious, especially when traditional human cleaning practices can be optimized.

Touchless Device Killing Efficacy

Studies relating to the efficacy of HP and UV devices typically employ two different methodologies: (1) an "in vitro" assessment in which known quantities of bacteria inoculated onto carrier materials or biologic indicators are deliberately placed in a test space, and (2) an "en vivo" assessment in which the real contamination in a room formerly inhabited by a patient is assessed by environmental cultures both before and after application of a device. Killing efficacy depends on the method employed to measure killing, the type of touchless cleaning device, the time of application, type of microorganisms evaluated, and a multitude of room and surface features such as complex equipment, fabric materials, and large or irregularly shaped rooms.

In general, studies suggest that killing power of vaporized HP is slightly higher than for aerosolized HP and UV devices [2]. For example, several studies using vaporized hydrogen peroxide have reported killing rates for experimentally placed inoculum to be essentially complete, averaging >5–6 log reductions [3–7]. This is in contrast to aerosolized hydrogen peroxide devices, in which the particles are larger at 1–10 um and reported kill rates vary more widely by type of device and experimental protocol [3, 8]. Direct comparisons between aerosolized hydrogen peroxide (aHP) devices and vaporized hydrogen peroxide (HPV) devices have been made. In one study, biological indicators with a six log load of bacteria were tested against each HP device; HPV was able to completely eradicate the experimentally placed bacteria while

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_7

aHP decreased the bacterial load by 10–79% [9]. Fu et al. also noted a difference in killing ability between the systems, with an HPV-based device achieving complete eradication of experimentally placed methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter* (ACB), and *Clostridium difficile*, whereas the aHP device achieved variable and incomplete killing of these same organisms. The study team also noted that the distribution of aHP levels in the room was not uniform, potentially explaining gaps in coverage area and decreased effectiveness compared to HP vapors [3].

UV devices most often employ UVC or pulsed xenon, with wavelengths of 240–280 nm [10] and 200–230 nm [11] respectively. UVC devices have been reported to achieve two–four log reductions in experimentally placed bacteria, depending on the type of carrier or surface being inoculated and the placement arrangement within the room [12–14]. This is in contrast to pulsed-xenon UV devices which reportedly yields <1 log reductions in bacterial colonies [15]. Time required to run devices favors pulsed-xenon however, with a recommended run time of 15–20 minutes total for a given room, compared to 20–40 minutes for UVC devices and up to several hours for HP devices. However, UVC could potentially be run on cycles shorter than currently recommended by manufacturers. A study by Nerandzic et al. compared a UVC device to pulsed-xenon UV device and found that they could achieve superior reductions in colony forming units of experimentally placed *C. difficile*, vancomycin-resistant *Enterococcus* (VRE), and MRSA using a 10 minute UVC run time compared to a normal pulsed-xenon UV run time [15]. This suggests that the UVC device protocol could be individualized for optimal feasibility in a given healthcare setting by striking a balance between killing efficacy and run time requirements. Furthermore, to achieve an equal level of killing with shorter time duration, Rutala et al. document that use of a reflective paint allowed a UVC device to run less than 10 minutes while still achieving about a four-log reduction similar to a 30–40 minute cycle without the reflective coatings [16–18].

Building on the data accumulated from work with experimentally placed bacteria, several studies have undertaken extensive environmental sampling to determine the efficacy of these devices in cleaning actual patient rooms at the time of patient discharge. Several important observations have resulted: (1) percent reductions in site contamination tend to be equalized among different devices when measured in this way [11, 15, 19–21], (2) no device has the ability to completely eradicate residual bioburden from a real patient room at terminal cleaning [4, 11, 15, 19, 20, 22], and (3) certain structures and devices may be difficult for even touchless technologies to penetrate [23, 24].

Site contamination has been reported to decrease by around 70–90% when compared to a baseline dirty room [11, 15, 19–21], and 24–33% when compared to a room cleaned by standard methods when using a variety of UV and HP devices [22, 25]. Havill et al. found a much lower percent decrease of 51% for a UVC device compared to 91% from an HPV device in the same study [4]. Of note, two-thirds of the environmental samples that UVC failed to decontaminate came from the patient bathroom. Anderson et al. also observed that the bathroom had decreased reductions in site contamination using a UVC device: 74% versus up to 98% for structures in the main room [19]. Timing does influence the efficacy of environmental decontamination; in a study by Ali et al., running HPV devices for shorter 2-hour run times resulted in a higher percentage of low level site contamination when compared to previously reported 3–4-hour run times. They argue that the actual bioburden of these residually contaminated sites was quite low in terms of colony forming units (CFUs) recovered, such that the remaining risk to future patients was also low [24]. Wong et al. also point out that UVC not only decreased the percentage of positive sites, but also significantly decreased the remaining CFU bioburden of those sites that did remain positive [26]. There may be flexibility to balance the duration of device cycles with a desired level of cleaning effectiveness.

It is unknown how much of a decrease in residual contamination is needed to impact clinically important outcomes. Given that the purposes of these devices are disinfection and certainly not sterilization, there will always be some residual bioburden expected in patient rooms. It is also important to remember that regardless of device efficacy, patient rooms are recontaminated soon after receipt of a new patient [27]. Certain structures may be more susceptible to residual contamination. In the case of HP devices, these include complex structures such as Velcro [23] and furniture seating [24]. In the case of UV devices, shading such as the underside of tables and areas behind toilets is problematic [28, 29]. Also, heavy contamination with organic matter or bacterial colonies themselves impact killing efficacy [30, 31]. Since the performance of touchless technologies is less variable than human workers, they will also likely experience the same limitations with every cycle run, leaving certain areas or structures consistently contaminated. It is up to individual institutions to be aware of the limitations of these technologies and to maintain a rigorous traditional cleaning program to complement touchless devices.

Touchless Device Efficacy in Clinical Outcomes

Clearly UV and HP devices are able to decrease the bioburden of the hospital environment further than with traditional cleaning alone. Yet to justify the time, cost, and effort required to implement touchless devices, this decrease in bioburden must translate into tangible patient outcomes. Several studies have attempted to demonstrate decreases in hospital acquired infection rates among patients (Table 7.1). Manian et al. compared their *C. difficile* rates for 23 months

Table 7.1 Evidence for UV and HP device reductions in healthcare-associated acquisitions or infections

Author	Device type	Main outcomes	Study design	Main findings	Main limitations
Manian et al., 2013 [32]	HPV	C. diff rates from clinical cultures	Quasi-experimental	C. diff rates fell 0.88 to 0.55 per 1000 patient days, a 38% decrease	Bleach clean ×4 used in place of HPV in cases of room double occupancy
Levin et al., 2013 [33]	PX-UV	C. diff rates from clinical cultures	Quasi-experimental	C. diff rates fell 0.95 to 0.45 per 1000 patient days, a 53% decrease	Overall decrease in fluoroquinolone usage over the same time period, small center, rates of device usage not reported
Haas et al., 2014 [34]	PX-UV	C. diff, MRSA, VRE, MDR GNRs rates from clinical cultures	Quasi-experimental	20% decrease in infections with MDROs from 2.67 to 2.14 per 1000 patient days, each individual MDRO was also significantly decreased	Multiple other interventions occurring at the same time
Passaretti et al., 2013 [35]	HPV	MRSA and VRE acquisition by screening swabs, MDR GNRs and C. diff infections by clinical cultures	Prospective cohort with matched control units	64% decrease in acquisitions of organisms of interest combined, driven largely by VRE; trend toward decreases in other organisms	Variable compliance with screening cultures
Anderson et al., 2015 [36]	UVC	New MRSA, VRE, ACB, C. diff from clinical cultures in patients linked by location to previously colonized room occupants	Cluster randomized, multicenter crossover study	Relative rate for all organisms of interest decreased significantly for only the UVC + quaternary ammonium cleaning group; rates trended down for all intervention arms. Combined outcome driven by VRE: no difference in MRSA and C. diff in intervention arms, and not enough ACB for comparisons	Limited sample size despite multicenter design due to restrictive inclusion criteria for analysis
Nagaraja et al., 2015 [38]	PX-UV	C. diff rates from clinical cultures in an ICU subset from Haas et al. study above	Quasi-experimental	C. diff rates in the ICUs fell from 1.83 cases per 1000 patient days to 0.55	Authors note clustering of cases on some units, such that the possibility of outbreak over endemic rates of C. diff is raised
Napolitano et al., 2015 [41]	UVC	Clinical cultures for MRSA, VRE, ACB, C. diff, Klebsiella pneumonia	Quasi-experimental	All HAIs decreased from 3.7 cases per 1000 patient days to 2.4. Individual ACB, C. diff, Klebsiella rates also fell significantly.	Small sample size of in terms of both time of study (6-month pilot) and beds ($N = 239$).
Horn et al., 2015 [40]	HPV	Cases of C. diff infection, MRSA, VRE, ESBL	Quasi-experimental	All HAIS decreased by 47% in the 2 years post-intervention compared to the year before intervention; combined endpoint driven by C. diff and ESBL	Dual intervention of increased hand hygiene and HPV
Miller et al., 2015 [42]	PX-UV	C. diff rates from clinical cultures	Quasi-experimental	C. diff rates decreased from 2.33 to 0.83 per 1000 patient days in long-term care center	Small single center study with a dual stepped intervention of a C. diff multidisciplinary team
Vianna et al., 2016 [39]	PX-UV	Clinical cultures for MRSA, VRE, C. diff	Quasi-experimental	All HAIs decreased from 1.51 cases per 1000 patient days to 1.07; this was driven by a decrease in VRE in the ICU and C. diff in non-ICU areas	Small single center study (126 beds)
Anderson et al., 2018 [37]	UVC	New MRSA, VRE, ACB, C. diff from clinical cultures in patients hospital-wide (secondary analysis)	Cluster randomized, multicenter crossover study	No difference in HAIs hospital wide comparing intervention arms (including UVC arm) to standard cleaning	Post-hoc analysis of patients admitted to rooms of prior *C. difficile* inhabitants revealed decreased risk of *C. difficile* acquisition in the UV arm
Murphy et al., 2020 [43]	UVC	CLABSI, C. diff, and respiratory viral infection diagnosis	Quasi-experimental	CLABSI and *C. difficile* infections were decreased post intervention in a BMT unit	Small single unit study (21 beds)

Abbreviations: *C. diff Clostridium difficile*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ACB Acinetobacter*, *VRE* vancomycin-resistant *Enterococcus*, *GNRs* gram-negative rods, *MDR* multidrug resistant, *MDRO* multidrug resistant organisms, *HAI* hospital acquired infection, *HPV* hydrogen peroxide vapor, *UVC* ultraviolet-C, *PX-UV* pulsed xenon ultraviolet, *ICU* intensive care unit, *CLABSI* central line-associated bloodstream infection, *BMT* bone marrow transplant

pre-intervention with 12 months post-implementation of an HPV device in their 900-bed community hospital. While only capturing 54% of their *C. difficile* rooms at terminal discharge, they were employing the device in other rooms around the hospital and saw a significant reduction in *C. difficile* rates from 0.88 to 0.55 cases per 1000 patient days. However, no information regarding detailed trends in these rates were available as only yearly aggregated rates were reported [32]. Levin et al. also evaluated *C. difficile* rates before and after implementation of a pulsed-xenon UV device in their 140-bed community hospital. They captured 56% of their discharged rooms over a 1-year period. They also reported rates in yearly aggregates, finding a significant decrease from 0.95 cases per 1000 patient days in 2010 to 0.45 cases per 1000 patient days in 2011; rates had been stable 2008–2010 at 0.92 per 1000 patient days [33]. Haas et al. also shared their experience in implementing a pulsed-xenon UV device in a 643-bed tertiary care center comparing 30 months pre-intervention with 22-month post-intervention. They retrospectively assessed rates of MRSA, VRE, multidrug-resistant gram-negative rods (MDR-GNRs) and *C. difficile* from clinical cultures in both time periods, finding significant reductions in each of these organisms in the period after device implementation. The device capture rate for their contact rooms was 76% [34].

Attempting to limit bias inherent to retrospective quasi-experimental designs, Passaretti et al. performed a prospective study of an HPV device on three units attempting to match them to three other high risk units for comparison. They analyzed screening cultures for MRSA and VRE, as well as clinical cultures for MDR-GNRs and *C. difficile*. They found a trend towards decreased acquisition of all organisms in patients in the HPV units; only the decrease in VRE risk was statistically significant, despite the large number of room occupations analyzed ($N = 8813$) [35]. Finally, in a large, multicenter, cluster-randomized, crossover trial, Anderson et al. compared manual cleaning with quaternary ammonium (reference arm), manual cleaning with bleach, and each of these manual methods + UVC device cleaning. The main outcome was a new diagnosis of an organism of interest by clinical culture in a patient who stayed >24 hours in a room previously occupied by another patient with known colonization or infection history with the same organism of interest. This restrictive criterion was meant to capture presumed transmission of infection from an environmental source and provide strong justification for enhanced cleaning. All intervention arms showed a decreased risk of patient acquisition of the combined multidrug-resistant organisms of interest (MRSA, VRE, ACB, *C. difficile*). However, this decrease in relative rate was due exclusively to the significance of VRE reductions; MRSA decreases failed to reach statistical significance, and there was no difference significant or not, found between arms using bleach + UVC or bleach alone for *C. difficile*. There were not enough ACB in the study for comparisons to be made [36].

A subsequent secondary analysis by Anderson et al. was performed to evaluate hospital-wide hospital-acquired infections (HAI) [37]. Compared to the reference intervention of standard cleaning, there was no difference in the study period for risk of HAI in the enhanced cleaning arms, including the UV device arm. Post-hoc analysis demonstrated a small increased risk for HAI *C. difficile* in patients admitted to rooms of prior *C. difficile* patients when UV study periods were compared to other non-UV cleaning groups [37].

The seemingly disappointing results from the well-designed studies of Passeretti et al. and Anderson et al. have not resulted in abatement of interest in touchless devices. Additional single center quasi-experimental designs continue to appear in the literature to report modestly positive results after implementation of a given device in their institution [38–43]. The natural fluctuation of infection rates and the ability of a small change in case numbers to influence rates and statistical significance demands caution in interpreting such results. The study by Miller et al. is unique in its application of a pulsed xenon UV device to cleaning protocols in a long-term care center. The device was used primarily to do weekly cleaning of common areas shared by residents; less frequently it was used for resident rooms after discharge [42]. As part of regional approaches to controlling MDROs, enhanced cleaning of long-term care facilities with touchless devices may be an advantageous strategy.

Outbreak Management

In addition to attempts to reduce hospital acquired infections (HAIs) in endemic situations, touchless technologies have also been used in outbreak scenarios. Most frequently, HP devices have been used, and have been successful in halting outbreaks from a variety of organisms. For example, MRSA polyclonal outbreaks [44] and hyperendemic rates [45] have been combated with hydrogen peroxide vapor and essentially eradicated. Numerous studies have reported a rapid recontamination rate after the use of touchless technologies [44–47], however, Dryden et al. noted that MRSA environmental contamination levels remained at a lower post-intervention baseline. They attributed this to extensive concurrent decolonization efforts targeting staff and patients [44]. This illustrates the point that closure of a unit for decontamination may be very effective at aborting the active outbreak, but improvements in standard cleaning, hand hygiene, and other infection prevention initiatives remain important in maintaining these results. Barbut et al. also documented a sustained decrease in MRSA and *Acinetobacter* following an outbreak. Their response included closure and decontamination of an entire burn unit using an HP vapor device, then

reopening the unit with incorporation of an infection control bundle that included preemptive isolation of patients, cohorting of infected or colonized patients, increased emphasis on hand hygiene, and regular use of the HP device for terminal discharge cleaning (Barbut) [48].

Most recontamination of units post-intervention are assumed to occur from newly admitted colonized patients. For example, Ray et al. describe their experience using an aerosolized HP device to control and *Acinetobacter* outbreak at a long-term care facility. They were able to successfully stop the outbreak, but noted rapid recontamination of the environment that was presumed to be due to high risk colonized patients readmitted to the space. They were also able to identify a wound care cart that was a potential source linking infected patients [46]. In addition to colonized patients, occult environmental reservoirs that persist after touchless device interventions may also contribute to recontamination of wards. This may explain the difficulties that other groups have reported in controlling outbreaks due to *Acinectobacter*. Otter et al. were able to halt an outbreak in their 12 unit ICU, but noted subsequent recontamination with *Acinetobacter* that was genetically related to the strains infecting the previous patients; none of the current patients could be linked to the patients prior to the unit closure and decontamination intervention [49]. Alfandari et al. were able to identify a reservoir that was felt to be contributing to the propagation of an *Acinetobacter* outbreak in their ICU when Velcro on a shared blood pressure cuff yielded the same clone that infected 12 of their 14 case patients. This residual contamination had persisted despite decontamination with an HP device, and only removal of the cuff from the unit finally ended the outbreak [23]. HP vapor was used as an adjunct to multiple other interventions in protracted [50] and recurrent [51] *Acintebacter* outbreaks at two centers in Europe. Both groups emphasize the need for a multifaceted approach to these outbreaks. In fact, Landelle et al. note that only by cohorting of both patients and staff on a separate unit were they able to finally end their 18-month battle with *Acinetobacter* [50]. Residual environmental reservoirs may contribute to ongoing transmission if general infection prevention principles are not meticulously applied. Thus touchless devices are not magic bullets; these devices provide a useful adjunct strategy to outbreak mediation, but require concomitant application of broadly reaching infection prevention bundles.

Other Applications of Touchless Technology

Cleaning of Occupied Rooms

High intensity narrow beam light at 405 nm has been used in a series of experiments by a group in the United Kingdom to reduce Staphylococcal bioburden in burn units and an intensive care unit [52–54]. These devices use visible violet light to exert a bactericidal effect on organisms that is thought to occur due to excitation of bacterial intracellular porphyrins and resulting oxidative damage [53]. They have the benefit of safe continuous use in a room occupied by patients and/or staff. The violet light is combined with white light to exist as part of the normal light fixture of a patient room and is operated by a light switch. The device has demonstrated an ability to decrease bioburden in an occupied room with ongoing use. However, the studies were small including few occupied rooms and focused mainly on *Staphylococcus* species [52–54].

In the operating room, UVC air disinfection devices have been employed to collect, disinfect, and then recirculate air within the room [55, 56]. These devices have the ability to decrease overall airborne particle counts, both in simulated conditions [55] and during total joint arthroplasty [56].

Cleaning of Medical Supplies and Equipment

Apart from whole room cleaning, touchless devices have been employed specifically to clean mobile medical equipment [57] and unused medical supplies [58]. In the later study, each item had to be removed from drawers in the patient room and spread out to allow the HP vapor to access the items. However, the authors note that this effort would have the potential to save the institution $387,055 per year, because they otherwise discard all unused supplies from the rooms of isolation patients at discharge [58]. Penetration into crevices of complex medical equipment was achieved in the study by Andersen et al., when hydrogen peroxide fumigation was used to decontaminate intentionally placed Bacillus spp. spore strips in ambulances and rooms [57]. One cycle of the decontamination device resulted in efficacy of 87% decontamination success on room surfaces and 62% efficacy on internal parts of equipment; but three cycles resulted in 100% efficacy in these sites [57].

Another option for small item touchless cleaning is a "nanoclave cabinet" consisting of a 129 cm × 94 cm × 89 cm box filled with UVC lamps which has been utilized to clean non-essential patient care items such as TV remotes and blood pressure cuffs in the test environment [59]. Authors observed significant reduction in bacterial loads after 30 second cycles, while *C. difficile* spores and viruses took longer to kill: 2–6 minutes. Items difficult to clean with disinfectant wipes remained difficult to clean in the cabinet (i.e., blood pressure cuffs) and durability of items after repeated subjection to the UV light was not assessed [59]. A similar study reported the use of a UVC lamp to decontaminate provider mobile phones, decreasing bioburden of MRSA by 2.91 log CFU reductions and 3.95 log CFU reductions after 1.5 or 2.5 minutes under the lamp respectively [60]. Handheld

devices have been trialed on units for staff driven decontamination of commonly touched objects such as keyboards, phones, and documents, noting a reduction in the time required for cleaning compared to disinfectant wipes: 22 minutes versus 43 minutes [61].

Decontamination for Reuse of Personal Protective Equipment

During the COVID-19 pandemic, many facilities used touchless devices to assist in decontamination of personal protective equipment during supply shortages. Both hydrogen peroxide and UV light have been used during and prior to the COVID-19 pandemic to decontaminate N95 filtering respirators with apparently limited impact on N95 function [62]. UV light may suffer from some of the same challenges as room cleaning where direct exposure to the light is optimal for microbial killing. In a series of experiments using bacteriophages as viral surrogates, Cadnum et al. found that using a disinfection cabinet filled with aerosolized peracetic acid and hydrogen peroxide produced better decontamination of N95 respirators compared to UV light used as a room cleaning device and also as a UV light box [63]. There was variability in the decontamination provided by the UV devices by respirator brand and by respirator location [63].

Challenges and Limitations of Touchless Devices

The existing literature on touchless devices for cleaning of the hospital environment is limited by non-standardized methods of evaluation of different devices and industry influence on study design and reporting of data. Robust study designs sufficiently powered to compare devices to optimized cleaning procedures are lacking with few exceptions. Even in the largely positive reports of device effectiveness, several shortcomings are evident such as the inability to penetrate all surfaces. Problem areas seem to include floor corners [24], heavily soiled areas [30, 31], and complex structures [23].

There are also implementation challenges that include the impact on room turn-over time, the human resources needed to run the touchless device cleaning program, and ensuring the rooms are sealed/vented appropriately for devices using hydrogen peroxide and barred/closed for devices using UV lights [64]. These technologies can also be costly to purchase and fix when maintenance is required.

Touchless devices for room cleaning may have an important role in providing some consistency to terminal cleaning. However, rapid recontamination emphasizes the importance of standard and daily cleaning efforts to maintain a low overall bioburden in clinical areas. If the limitations of these devices are not fully understood by staff, they could actually compromise standard cleaning efforts by inducing a false sense of security; staff depending on the robot to clean could be neglecting important infection prevention practices. Education regarding the role of touchless devices as one of many important concomitant strategies for improving the environment of care is essential to preserve human participation in these efforts.

Antimicrobial Surfaces

Given the challenges involved in cleaning the hospital environment, there is substantial interest in self-disinfecting surfaces. While many materials remain in pre-clinical investigations of their antimicrobial effects, a few have been installed and assessed in the clinical environment. As with touchless devices, these technologies are difficult to compare between studies due to differing material compositions, culturing techniques, and timing of the study protocols [65]. In 2010, Casey et al. conducted a 10 week crossover study of 60–70% copper containing materials implanted on high touch surfaces. Surfaces were cultured weekly for aerobic colony counts and compared to control surfaces. After 5 weeks, the hospital switched the copper and control surfaces and repeated the experiment. The group found significant reductions in bacterial counts on all sampled sites and an overall 90% reduction in bacterial contamination of the copper alloy surfaces [66]. In contrast, Mikolay et al. applied a copper alloy to certain high touch surfaces and then sampled them 1–2 times per week for 16 weeks in summer months and another 16 weeks in winter months; aerobic heterotrophic colony counts were compared between the copper alloy surfaces and control surfaces. The authors found a disappointing overall 33% reduction in bacterial load from the copper surfaces that was statistically significant only on door knob sites. The authors hypothesized that their cleaner may have obstructed the antimicrobial copper effects. Also, the exact composition percentage of copper in the study was not reported [67]. The amount of copper present in the material is known to be important in antimicrobial efficacy [65]. Sheets of 99.9% copper were installed in a clinic consultation room and compared to a regular room by series of cultures every 6 weeks over 6 months. There was a 71% overall reduction in bacterial colony counts as well as significant reductions on all copper surfaces [68].

Prolonged exposure of organisms to copper raises concerns for the development of copper resistance. In a 24 week crossover study, Karpanen et al. also found significant reductions in aerobic colony counts on 8 of 14 surface types sampled comparing a copper alloy to standard surfaces. They also checked for and found no evidence of resistance to

copper in VRE, *Staphylococcal aureus*, and coliforms [69]. Duration of antimicrobial effect has been assessed in a longitudinal study that collected environmental samples for 23 months pre-intervention, then 20 months post-intervention, in 16 rooms split between 3 hospitals. Copper alloys containing 70–99.9% copper were installed on 6 high touch surfaces in 8 of the 16 rooms at month 23. The team found a sustained decrease in bacterial contamination of copper surfaces both compared to pre-intervention surfaces and to ongoing control surfaces [70].

Finally, copper surfaces have been evaluated for their ability to decrease HAI rates. Rivero et al. conducted a 13-month study comparing infection rates for central line-associated blood stream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP) in a 14 room ICU in which 7 of 14 rooms had 99% copper materials installed on high touch surfaces; they found no differences in HAIs in patients admitted for at least 24 hours, though admitted they were likely underpowered to do so [71]. In contrast, Salgado et al. performed a 11-month study comparing 8 copper rooms to 8 standard rooms among 3 ICUs at 3 separate facilities and found a significant decrease in HAIs in copper rooms as well as a 66% reduction in environmental contamination of copper surfaces when compared to non-copper surfaces in control rooms [72].

The use of a 16% copper oxide surfaces in combination with copper impregnated linens were studied in a community hospital when a wing was refurbished with these materials. HAI data from this unit was compared to a control unit and historical data [73]. The control unit saw no differences in HAIs during the 25.5-month study period. The copper unit demonstrated a reduction in HAIs (1.38 infections/10,000 patient days vs. 8.32/10,000 patient days, $p = 0.23$), driven by *C. difficile* reduction (0.69 cases/10,000 patient days vs. 3.65 cases/10,000 patient days in the control) [73].

Antimicrobial Fabrics

Textiles with antimicrobial properties have been developed and show promise in the laboratory setting in their ability to kill bacteria after a few hours of contact time [74]. A subset of these materials have been further tested in the clinical setting.

Antimicrobial Curtains

In an ICU, silver appeared to limit the contamination with bacteria when 14 curtains were tested over 6 months [75]. The same area from each curtain was cultured monthly and few nosocomial pathogens were recovered. However, there is a lack of microbiologic data provided regarding the organisms that were recovered from each sampling exercise as the focus of the report was on results of laboratory testing of swatches of the same silver impregnated textile. Furthermore, there was no control curtains used for comparisons in the testing done in the ICU [75]. A comparison to standard curtains was performed in a randomized controlled trial across 2 ICUs in which 15 curtains containing an antimicrobial metal-alloy and 15 standard curtains were cultured twice weekly for 4 weeks [76]. The study found no difference in the amounts of organisms of interest between the two curtains with the exception of VRE. VRE was recovered eight times more often from the standard curtains. In addition, they observed a significant increase in the median length of time until first contamination from 2 days for standard curtains to 14 days for antimicrobial curtains [76].

Healthcare Provider Antimicrobial Scrubs

Protection of industry advantage can limit the information available regarding the composition of antimicrobial scrubs. In one randomized controlled trial of healthcare worker scrub uniforms, standard scrubs were compared between two competing antimicrobial scrubs containing a "propriety antimicrobial chemicals". One of the scrubs also contained silver. Scrubs and skin of workers involved in direct patient care activities were cultured after an 8-hour shift and found to be no different in terms of total bacterial colony counts and colony counts of various MDROs between the three groups [77]. Comparison between studies is thus further limited by uncertainty about what materials are being tested.

Boutin et al. performed a randomized controlled trial using a Chitosan-based antimicrobial scrub and culturing staff skin and scrubs near the end of a 12-hour shift. Similar to the findings of Burden et al., they found no difference in total bacteria or individual MDROs of interest between the Chitosan scrubs and standard scrubs [78]. Another randomized controlled trial by Bearman et al. tested organosilane-based quaternary ammonium impregnated scrubs against standard scrubs in ICU clinical staff, finding a reduction in MRSA at a single scrub site (abdominal area) at the end of the shift. MRSA colony counts were also lower on the leg cargo pockets at the beginning of shifts. There were no significant differences in VRE or GNRs [79]. A veterinary clinic trialed a silver impregnated scrub uniform and compared bacterial contamination to a standard scrub. They found a significant difference only at the beginning of the shift, prior to any animal care, in which fresh silver scrubs had less bacteria present than the standard scrubs; no differences existed at 4 and 8 hours into the shift. They conclude that while the antimicrobial scrubs may be able to decrease contamination in storage, there are likely better ways to target infection

prevention in the clinical setting [80]. Similar findings are reported from a surgical ICU in which nurses were randomized to usual cotton-polyester scrubs, a silver-alloy impregnated scrubs, or scrubs containing an organosilane-based quaternary ammonium and hydrophobic fluoroacrylate copolymer emulsion in a 1:1:1 ratio, with each of the 40 participants wearing each scrub type for one shift. A comparison of the contamination of the scrubs at the end of shifts revealed no differences by scrub type [81].

Antimicrobial Patient Linens

In addition to provider scrubs, antimicrobial impregnated fabrics have been employed for patient bed linens and gowns with the goal of reducing bioburden in the immediate area of the patient. In a long-term care facility, a 7-month crossover controlled trial used a copper-oxide containing linen versus usual linens was performed in two ventilator units; each unit received the intervention linens for 3 months, and periods were separated by a 1-month washout in which both unit received non-antimicrobial scrubs [82]. Surrogates for HAIs were measured including new initiation of antimicrobial treatments, fevers, and days of antibiotic therapy. The study found significant reductions in each of these surrogates in the intervention arms [82]. A multicenter study encompassing six community hospitals that adopted copper oxide impregnated linens across each facility as a quasi-experimental before-and-after implementation design [83]. *C. difficile* rates significantly decreased in the post intervention periods; less of an effect was found on MDRO infection rates [83].

Other Applications

Rather than coat all hospital surfaces with antimicrobial compounds, Schmidt et al. focused on a high risk item for patient to patient transmission of microbes in the hospital: the stethoscope [84]. Twenty-one healthcare providers in a pediatric emergency room and an adult ICU alternated between using a standard stethoscope or a stethoscope with a custom fabricated with copper alloys over the course of 1 week. The non-antimicrobial surfaces of all stethoscopes were highly contaminated, but the copper surfaces from the intervention stethoscope had significantly less bioburden (11.7 CFU/cm^2 vs. 127.1 CFU/cm^2) [84].

Despite the apparent powerful bactericidal effects of self-disinfecting surfaces and fabrics in the laboratory, utilization in the clinical setting has been unable to demonstrate consistent and enduring decreases in environmental and healthcare worker contamination. Caution is clearly required in interpreting the wealth of basic science data for infection prevention technologies that is available from the bench; it does not always translate to the bedside. Additional real-world experience with attention to cost effectiveness is needed to find the niches where antimicrobial surfaces and fabrics can be most useful in healthcare facilities.

Conclusion

The search for new technologies to assist in infection prevention will continue to intensify as programs strive to raise their standards and accomplish more with less human resources. However, clearly some skepticism is required in the evaluation of new technologies in a literature infused with industry agendas and weaker study designs with potential for bias. More technologies must be integrated into the real clinical environment in pragmatic research designs that can be sustainable in the long term. Under such circumstances, many of the products discussed here have the potential to be useful adjuncts to more traditional infection prevention efforts and may be important in providing some standardization to practices that until recently have depended on individual human behaviors.

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What Is the Role of Mobile No-Touch Disinfection Technology in Optimizing Healthcare Environmental Hygiene?

8

Philip C. Carling

Introduction

As a result of epidemiologic and microbiologic studies over the past decade, it has become increasingly evident that interventions to mitigate environmental surface pathogen contamination constitute an important component of healthcare-associated infection (HAI) prevention. It has now become widely appreciated that, "Cleaning of hard surfaces in hospital rooms is critical for reducing healthcare-associated infections" [1] (p. 598). Indeed, as noted by the directors of the Duke Prevention Epicenter Program, "the contaminated hospital environment has emerged as a key target area to prevent the spread of HAIs" [2] (p. 872).

Preliminary studies documenting patient zone surface contamination with healthcare-associated pathogens (HAPs) more than a decade ago raised concerns that cleaning practice should be improved [3]. It was not until actual cleaning practice was objectively monitored, initially using a covert visual monitoring system [4] and later with covertly applied fluorescent markers [5], that actual cleaning practice itself was objectively evaluated [6, 7]. The discovery that near-patient surfaces, also referred to as patient zone surfaces, in many acute care hospitals and other healthcare settings were not being disinfection cleaned according to hospital policies [7], along with the landmark study by Huang et al. [8] which quantified the risk of MRSA and Vancomycin-resistant enterococci (VRE) acquisition posed by occupying a room previously occupied by a patient colonized or infected by these pathogens that the clear risk of suboptimal disinfection cleaning became widely appreciated. Eight similar studies have now confirmed an average 120% increased risk of the subsequent occupant becoming colonized or infected with MRSA, VRE, *Clostridium difficile* (CD), *Pseudomonas*, and *Acinetobacter* [9].

Shortly after confirming the sensitivity and specificity of the covert use of fluorescent markers to objectively and reproducibly identify opportunities to improve terminal cleaning thoroughness, process improvement interventions based on structured educational activities and direct performance feedback to environmental services (EVS) staff were shown to be highly effective in improving cleaning thoroughness [10]. Published reports have now confirmed the effectiveness of such programs in more than 120 hospitals in the United States, Canada, and Australia [7]. In the study hospitals, not only has cleaning improved as demonstrated by the thoroughness of disinfection scores (proportion of objects cleaned relative to objects expected to be cleaned by hospital policy or TDC) increasing from approximately 40–60% to 80–90% or higher as a result of similar programmatic intervention, there has also been excellent sustainability of the results over at least 3 years where ongoing programs have been evaluated [11–13].

Several studies have now confirmed that improved environmental cleaning decreases HAP contamination of surfaces [4, 14, 15]. Although the complexity and cost of studies to evaluate the impact of decreased patient zone HAP contamination on acquisition have limited such undertakings, two landmark studies found similar statistically significant results. The 2006 study by Hayden confirmed a 66% ($p < 0.001$) reduction in VRE acquisition as a result of a 75% improvement in thoroughness of disinfection cleaning [4]. A more recent study by Datta found a 50% ($p < 0.001$) reduction in MRSA acquisition and a 28% reduction ($p < 0.02$) in VRE acquisition as a result of an 80% improvement in environmental cleaning [14]. The latter study also confirmed significantly decreased prior room occupant transmission for both pathogens during the intervention period. These studies clearly show that direct patient safety benefits can be realized by improving the thoroughness of patient zone surface disinfection cleaning.

Unfortunately, the complexity of the interrelated factors necessary to optimize the safety of surfaces in the patient zone remains an evolving challenge [7, 16]. Furthermore, defining how the impact of various surface cleaning interventions and optimized hand hygiene practice can be vali-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_8

Vertical approaches reduce risk of infections due to specific pathogens:
- Active surveillance testing to identify asymptomatic carriers
- Contact precautions for patients colonized or infected with specific organisms
- Decolonization of patients colonized or infected with specific organisms

Horizontal approaches reduce risk of a broad range of infections and are not pathogen specific:
- Standard precautions (e.g. hand hygiene)
- Universal use of gloves or gloves and gowns
- Universal decolonization (e.g. chlorhexidine gluconate bathing)
- Antimicrobial stewardship
- Environmental cleaning and disinfection

Fig. 8.1 Vertical and horizontal approaches to preventing healthcare-associated infections. (Reprinted from, Philip [7], with permission from Elsevier)

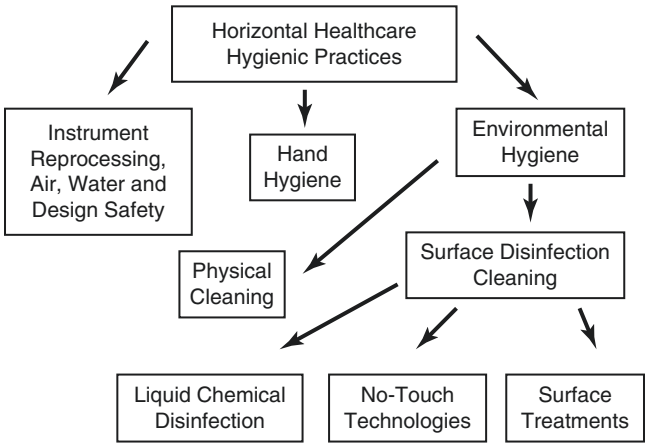

Fig. 8.2 Horizontal healthcare hygienic practices

dated to develop clinically grounded implementation guidance has yet to be substantially realized [7]. In this context, it is important to recognize that environmental hygiene represents a critical element of what Wenzel and Edmonds defined as "horizontal interventions" that are central to mitigating a wide range of HAIs [17]. These approaches aim to reduce the risk of infections caused by a broad range of pathogens by implementing standard practices that are effective regardless of patient-specific conditions (Fig. 8.1). In contrast to the horizontal interventions, "vertical interventions" are pathogen and/or condition specific. They remain important in defined settings and become most cost-effective when the indications for their use are clearly defined. While vertical and horizontal approaches are not mutually exclusive, there is evolving evidence that, in endemic situations, horizontal interventions represent a best use of HAI prevention resources [17]. Indeed, recent well-designed studies of horizontal interventions such as chlorhexidine bathing and decolonization as well as expanded use of contact precautions in intensive care units appear to have significant potential for HAI reduction, at least in certain settings [17].

In order to facilitate discussion of the many elements necessary to optimize healthcare hygienic cleaning, it is useful to put these interventions into a defined construct of HAI prevention activities. As noted in Fig. 8.2, hygienic cleaning and hand hygiene as well as interventions related to instrument reprocessing, air quality, water quality, and physical setting design are all horizontal interventions [7]. All of these horizontal interventions represent elements of "healthcare hygienic practice." While these elements have traditionally been discussed independently, their effectiveness in clinical settings is substantially interrelated, particularly environmental hygiene and hand hygiene, as will be discussed below. The term "environmental hygiene" with respect to healthcare can be defined as "cleaning activities directed at removing and/or killing potentially harmful pathogens capable of being transmitted directly from surfaces or indirectly to susceptible individuals or other surfaces." As such it consists of both the physical cleaning of surfaces and surface disinfection cleaning (Fig. 8.2). While liquid chemistries are well established as the most clinically useful approach to surface disinfection, innovative approaches which may have the potential for complementing traditional liquid chemistry have been developed over the past several years.

No-Touch Disinfection Environmental Hygiene Interventions Technologies

Prior to 2005, ultraviolet (UV) radiation devices had been used for the disinfection of endocavity ultrasound transducers and ventilation ducts [18] and hydrogen peroxide (HP) as a liquid disinfectant. The first detailed evaluation of the use of HP vapor to disinfect multiple patient rooms was reported in 2004 [19]. The documentation of suboptimal near-patient surface cleaning [3, 16] prompted more extensive evaluation of HP systems and the development of UV no-touch disinfection systems (NTDS) [20]. Both these technologies can only be used in closed spaces, such as vacated patient rooms or dedicated equipment closets. Currently there are two somewhat different forms of each technology [18, 20, 21]. Hydrogen peroxide vapor (HPV), the earlier technology, utilizes a generated vapor, 30–35% aqueous H_2O_2, which is characterized by small-particle generation [20]. Dry mist HP is pressure generated and combines 5–6% H_2O_2 with <50 ppm silver cations. UV-C technology utilizes a continuous mercury bulb-generated high-intensity light focused on a wavelength of 250 nm which is capable of damaging mitochondrial DNA [18]. Pulsed xenon UV technology utilizes pulses of high-intensity xenon-generated UV light [22].

Methods

PubMed was used to search the terms disinfection cleaning, hydrogen peroxide environmental disinfection, ultraviolet environmental decontamination, or environmental hygiene, between 2000 and 2016. Studies which were published in English in peer review journals were reviewed. Abstracts, conference proceedings, and review articles were not part of the evaluation process. Articles were also identified by hand-searching references in the reviewed articles. No financial support was received for this review. The review was performed in accordance with PRISMA recommendations [23].

In order to facilitate discussion of the studies that over the past decade have investigated both the in vitro potency and potential clinical roles of these NTDS, studies related to each system will be categorized using the CDC evidentiary hierarchy proposed by McDonald and Arduino in 2013 [24] (Fig. 8.3). Given the availability of Level I and III studies utilizing healthcare-associated pathogens, the limited number of Level II studies looking at simple (non-pathogen) heterotrophic bioburden reduction was not reviewed. Furthermore, this analysis of NTDS will relate exclusively to large (non-handheld) portable technology for which at least two clinical (Level IV or V) studies have been published in a peer-reviewed medical journal through December 2015.

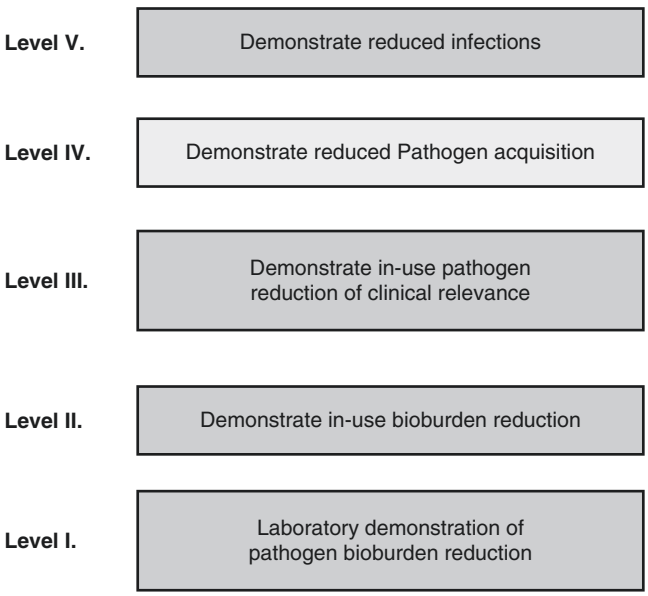

Fig. 8.3 Evidence hierarchy for healthcare environmental hygiene studies. (Adapted from McDonald and Arduino [24])

Hydrogen Peroxide No-Touch Systems (HP No-Touch Systems)

Level I HP Studies: Laboratory Demonstration of Meaningful Pathogen Bioburden Reduction (In Vitro Studies)

Both the HP vapor system (Bioquil) and the vaporized HP system (Steris) have shown a >6 $\log^{10}$ reduction (LR) of all vegetative bacteria and microbacterial pathogens evaluated as well as *C. difficile* spores [20]. Recent studies with a range of human viruses have confirmed HPV to be broadly viricidal [25]. While viricidal effectiveness does not appear to be impacted by high titers, studies have yet to determine the impact of organic load such as fecal material on viricidal efficacy [26]. Microbicidal efficacy is adversely impacted by both pathogen load and organic soil, but the impact has been incompletely quantified [27]. Given the fact that HP systems have been designed to be used only after surfaces are cleaned effectively prior to treatment, it is conceptually possible that the efficacy of these systems would be compromised in clinical settings where the thoroughness of disinfection cleaning is suboptimal. A recent report found that HPV decontamination was effective in killing both *C. difficile* spores and vegetative bacteria seeded onto cotton material, but potency and dose effectiveness needed to be evaluated further [25].

Level III HPV Studies: Demonstrate In-Use Pathogen Reduction of Clinical Relevance (In Situ Studies)

As noted in Table 8.1, nine studies have evaluated the impact of HPV technology on healthcare pathogen environmental contamination since 2004 [19, 28–35]. One of the studies employed a two-arm design, and the other eight evaluated the same clinical surfaces before and after HPV treatment. Rooms previously occupied by methicillin-resistant *Staphylococcus aureus* (MRSA)-colonized or MRSA-infected patients [6] or patients treated for *C. difficile* infection (CDI) [3] *Acinetobacter* (Ab) [1] were evaluated. Although not always quantified, all studies involved multiple rooms and 3–30 surfaces per room. The rate of pre-cleaning of surfaces contaminated with MRSA ranged widely (78%, 60%, 28%, 12%), possibly as a reflection of differences in the size of the areas cultured. As noted in Table 8.1, HPV treatment reduced or limited healthcare-associated pathogen (HAP) environmental contamination substantially in seven studies. In two studies, borderline significant [34] and non-

Table 8.1 Level III hydrogen peroxide vapor technology studies

Author year	Nature of study	Prior room occupant	Rooms studied	Surfaces per room	Intervention	Outcome
French (2004) [19]	Two-arm B/A Detergent B/A HPV	MRSA C/I	10 control	12	Control arm – P/P cultures in ten rooms cleaned with detergent	Control arm – 78% surface MRSA +, after detergent cleaning 74% +
			6 HPV		HPV arm – P/P cultures in nine rooms given HPV Tx	HPV arm 72% surface MRSA +, post-HPV Tx – 1%
Otter (2007) [28]	Before cleaning, after cleaning, after HPV	MRSA	12	15	Cultures done before cleaning, after cleaning with QAC, and after HPV Tx	Surface sites with MRSA decreased significantly from 60% to 40% and 3% following each intervention. VRE decreased similarly from 30% to 10% to 0%
Hardy (2007) [29]	Before cleaning, after cleaning, after HPV Tx	NA	Multiple ICU rooms	3	Cultures over 3 months pre-intervention after routine cleaning compared to HPV Tx	Just before the intervention after standard cleaning, 17% of sites showed MRSA Following HPV Tx, no sites were positive
Boyce (2008) [30]	Observational B/A HPV	CD	18	Multiple	"Intensive" HPV decontamination of CD patient rooms on five "high-incidence" wards	Pretreatment surface contamination rate of 25% fell to 0 immediately after HPV Tx
Barbut (2009) [31]	Two-arm comparison	CD	30	12–13	CD D/C rooms were randomized to 0.5% bleach (5000 ppm available chlorine) cleaning vs. HPV Tx	Contamination decreased by 50% after bleach and 91% after HPV treatment (p 0.005)
Otter (2010) [32]	Single culture B/A decontamination activity	MDR-GNB	ICU	Multiple sites combined	Pooled site cultures done before and after HPV Tx decontamination of an ICU	46% of areas were + for GNB (only two for MDR *Enterobacter*) before treatment and none after HPV Tx
Passaretti (2013) [33]	Observational B/A HPV	CD	12	18	Proportion of surfaces with MRSA, CD VRE, or MDRG-GNB before and after HPV Tx compared	Proportion of surfaces contaminated before and after HPV Tx were not significantly different
		MRSA				
		VRE				
		MDR-GNB				
Manian (2011) [34]	Observational B/A HPV	MRSA and/or Ab	Multiple	9–30	Room surface cultures before and after HPV Tx	MRSA and AB room surface contamination was low but decreased after HPV Tx for both organisms (p 0.04)
Dryden (2008) [35]	Observational B/A HPV	MRSA	Single ward	Not stated	Room surface cultures before and after HPV Tx	MRSA contamination of surfaces decreased from 28% before to 10% after HPV Tx, but was not significant (p 0.2)

significant [33] reduction of target pathogens were noted. In the only study which compared HPV to bleach, the intervention did decrease CD environmental contamination in rooms from 12% of surfaces following bleach cleaning to 2% with HPV treatment (p 0.005) [31].

Level IV HPV Studies: Demonstrate Reduced Pathogen Acquisition

As noted in Table 8.2, there has been only one study to evaluate the impact of an HPV program to decrease HAP acquisition [33]. Passaretti et al. used weekly screening cultures to measure MRSA and VRE acquisition in three surgical intensive care units compared with three control units during a 30-month study. While VRE acquisition decreased significantly from 8.1% to 1.7% of at-risk patients ($p < 0.01$), MRSA acquisition decreased nonsignificantly from 2.8% to 0.9% ($p = 0.30$). The findings of the study are particularly difficult to interpret given the fact that chlorhexidine bathing and "multiple" HAI prevention interventions were initiated during the course of the study and may have had an impact on the findings.

Level V HPV Studies: Demonstration of Reduced Infections

As noted in Table 8.3, three studies have evaluated the addition of HPV treatment to routine disinfection cleaning with

Table 8.2 Level IV hydrogen peroxide vapor technology studies

Author year	Endemic setting	Clinical outcome	Pre-int mo.	Post-int. mo.	Outcome	Confounder evaluated
Passaretti (2013)	Endemic	Rectal VRE nasal MRSA	12 months	18 months three units HPV on D/C three units studied	VRE acquisition decreased from 8.19% to 1.7% ($p < 0.01$). MRSA acquisition decreased from 2.8% to 0.9 (p 0.3)	A dedicated HPV team led to 71% of eligible rooms being treated
						Multiple infection control interventions implemented during the 30-month period including CHG bathing

Table 8.3 Level V hydrogen peroxide vapor technology studies

Author year	Endemic setting	Clinical outcome	Pre-int mo.	Post-int. mo.	Outcome	Confounder evaluated
Manian (2013) [34]	Yes	HA-CDI	24 months bleach	11 months enhanced bleach (four cycles) or HPV	HA-CDI rate of 8.8 decreased to 5.5 during the intervention period ($p < 0.0001$)	Patient days (stable)
						HH (stable)
						Isolation precaution compliance (stable)
						Antimicrobial use – Zosyn increased while clindamycin and cephalosporin use decreased
						Personnel – HPV technicians one or more
Boyce (2008) [30]	No	HA-CDII	9 months bleach	9 months	HA-CDI rates before intervention on five units were between 10 and 30 cases/10,000 PTD (mean 28) which decreased to 2.5–20/10,000 PTD (Mean 1.3) ($p = 0.05$)	No significant difference in antimicrobial use, but linear regression analysis showed a significant correlation with third-generation cephalosporin use
						No changes in IC P/P
						No differences in HH or CP
						No difference in NAP – 1 prevalence
Passaretti (2013) [33]	No	HA-CDI	12 months non-bleach	3 months	HA-CDI incidence decreased HPV Tx. units decreased from 27/10,000 PTD to 10/10,000 PTD but was not significant ($p = 0.19$)	See Passaretti (Table ___)
Chmielarczyk (2012) [36]	No	MDR AAb	18	12	Incidence density resolved from 24/1000 PTD to zero during the program	A combination of infection prevention initiatives was implemented (Not described in detail)
Horn (2015) [37]	Yes	Pathogen "rate"/1000/PTD	12	12	Rates (not defined) decreased significantly for CD, VRE, and MDRO-GNB but not for MRSA	Hand hygiene improved significantly from 78% before to 89% during the intervention with HPV Tx ($p < 0.001$)
Fishner (2016) [38]	No	VRE	55	28	Modeling analysis showed decreased VRE infection/colonization	Increased active surveillance and isolation practices
						The use of cleaning improved from 60% at baseline to >79% during the study period ($p < 0.001$)
						Increased educational interventions

bleach on healthcare-associated CDI (HA-CDI) rates during intervention periods between 3 and 11 months [30, 33, 34] and three others evaluated MDR Ab, VRE, and "pathogen rates" [36–38]. Unlike other studies discussed below, the pre-intervention HA-CDI rate of 8.8/10,000 PTD in the study by Manian was similar to that seen in many acute care

hospitals. While the addition of HPV in this report was associated with a significant decrease in HA-CDI from 8.8 to 5.5/10,000 PTD ($p < 0.001$), the fact that just prior to the addition of the HPV intervention program 21% of the rooms had undergone four serial cycles of bleach cleaning and the fact that only 53% of eligible rooms received HPV treatment suggests that the modest improvement in HA-CDI may have been multifactorial. Although not discussed by the authors, the substantial increase in piperacillin–tazobactam use might have also had a favorable impact on HA-CDI rates during the intervention period. HO-CDI rates in the other two studies of 27 and 28/10,000 PTD were quite high [30, 33]. While the two studies in settings with very high HA-CDI rates observed a decrease in incidence in cases following implementation of the HPV programs, the statistical significance of the change was borderline ($p = 0.05$) in the report by Boyce [30] and not statistically significant in the report by Passaretti [33] ($p = 0.19$). Fishner evaluated VRE colonization/infection noting that it was lower during a 28-month study of HPV use than during the preceding 55 months, but multiple other interventions were implemented during the HPV study period [38]. While Chmielarczyk in 2012 reported that overall MDR Ab incidence density decreased dramatically during an HPV intervention program, the impact of a "combination of rigorous infection control measures" most probably impacted the observed change in Ab rates [36]. Horn in 2015 attributed decreased rates of several HAPs to an HPV program during which an average of only two rooms a day in the 270-bed hospital received HPV treatments [37]. Given the limited nature of the intervention and the observation that hand hygiene increased very significantly during the intervention period, it would appear difficult to attribute the changes substantially to the HPV program.

Summary of Hydrogen Peroxide Vapor Disinfection Studies

Extensive testing of HPV environmental disinfection systems has confirmed in vitro (Level I) effectiveness in killing all tested vegetative microorganisms, viruses, and spores evaluated. While incompletely quantified, the observation that high titers of microbes/spores as well as organic material can decrease the potency of HP disinfection reinforces the importance of cleaning of environmental surfaces prior to HP treatment. The impact of HPV treatments on environmental pathogen contamination in clinical settings (Level III) has been evaluated in nine reports over the past 12 years (Table 8.1). Although most studies reported substantial or complete resolution of environmental contamination after HPV treatment, two studies failed to show a significant decrease in the proportion of surfaces still contaminated with the target organism during the HPV treatment program [33, 35]. While not directly evaluated in the latter report, the documentation by Hardy and Dryden that HPV-treated surfaces can quickly become recontaminated [29] raises the possibility that the findings of the study by Passaretti may have been adversely impacted by recontamination during the study, particularly since 30% of eligible rooms did not receive HPV treatment. The only study which objectively measured actual acquisition during an ICU admission (Level IV) observed significantly decreased VRE ($p < 0.01$) but not MRSA ($p = 0.30$) acquisition [33]. While these findings could have been a reflection of different routes of acquisition, it is of note that Datta in 2011, in the only other large study to analyze the impact of an environmental disinfection intervention on HAP acquisition, observed a highly significant ($p < 0.001$) decrease in MRSA with only borderline significant ($p < 0.02$) decrease in VRE acquisition in response to objectively improved standardized ICU disinfection cleaning [14]. Six studies evaluated clinical outcomes (Level V) before and after implementing HPV programs (Table 8.3). In the single study that reported a highly significant impact on HA-CDI, the actual endemic HA-CDI rate only fell slightly from 8.8 to 5.5/10,000 PTD. As discussed above, improving environmental hygiene and hand hygiene precluded accurate assessment of the HPV technology and may have substantially impacted two of the reports evaluating clinical outcomes following the implementation of HPV programs [36, 38].

Ultraviolet No-Touch Systems

Level I Studies: Laboratory Demonstration of Pathogen Bioburden (In Vitro Studies) Reduction

Eight studies have evaluated the in situ effectiveness of UV-C systems, and one study evaluated PX-UV technology for killing CD spores, MRSA, and VRE [22, 39–45]. One study each also evaluated the potency of UV-C against *A. baumannii*, and one study evaluated *Aspergillus* species (Table 8.4). All studies used 3–6 log ^{10} organisms dried onto stainless steel or *Formica* discs which were then exposed to varying doses of UV light for 10–90 min. Between one and ten strains of test organisms were evaluated in each study. No study which evaluated multiple strains disclosed any significant difference in sensitivity to UV light between strains of the same pathogen.

UV-C – As summarized in Table 8.4, each of the seven studies evaluating UV-C technology found three to four LR reduction of vegetative bacteria with UV intensity settings between 12,000 and 36,000 uWs/cm^2 and exposure times between 15 and 73 min. Similar exposure led to a two to three LR of CD spores. Mahida reported that an exposure time (distance not documented) of 60–90 min led to a greater

Table 8.4 Level I ultraviolet technology studies

Author year	Device	Pathogen (strains tested)	Inoculum log^{10}	Distance	Dosage uWs/cm^2	Duration (minutes)	Log^{10} reduction (LR)	Log^{10} reduction shaded
Rutala (2010) [39]	UV-C	MRSA [10]	4.9	NS	12,000	15	4.3	3.9
		VRE [10]	4.4	NS	12,000	15	3.9	3.2
		AB [10]	4.6	NS	12,000	15	4.2	3.8
		CD [10]	4.1	NS	36,000	50	4	2.4
Nerandzic (2010) [40]	UV-C	CD [3]	3–5	20″–10.5′	22,000	45	2.3	
		MRSA [3]	3–5	20″–10.5′	22,000	45	3	
		VRE 3	3–5	20″–10.5′	22,000	45	3.5	
		CD	3–5	20″	22,000	45		1.0
Boyce (2011) [41]	UV-C	CD	5	NS	22,000	NS	1.7–2.9	
Havill (2012) [42]	UV-C	CD	6	NS	22,000	73	2.2	
Mahida (2013) [43]	UV-C	VRE	NS	NS	22,000	60–90	>4	(3.5)
		AB	NS	NS	22,000	60–90	>4	(3.0)
		Aspergillus	NS	NS	22,000	60–90	>4	(1.0)
Nerandzic (2014) [44]	UV-C (two machines)	CD [2]	5	4′	NS	40	3	
		MRSA [2]	5	4′	NS	40	4	
		VRE [2]	5	4′	NS	40	5	
		CD [2]	6	4′		10	<1	
		MRSA [2]	6	4′		10	3	
		VRE [2]	6	4′		10	4	
Nerandzic (2015) [22]	PX-UV	CD [2]	3–5	4′	NS	10	0.5	
		MRSA [2]	3–5	4′	NS	10	1.85	
		VRE [2]	3–5	4′	NS	10	0.6	
	PX-UV	CD [2]	5	6″, 4′,10′	NS	10	1.8, 0.5, 0.25	
		MRSA [2]	5	6″, 4′, 10′	NS	10	33, 1.8, 0.7	
		VRE [2]	5	6″, 4′, 10′	NS	10	2.5, 0.5, <0.2	
	UV-C	CD	5	4′	NS	10	1.0	
		MRSA	5	4′	NS	10	3.0	
		VRE	5	4′	NS	10	3.5	
Zhang (2013) [45]	UV-C	CD [7]	6	10.5′	22,000	45	4.5	
		CD	6 + 10% calf serum	10.5′	22,000	45	3.0	
		CD [3]	6 + 5% calf serum	10.5′	22,000	45	3.5	
		CD [5]	6+ light organic load	10.5′	22,000	45	4.5	
		CD	6+ moderate organic load	10.5′	22,000	45	<4.5 ($p = 0.01$)	

than four LR of VRE, AB, and *Aspergillus* sp. [43]. Havill documented only a 1.7–3.0 LR of CD spores exposed to high-dose UV-C for 73 min [42]. Using a 10-min exposure, Nerandzic found a somewhat decreased potency against vegetative bacteria but a substantial decrease in CD killing with only a one LR at a 4-ft. exposure distance [22]. Several stud-

ies found that shading had a significantly adverse impact on killing, particularly for *C. difficile* spores [39, 40, 43]. Even at short distances (20 in.) LR fell from 2–3 to 1.0 as a result of shading in the 2010 study by Nerandzic [40]. Similarly shading decreased LR from 4 to 2.4 despite very high intensity (39,000 uWs/cm^2) and a long exposure time (50 min) in the 2010 study by Rutala [39], while the study by Zhang documented significantly decreased killing UV-C of CD spores with dilute (10%) calf serum and "heavy" organic loads ($p < 0.001$ and $p = 0.01$) [45]. Lesser amounts of organic material led to no loss in LR compared to controls. To date there have been no additional studies using full-strength human serum, blood, or fecal material to further evaluate these preliminary findings. Although only evaluated by Mahida, it is of note that shading greatly decreased the LR of *Aspergillus* sp. using an exposure time of 60–90 min [43]. Given the importance of fungal pathogens in high-risk patient areas, it will be important to further evaluate UV-C's efficacy against these pathogens.

PX-UV – Only one published study, by Nerandzic, has evaluated the potency of this type of UV disinfection system in comparison to UV-C [22]. The authors found only limited (0.6–2) LR for MRSA and VRE at 4 ft. and <1 LR for CD spores at 4 and 10 ft. Furthermore, at a distance of 6 in, LR was only 3.3 for MRSA, 2.5 for VRE, and 1.8 for CD. In addition, this study also showed the dramatic adverse impact of distance from the unit which was greater for CD spores than for MRSA and VRE.

Level III UV Studies: Objectively Demonstrate Clinical Relevance (In Situ Studies)

As outlined in Table 8.5, there have been eight studies evaluating the impact of UV technology on healthcare-associated pathogen environmental contamination since 2010 (UV-C, 3; PX-UV, 5) [15, 22, 39, 40, 45–49].

UV-C – The three studies evaluating pathogen bioburden reduction with UV-C evaluated individual rooms primarily occupied by MRSA-infected or MRSA-colonized patients or CD-treated patients prior to and following UV treatment. In 2010, Rutala found only 9.5% of ten surfaces still contaminated with MRSA after UV-C treatment in comparison to 20% prior to routine cleaning ($p < 0.001$) [39]. Similar results were noted for VRE but not described. Contaminated CDI patient rooms were not studied and a vegetative microbicidal, not sporicidal, UV cycle of 15 min was utilized. Similar results were noted by Nerandzic for MRSA and VRE with a borderline significant decrease in CD contamination using a 45-min "sporicidal" UV treatment cycle [40]. In 2013, Sitzlar and associates described a three-phase clinical intervention which compared terminal cleaning following educational interventions, the addition of a UV-C cycle to standard terminal disinfection with bleach, and the use of a special team for daily and terminal cleaning of CD-infected patient rooms [15]. While the addition of UV-C treatment during phase III decreased residual contamination in comparison to phase II, 35% of surfaces remained CD culture positive after UV-C treatment. Subsequently with a dedicated cleaning team intervention utilizing daily cleaning, residual *C. difficile* contamination was eliminated from the study rooms during the final 2 months of the program.

PX-UV – Two of the five PX-UV studies utilized a two-arm evaluation of environmental pathogen reduction in treated rooms vs. routinely disinfected rooms [47, 49]. The other three studies were uncontrolled measurements of pathogen prevalence on between 5 and 11 surfaces before and after treatment in the same rooms. Two studies utilized rooms previously occupied by patients treated for CDI, two studies by MRSA-colonized or MRSA-infected patients, and one VRE study by colonized or infected patients. All but one of these studies performed environmental cultures only for the pathogen associated with the prior room occupant. As noted in Table 8.5, outcomes reported by the authors varied between studies. Stibich evaluated VRE contamination but failed to find a significant difference in the treated vs. routinely cleaned rooms [46]. A study by Ghantoji compared PX-UV to bleach disinfection for CDI patient rooms and noted no significant difference between the interventions [49]. Jinadatha documented a borderline significant decrease in MRSA colony counts per site before and after treatment but no clear difference in the number of contaminated sites [48]. Nerandzic compared bleach disinfection to PX-UV treatment in CDI-associated contaminated rooms and found no difference in the proportion of sites still contaminated with *C. difficile* spores following either treatment [22].

Level V UV Studies: Demonstrate Decreased Infections

Over the past 3 years, there have been five published studies which evaluated the clinical impact of NTDT UV technologies (UV-C, 1; PX-UV, 3) [50–54]. As outlined in Table 8.6, all studies were uncontrolled retrospective before and after (quasi-experimental) in design. Of the three CDI studies, two were in epidemic setting with rates of 23.3 and 18.3/10,000 PTD [53, 54] and one in a high-level endemic setting with a rate of 9.22/10,000 PTD [50]. Several of the studies inconsistently noted possible confounders whose impact on observed outcomes was not directly evaluated. The specific limitations of these studies will be discussed in a subsequent portion of this review.

UV-C – In the single study evaluating the clinical impact of a UV-C disinfection intervention program, Napolitano compared "overall HAI rates" during a 6-month pre-

Table 8.5 Level III ultraviolet technology studies

Author year	System	Nature of study	Prior room occupant	Rooms studied	Surfaces per room	Intervention	Outcome
Rutala (2010) [39]	UV-C	Observational P/P	MRSA	NS	10	UV-C treatment 15 min before cleaning	MRSA-positive sites decreased from 81/4000 (20%) to 4/400 (0.5%) ($p < 0.001$). Similar results were noted for VRE (data not shown)
Nerandzic (2010) [40]	UV-C	Same room P/PTX	MRSA I/C (59 rooms) CDI treated (seven rooms)	66	4	No pre-cleaning UV-C treatment 20–45 min depending on size of room	MRSA 10% of surfaces before and 0.8% of surfaces after UV-C Tx ($p < 0.0001$) VRE 2.7% positive before and 0.38% after Tx (p 0.07) CD 3.4% before 0.38% after Tx (p 0.02)
Sitzlar (2013) [15]	UV-C	Observational P/P	CDI	20–25	Multiple standard sites	Four phases Baseline, terminal cleaning Education and positive feedback; terminal UV-C added, special team cleaning	Addition of UV-C treatment decreased but did not eliminate CD from 35% of surfaces. During final phase increased daily cleaning eliminated CD from tested surfaces
Stibich (2011) [46]	PX-UV	Observational P/P	VRE I/C	12	11	Routine cleaning with QAC followed by PX-UV Tx – three positions 4 min each	No significant impact of PX-UV on VRE contamination in comparison to standard cleaning with QAC (p 0.13)
Jinadatha (2014) [47]	PX-UV	Two arms	MRSA I/C	10 per arm	5	Control arm – 1:10 bleach routine cleaning Intervention arm – 1:10 bleach for visible soil plus PX-UV 15 min	MRSA contamination was found on 86% of sites prior to intervention and 76 in the two-arm study; manual cleaning decreased contamination to 16% in the control arm and 8% in the treatment arm (p 0.23)
Nerandzic (2015) [22]	PX-UV	Observational P/P	CDI	16	7	Cultures for CD, MRSA, and VRE before cleaning and after routine bleach cleaning + PX-UV-C 25-min cycles <3 sect from cultured sites	While CD+ sites decreased by 50% (p 0.34), the difference was not significant and may have been in part due to bleach cleaning
Jinadatha (2015) [48]	PX-UV	Observational P/P	MRSA	14 confirmed >1 site + MRSA	5	PX-UV three locations for 5 min	Mean colony count per site decreased from 5.7 to 4.3 after treatment ($p < 0.01$)
Ghantoji (2015) [49]	PX-UV	Two arms	CDI treated	15 per arm	5	Intervention arm: activated HP for visible soil + PX-UV three locations each <3′ for unit for 5 min each	35–40% of surfaces + for CD pre-intervention in both arms. Both methods equal in reducing positive cultures

intervention period followed by a 5-month evaluation period [52]. Average HAI incidence decreased minimally from 3.7 to 2.4/1000 PTD. Although HA-CDI decreased from 12.3 to 6.6/10,000 PTD, no impact on either MRSA or VRE infections was noted. During the study, 70–100% of available discharge rooms were treated by three UV system technicians.

PX-UV – In 2013, Levin described the use of a PX-UV system on 73% of patient rooms previously occupied by individuals treated for CDI [50]. A single machine was used to deliver three cycles for 7 min each, two in the patient room and one in the bathroom. Pre-intervention, the HO-CDI rate had been stable at 9.22/10,000 PTD for 30 months. Following intervention, the rate decreased moderately to 4.5/10,000 PTD during the following 12 months ($p = 0.01$). Haas evaluated overall HAI rates comparing 30 months before and 22 months after intervention using a PX-UV system on 76% of contact precaution patient rooms [51]. The authors note that they also had implemented "multiple" other infection prevention interventions during the study period (not described). The overall HAI rate decreased minimally but significantly from 2.7 to 2.1/1000 PTD. In 2015, Miller reported a decrease in HO-CDI from 23.3 to 19.3/10,000 PTD following "improved emphasis on environmental hygiene." The rate subsequently fell further to 8.3/1000 PTD

Table 8.6 Level V ultraviolet technology studies

Author year	System	Endemic setting	Clinical outcome	Pre-int. Mo.	Post-int. mo.	Outcome	Confounder noted
Levin (2013) [50]	PX-UV	High-level endemic	HA-CDI	36	12	Pre-intervention HA-CDI of 9.22 decreased to 4.5/10,000 PTD (p 0.002)	CA-CDCI (stable)
							Intervention use – 56% of CDI rooms
							Hospital PTD (stable)
							MCCMI (stable)
							Quinolone use (stable)
Haas (2014) [51]	PX-UV	Yes	HAI	30	22	HAI average incidence decreased to 21% from 2.7 to 2.11/1000 PTD	76% of CD rooms treated. Multiple infection control interventions implemented serially during the >4 years studied. Cleaning thoroughness monitored but not reported
Napolitano (2015) [52]	UV-C	Yes	HAI (not defined)	5	6	HAI incidence 3.7/1000 PTD before to 2.4 after program but no impact noted on MRSA and VRE rates	Personnel added – 3 UV-C technicians
Miller (2015) [53]	PX-UV	No	HA-CDI	12	12	HA-CDI decreased from 23.3 baseline to 19.3/10,000 PTD with increased focus on EH. Following additional PX-UV, the rate declined to 8.3/10,000 PTD over the next 12 months	Hand hygiene did not change over time
Nagaraja (2015) [54]	PX-UV	No	HA-CDI	12 months	12 months	Hospital-wide HA-CDI pre-intervention rate of 10.6/10,000 PTD fell to 8.6 (not significant), but the ICU rate decreased from 18.3 to 5.5 ($p < 0.001$)	Admission CDI incidence increased to 18% during the intervention phase
							New ES coping contract implemented 3 months before intervention. Fifty percent of CDI rooms treated

during a 12-month period following the addition of a PX-UV program [53]. In 2015 Nagaraja reported that the implementation of a PX-UV program decreased the incidence of HA-CDI from 18.3 to 5.5/10,000 PTD ($p < 0.001$) in the intensive care unit but did not significantly impact the overall HO-CDI rate for the hospital [54].

Summary of UV Disinfection Studies

As outlined in Table 8.4, Level I studies of UV technology have clearly defined the relative microbicidal potency of both UV-C and PX-UV systems. The most recent studies have confirmed the substantial and significant adverse impact of both shading and distance from the light source with UV technologies. While reflective paint [53] and modifications in light source placement within the rooms as well as cycle duration modification might affect these limitations, these possibilities await further investigation. Taken together, the in vitro studies of UV-C technology document that the effectiveness of the tested machines increased moderately with greater light intensity and duration of exposure. Conversely, potency decreased moderately to substantially with shading, especially for CD spores. While UV-C LR for vegetative pathogens was consistently in the three to four range with direct exposure, impact on CD spores was clearly less and varied quite widely (<1, 1.0, 1.7, 2.2, 2.3, 2.9, 3.0, 4.0). Although only evaluated in the 2014 study by Nerandzic using two machines, the wide range in CD spore LR suggests that there may be significant differences in the potency of different UV-C machines. Furthermore, it is of note that the only study that found a four LR of CD spores used a very high dosage of UV light (36,000 uWs/cm^2) and a long exposure time (90 min) [39].

The only published Level I study of P-UV by Nerandzic et al. raises serious concerns regarding the potency of the technology when tested against log 10^5 vegetative organisms and spores and compared to UV-C treatment [44]. The

authors also found a particularly striking fall off in PX-UV LR with increasing distance from the light source. Killing was similar to UV-C at 6 in., about half as potent at 4 ft. and minimal at 10 ft. from the light source. Although LR for VRE was similar to MRSA in the UV-C studies cited, VRE was found to be less sensitive to PX-UV in this study. Although the UV-C studies by Rutala and Nerandzic described a significant impact of UV treatment with fairly short treatment cycles (45 and 15 min, respectively), it is of note that pre-cleaning was not performed in either study [39, 40]. While it might be suggested that such modeling could relate to settings where routine terminal disinfection cleaning is not being performed thoroughly, the study design, for this reason, likely overestimated the relative impact of the UV-C treatment in the clinical setting where 40–60% of surfaces were cleaned during terminal cleaning in nonperformance optimized hospital settings [7].

With respect to the impact of UV-C systems on in situ patient room contamination (Level III), Rutala (2010) found that treatment reduced MRSA surface contamination prior to disinfection cleaning [39]. Using a similar study design, Nerandzic, with a 20–45 a minute UV-C treatment cycle, noted that both MRSA and VRE contamination were decreased but surfaces had a low prevalence of pretreatment contamination (MRSA, 10%; VRE, 2.7%) [40]. Treatment employing a PX-UV system in a heavily MRSA-contaminated environment was found by Jinadatha to be equivalent to cleaning with bleach [47]. The two studies evaluating the impact of PX-UV on surface contamination with *C. difficile* and VRE found equivalence but no advantage in comparison to bleach cleaning [22, 49]. While the Sitzlar study found that adding UV-C to routine daily cleaning was associated with a decrease in *C. difficile* contamination, 35% of surfaces remained contaminated after treatment in the setting of low-level thoroughness of routine daily cleaning. Subsequently daily cleaning by a dedicated team eliminated *C. difficile* environmental contamination from patient room surfaces during the final 2 months of the study [15].

Since 2013, five Level V studies have retrospectively evaluated the impact of UV treatment in acute care hospitals (HAI rates, 2; HO-CDI, 3) [50–54]. None of the three studies of PX-UV evaluating patient room MRSA, VRE, or CD found a substantial impact on pathogen contamination in comparison to "standard" (not objectively measured) disinfection cleaning [51, 53, 54]. Given the fact that the improvement in the studies with very high rates of HA-CDI may have substantially reflected a regression to the mean phenomenon and that two of the studies in endemic settings employed multiple other infection control interventions during the study, it becomes quite difficult to draw clinically generalizable conclusions regarding the clinical relevance of these studies. While the UV-C study of endemic HAI rates by Napolitano found that a decrease from 3.7 to 2.4/1000 PTD in association with implementing a UV-C disinfection program was consistent with an effect of the program, the finding that neither MRSA nor VRE HAI rates decreased is difficult to explain [52]. Intrinsic study design limitations that further compromise evaluation of the clinical relevance of these Level III and V studies will be discussed below.

Assessment of the Limitation of Published Clinical Studies

Level III Studies

Given the well-documented finding that environmental surface contamination with HAPs including MRSA, VRE, CD, Ab, and GNB is substantially and quantitatively impacted by disinfectant cleaning, it is of particular note that only one Level III study used an objective monitoring system to quantify the thoroughness of disinfection cleaning against which the NTDT system was being evaluated [22]. Since no Level III study utilized a sham machine control, it is quite conceivable that the thoroughness level of disinfection cleaning either increased or decreased during the intervention phase of the study. While the three studies of UV-C technology studies and seven of the nine HPV studies evaluated uncleaned rooms, the relevance of the findings of these studies is difficult to relate to a clinical setting where complete bioburden elimination was realized for 40% of surfaces objectively cleaned with a quaternary ammonium compound and 77% of surfaces cleaned with a novel sporicidal disinfectant in a clinical setting [55].

Level IV and V Studies

In the context of the intrinsic limitations of quasi-experimental studies [56] and given the limited and often incomplete assessment of evaluable confounders in these 11 reports, it is quite plausible that confounders had an impact on the veracity of what appeared to be an effect of the tested technology. Table 8.7 presents a summary of the manner in which confounders related to disinfection cleaning intervention studies were and were not analyzed in the Level V studies. In the analysis which follows, if a specific confounder was considered but not objectively quantified or specifically evaluated, it was categorized as a "limited" assessment in Table. As outlined, eight factors were recognized in at least one of the 11 Level V reports as representing significant quantifiable confounders with potential impact on measured outcomes. Of the 11 studies, 64% described changes in

Table 8.7 Confounder evaluation pre-/post-intervention in 11 Level V NTDT studies (2004–2016)

Confounder	Objectively evaluated	Limited evaluation	Not evaluated
Changes in infection prevention interventions	7/11 (64%)	2/11 (18%)	2/11 (18%)
Compliance with planned intervention use	6/11 (55%)	3/11 (27%)	2/11 (18%)
Admission incidence density	3/11 (27%)		8/11 (73%)
Hand hygiene compliance	3/11 (27%)		8/11 (73%)
Isolation practice compliance	2/11 (18%)		9/11 (82%)
Thoroughness of disinfection cleaning	2/11 (18%)		9/11 (82%)
Antibiotic use trends	1/11 (9%)	2/11 (18%)	8/11 (73%)
Case mix	1/11 (9%)		10/11 (91%)

infection control practice between pre- and post-intervention periods. While two of the studies describing this confounder noted no changes in their programs, in five (71%) of the reports, interventions were described by the authors as "multiple" (2), "several initiatives" (1), a "multidisciplinary intervention" (1), and an "intervention bundle" (1). Although these enhancements to routine infection prevention and environmental cleaning practices were described in varying detail, the authors clearly believed the enhancements were substantive, yet none of the discussion portions of the manuscripts considered the substantial possibility that such broadly improved infection prevention activities may have impacted the outcomes they attributed to the NTDT program. Evaluation of compliance with the use of the planned NTDT intervention was reported for 6 of 11 (55%) studies. In these studies, use of the NTDT program averaged 66% (range 53–93%). Hand hygiene compliance was objectively evaluated in three studies (27%). A significant improvement was noted in one study ($p < 0.001$) [37] and was without change in the other two. None of the eight other studies considered or evaluated hand hygiene as a confounder. Given the known impact of the thoroughness of disinfection cleaning on HAP acquisition [4, 14, 16], it is of note that 9 of 11 (82%) studies failed to consider the probability that routine thoroughness of disinfection cleaning could have impacted the objective clinical evaluation of the NTDTS. Although one report describing the use of nonstandardized fluorescent marker monitoring found that thoroughness of cleaning had improved significantly from 60% to 78% in association with an HPV program intervention ($p < 0.001$), the relevance of this observation was not discussed by the authors [35]. The other study which evaluated the thoroughness of cleaning used a standardized fluorescent marking system but did not describe the results of the monitoring [38]. While the impact of changes in antibiotic use was thoroughly evaluated in one study [29] and to a limited degree in two other studies, no consideration of the potential impact of changes in antibiotic use on the index HAI prevalence was evaluated in the remaining eight studies (83%). As noted in Table 8.7, only a limited number of studies considered other relevant confounders, including admission incidence density, isolation practice compliance, and case mix.

While the phenomenon of regression to the mean is an intrinsic limitation of single-site quasi-experimental evaluations of NTDTs, the fact that 5 of 11 studies (45%) were described as interventions implemented to address specific pathogen "outbreaks" and 3 others were associated with very high pre-intervention rates of HO-CDI substantially limits the generalizability of the findings of these reports. In addition, the use of overall HAI rates in three studies likely affected the analysis of the apparent impact of NTDTs since urinary tract infections and many surgical site infection rates would not have been substantially impacted by the effectiveness of environmental hygiene practices.

Conclusions

Despite the substantial antimicrobial potency of HPV on both vegetative pathogens and spores, it is concerning that in the five clinical (Level III, IV, V) studies published over the past 12 years, consistent clinical effectiveness commensurate with the potency of the technology has not been clearly confirmed. While several of the nine studies evaluating the impact of HPV on surface pathogen contamination observed an impact on contamination, two of the studies did not [33, 35]. Despite the implementation of a dedicated technician-supported HPV program as well as a broad-based environmental hygiene initiative, it is of note that an extensive and well-controlled program documented only a modest decrease in VRE acquisition but not in MRSA acquisition [33]. While the six Level V studies of HPV observed what may have, in part, been a response to the HPV program, the limitations of study design and the limited evaluation of the impact of confounders as well as intrinsic design limitations preclude defining a role for the routine use of this technology in endemic HAI settings based on published reports.

Level I in vitro studies of UV technology have clearly documented both the effectiveness and limitations of UV-C and PX-UV. Given the particular challenge of killing CD spores with UV systems, it is unfortunate that none of the three studies evaluating a program's impact on HO-CDI were in other than epidemic or high-level endemic settings [50, 53, 54]. Given the limited measureable impact of the UV programs described as well as limitations in study design and oversights in confounder analysis, it must be concluded

that the published literature in this area has yet to provide clear support for the use of UV technology in clinical settings.

Taken together, the fact that less than one-third of confounders were objectively evaluated, the fact that most (64%) of the studies implemented a broad range of activities to improve infection prevention interventions along with the NTDT program and the fact that 8 of 11 (83%) studies were carried out in outbreak or high-rate HAI settings all limit the feasibility of defining a role for these technologies in clinical practice, particularly in endemic settings.

Recommendations for Future Studies of Environmental Hygiene Interventions

In light of this review of both study design limitations and the relatively inconsistent clinical impact of the NTDT studies reported to date, it is evident that further studies of these technologies will be needed before their role in HAI prevention can be objectively defined. While advanced-level study design would be most valuable [24] given the complexity and cost of such studies, the importance of optimizing quasi-experimental studies must be considered. Given the fact that some intrinsic limitations of such studies are unavoidable even with the use of interrupted time series design, crossover studies, and multisite studies which intrinsically have the potential for significantly nullifying undefined confounders, well-designed studies which directly and objectively compare environmental hygiene interventions could prove to be very informative [7, 16, 57, 58]. Aside from the elements noted in Table 8.8, unique issues such as selection bias, physical plant alterations, and changes in personnel resources will need to be evaluated as potential confounders in future clinical studies of NTDT. Study design issues specifically related to Level III studies would include environmental culturing methods which are standardized and optimally sensitive [59] as well as assuring expedient culturing before and after the intervention to minimize the possibility of recontamination of tested surfaces. In reporting the results of all Level III, IV, and V studies, it will be important to optimize and allow for the assessment of generalizability of the findings by clearly defining the study setting, openly discuss observations related to confounder monitoring results, and consider the relevance of potential confounders which were not evaluated. Finally, reports of such studies should discuss both the justification for and the specific limitations of the study's quasi-experimental design [60]. Developing such studies with careful attention to the design elements noted could provide clear, objective outcomes with substantial potential for moving all elements of hygienic practice (Fig. 8.2) toward a solidly evidence-based foundation for optimizing patient and healthcare worker safety across the entire spectrum of patient care.

Table 8.8 Suggested elements for clinical studies of NTDT

Aspect of the study	Issue	Rationale
Design	Endemic setting	Minimize the potential for regression to the mean errors
	Single intervention	The need to minimize the impact of major confounders
	Adequate duration of pre-/post-intervention analysis	Minimum of several months during which potential confounders are objectively quantified
	Minimize or eliminate performance bias	The impact of the Hawthorne or novelty effect can be particularly problematic
	Quantify completeness of intervention use	Significant confounder
	Minimize room/patient unit selection bias	Possible confounder
Ongoing confounder analysis	Minimize changes in infection prevention initiatives	Significant confounder
	Objective analysis of thoroughness of routine disinfection cleaning	Significant confounder
	Antibiotic use trends	Significant confounder
	Hand hygiene compliance trends	Significant confounder
	Isolation precaution compliance trends	Significant confounder
	Monitor case mix trends	Possible confounder
	Monitor for target HAP admission incidence density trends	Possible confounder
	Monitor for introduction of new laboratory testing which could impact data	Possible confounder
	Monitor for increased or decreased frequency of testing which could impact data	Possible confounder
	Evaluate potential changes in HAI definitions which could impact data	Possible confounder

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9 Universal MRSA/Staphylococcal Decolonization for Hospitalized Patients

Edward J. Septimus

Introduction

Hospital-acquired infections (HAIs) burden patients, complicate treatments, prolong hospital stays, increase costs, and can be life-threatening. Up to 15% of patients develop an infection while hospitalized. The recent Centers for Disease Control and Prevention (CDC) report "Antibiotic Resistance Threats in the United States, 2013" highlights that at least 2 million Americans acquire serious infections from microorganisms resistant to one or more antimicrobial agents each year including methicillin-resistant *Staphylococcus aureus* (MRSA), resulting in 23,000 deaths annually. That CDC report recommends attempting to prevent these infections through appropriate use of antibiotics and adherence to infection prevention practices [1]. HAIs are now the fifth leading cause of death in US acute-care hospitals [2]. The substantial human suffering and financial burden of these infections are significant. Recent reports have estimated that US healthcare system costs attributable to HAIs range from $9.8 to $45 billion per year [3]. Beyond direct financial costs, HAIs also contribute significantly to increased patient length of stay (LOS) in the hospital resulting in both operational cost loss and patient dissatisfaction.

In the last several years, major changes in US healthcare have had an impact on HAI prevention. First we now know a significant percentage of HAIs are preventable using evidence-based strategies [4]. Second there are now coordinated efforts among federal agencies aimed at HAI prevention, including public reporting of hospital-specific HAI rates and linking hospital-specific HAI performance measures to financial reimbursement in order to stimulate HAI prevention efforts [5]. Since 2011 hospitals have been required to report to the CDC's National Healthcare Safety Network (NHSN) all of their central line-associated bloodstream infections (CLABSIs) among intensive care unit (ICU) patients in order to qualify for annual payment updates. Five additional required data are now being reported through NHSN to CMS including MRSA bloodstream infections. In addition, invasive healthcare-associated (HA) MRSA infections have been identified as a focus area in Healthy People 2020 [6].

MRSA infections have significantly increased in most countries in the last decade. MRSA is one of the most common causes of HAIs in most hospitals, and the incidence of community-acquired MRSA has also increased dramatically. *S. aureus* is the most common pathogen to cause HA pneumonia and bloodstream infections [2]. In a recent report, 47.9% of *S. aureus* HAI were MRSA [7]. In addition, MRSA infections are associated with worse outcomes and higher costs compared to methicillin-sensitive *S. aureus* (MSSA) [8].

The primary human reservoir for *S. aureus* is the anterior nares. Between 15% and 30% of all US adults are nasally colonized with methicillin-sensitive *S. aureus* (MSSA), and 1–2% are nasally colonized with MRSA [9, 10]. Hospitalized patients and long-term care facility residents are even more likely to be colonized with MRSA. Up to 58% of long-term care facility residents are colonized with MRSA [11, 12]. *S. aureus* colonization at other body sites including the pharynx, groin, perianal region, or axilla is also associated with development of *S. aureus* infections. This is most common among high-risk groups such as ICU patients, men who have sex with men and HIV-infected patients [9, 13].

Endogenous infections occur when a colonizing isolate enters a different body site on the same person and causes an infection. These infection sites include open cuts or wounds, surgical sites, and device sites. Patients who are nasally colonized with *S. aureus* are more than twice as likely to develop a *S. aureus* infection compared with non-colonized patients [14]. Bacterial colonization can be categorized as persistent carriage, intermittent carriage, or noncarriage. Among *S. aureus* nasal carriers, approximately 40% are persistently

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_9

colonized and 60% are intermittently colonized [15]. Those who are persistently colonized with *S. aureus* have a higher risk of infection compared with intermittent carriers or non-carriers [16]. Persistent *S. aureus* carriers also have been found to carry a greater quantity of *S. aureus* in their noses (measured in $\log_{10}$ colony-forming units [CFUs]) compared with intermittent carriers [17]. Average *S. aureus* bacterial loads among nasal carriers tend to range between 1.8 and 2.9 $\log_{10}$ CFUs. One study found that this load increased among MRSA carriers when patients received antibiotics that did not have activity against MRSA (e.g., beta-lactams, fluoroquinolones) [18]. Another study found that higher log counts of MRSA in the nose were associated with colonization at other body sites. Additionally, log counts for each body site correlated with log counts for all other cultured sites. That study found that mean extranasal MRSA loads ranged from 0.87 $\log_{10}$ CFUs in the axilla to 1.65 $\log_{10}$ CFUs in the perineum to 1.70 $\log_{10}$ CFUs in the groin [19]. It has also been established that the odds of developing an infection increase as more body sites are colonized [20]. Some decolonizing agents claim to completely eliminate bacterial load from their application sites, while others only claim to decrease the load. Yet, there is little data on what level the bacterial load must be reduced to in order to prevent transmission and infections.

In contrast to endogenous infections, exogenous infections occur due to transmission from person to person via direct or indirect contact by hands of healthcare workers and shared hospital environments such as bed rails. Carriers with high bacterial loads or colonized at multiple sites are not only at higher risk of infection but are more likely to transmit the bacteria to their environments [21].

Decolonization strategies aim to prevent transmission and infection. Some decolonization can decrease the bioburden of microorganisms on the patient, the environment, and the hands of healthcare personnel. The two most common methods of decolonization are application of antimicrobial ointment alone to the nose or combined with an antimicrobial body washes to the skin usually with CHG. This approach has been shown to reduce infections in specific subsets of patients [22, 23].

Decolonization is the most effective among patient populations who are only at risk of infection for a short period of time. These include populations such as surgical patients who only need to be decolonized for the time period that it takes the surgical wound to heal and ICU patients who are at much lower risk once they are discharged from the ICU. This window of time is important because of concern regarding both recolonization and resistance to colonizing agents. Thus, patient populations who are only at risk for short periods of time can achieve short-term success with decolonization [24], since studies have found that patients tend to become recolonized within weeks or months of being decolonized [25]. In fact, recolonization rates at 1 year approached 50% for healthcare workers and 75% for patients on peritoneal dialysis [26].

Table 9.1 Vertical and horizontal approaches

Vertical (pathogen specific)
Active surveillance (e.g., for MRSA, VRE, gram-negative MDROs)
Contact precautions (e.g., for MRSA/VRE/gram-negative MDRO colonization or infection)
Targeted decolonization (e.g., MRSA)
Horizontal (reduces infections not pathogen specific)
Standard precautions (hand hygiene, universal gloving)
Environmental cleaning
Bundles of care (e.g., CLABSI, ventilator, surgical care improvement project)
CHG bathing
Antimicrobial stewardship

Modified from Ref. [27]

Over the last decade, the general approaches to healthcare-associated infection (HAI) prevention have taken two conceptually different paths (Table 9.1): (1) vertical approaches that aim to reduce colonization, infection, and transmission of specific pathogens including MRSA, largely through the use of active surveillance testing (AST) to identify carriers, followed by implementation of measures aimed at preventing transmission from carriers to other patients including targeted decolonization, and (2) horizontal approaches that aim to reduce the risk of infections due to a broad array of pathogens through implementation of standardized practices that do not depend on patient-specific conditions. Examples of horizontal infection prevention strategies include minimizing the unnecessary use of invasive medical devices, enhancing hand hygiene, improving environmental cleaning, antimicrobial stewardship, and CHG bathing. This has led investigators to ask whether a horizontal approach including universal decolonization is more effective than a vertical approach or targeted decolonization [27]. This chapter will explore the evidence comparing a vertical approach versus a horizontal approach (universal decolonization) in reducing MRSA infections in hospitalized patients.

Nasal Topical Decolonization Strategies (Vertical)

Nasal mupirocin has emerged as the most widely used topical antibacterial agent. Mupirocin is a topical antibacterial agent produced from *Pseudomonas fluorescens* that inhibits bacterial protein synthesis by reversibly binding to bacterial isoleucyl-tRNA-synthetase. It has excellent activity against staphylococci and most streptococci [28]. Mupirocin exists in two formulations: a nasal ointment in petrolatum and a generic topical ointment in a polyethylene glycol vehicle. Both have been used for nasal decolonization. Side effects

are uncommon mostly limited to local site reaction such as stuffy nose or burning/stinging of the nose. Mupirocin is applied to the anterior nares two times/day for 5 days. Perl et al. reported that nasal colonization of *S. aureus* was eliminated in 83.4% of patients who received mupirocin, as compared with 27.4% of patients who received placebo ($p < 0.001$). Nasal colonization of *S. aureus* was eliminated from 81.3% of carriers ($p < 0.001$) who received three to five doses of mupirocin and from 93.3% of carriers who received six or more doses of mupirocin [29].

In a recent systemic review, Ammerlaan et al. reviewed 23 clinical trials including 12 that looked at topically applied antibiotics. They concluded short-term nasal application of mupirocin is the most effective treatment for eradicating MRSA carriage with an estimated success rate of 90% at 1 week after treatment and approximately 60% after a longer follow-up [30].

Several studies have demonstrated that mupirocin alone is highly effective in eradicating nasal colonization with *S. aureus* resulting in decreased infections in patients in intensive care, hemodialysis, in surgical settings, and long-term care [31–34]. Mody et al. published a double-blind randomized study looking at the efficacy of intranasal mupirocin versus placebo in reducing colonization and preventing infections in two long-term care centers. Twice-daily treatment was given for 2 weeks with follow-up to 6 months. After treatment, mupirocin eradicated colonization in 93% of residents compared to only 15% in placebo group ($p = 0.001$). At 90 days after treatment, 61% of residents in the mupirocin group remained decolonized. The authors concluded that mupirocin was effective in decolonizing persistent carriers in long-term care and showed a trend toward reduction of infections [35].

A meta-analysis found that decolonization with mupirocin alone or in combination with agents such as CHG decreased the odds of *S. aureus* infection by approximately 60% among dialysis patients [31]. This was due to a reduction in both exit-site infections and catheter-related bloodstream infections among both hemodialysis patients and peritoneal dialysis patients.

In a Cochrane review, the authors sought to determine if the use of mupirocin nasal ointment in patients identified as *S. aureus* carriers reduced *S. aureus* infections. Only randomized controlled trials comparing mupirocin with no treatment or placebo or alternative nasal treatment were included. They found mupirocin ointment resulted in a significant reduction in *S. aureus* infections (RR 0.55, 95% CI 0.43–0.70) [34].

However, mupirocin resistance to *S. aureus* has now been identified in several studies especially with widespread use over prolonged periods [36]. A study found the use of mupirocin, especially when mupirocin is repeatedly applied to exit sites to prevent infections in chronic dialysis patients, was associated with an increasing risk of *S. aureus* high-level mupirocin resistance (HL-MR) exit-site infections [37].

There are two phenotypes of mupirocin resistance: low-level mupirocin resistance with minimum inhibitory concentrations (MICs) from 8 to 64 μg/mL and high-level mupirocin resistance with MICs ≥512 μg/mL [38]. Caffrey et al. reported risk factors associated with mupirocin resistance to MRSA. They identified 40 mupirocin-resistant cases and 270 matched controls and performed an adjusted conditional logistic regression model. They found three independent risk factors: exposure to mupirocin in the year prior to the culture date (OR 9.84; 95% CI 2.93–33.09), *Pseudomonas aeruginosa* infection in the year before the culture-related admission (4.85; 1.20–19.61), and cefepime use in the year prior to culture (2.80; 1.03–7.58). In sensitivity analysis, prior mupirocin exposure was associated with both low-level and high-level mupirocin resistance. This study highlighted the strong association between previous mupirocin exposure and subsequent mupirocin resistance to MRSA [39]. More importantly, studies have shown that high-level mupirocin resistance to *S. aureus* results in decolonization failure. The association with low-level mupirocin resistance and outcomes of mupirocin decolonization is unclear. Walker et al. [40] published a prospective evaluation to determine the efficacy of nasal mupirocin ointment in reducing colonization with mupirocin-susceptible, methicillin-resistant *S. aureus* (MS MRSA) as well as mupirocin-resistant MRSA both low level (LL-MR MRSA) and high level (HL-MR MRSA). All patients were treated twice daily with 2% topical mupirocin ointment for 5 days. Treated patients had post-treatment cultures at day 3 and weeks 1, 2, and 4. Post-treatment nares cultures on day 3 were negative for 78.5%, 80%, and 27.7% of patients with MS MRSA, LL-MR MRSA, and HLMR MRSA, respectively. However, at the 1–4-week follow-up, the sustained decolonization for patients with HL-MR MRSA and LL-MR MRSA was low (25% each) compared to 91% in patients colonized with MS MRSA. This result suggests that mupirocin in LL-MR MRSA probably temporally suppresses growth, but does not result in sustained decolonization. Post-treatment cultures were usually the same genotype and susceptibility phenotypes as the patient's baseline culture. This appears to reflect treatment failure rather than exogenous recolonization. In a recently published analysis from the REDUCE trial, the odds of mupirocin resistance were no greater in the intervention period versus baseline across all arms. However, given the wide confidence intervals, this result should be interpreted with caution [41].

In contrast to unrestrictive use, short-term use of nasal mupirocin as part of perioperative prophylaxis to prevent surgical site infections due to *S. aureus* has not been associated with increased mupirocin resistance. Perl et al. treated over 2000 patients and performed mupirocin susceptibility testing on 1021 *S. aureus* isolates, and only six isolates

(0.6%) were resistant [29]. Fawley et al. described the results of repeated point prevalence for 4 years to determine if mupirocin resistance had emerged in surgical units using a 5-day perioperative prophylaxis with nasal mupirocin. They found no evidence of sustained emergence or spread of mupirocin resistance. No HL-MR strains were identified [42]. Finally in a Dutch hospital, more than 20,000 patients received mupirocin prophylaxis who were undergoing major cardiothoracic surgery. No mupirocin resistance emerged [32].

Although mupirocin has emerged as the topical agent of choice for elimination of *S. aureus* nasal carriage, there is growing evidence of increasing mupirocin resistance and treatment failures, especially with widespread use over long periods of time.

Recently there has been increase attention to the use of nasal 5–10% povidone-iodine. Povidone-iodine (PI) is a complex of polyvinylpyrrolidone and tri-iodine ions that has been widely used as an antiseptic on the skin, wounds, and mucous membranes. PI has a broad activity against gram-positive and gram-negative bacteria. Specifically, PI has good activity against *S. aureus*, including MRSA. Hill and Casewell evaluated the in vitro activity of 5% PI as a possible alternative to mupirocin for the elimination of nasal carriage of *S. aureus*. The results suggested PI may have a role in the prevention of colonization and infection due to MRSA, including mupirocin-resistant strains [43].

Phillips et al. conducted a prospective, open-label trial of twice-daily application of nasal mupirocin ointment for 5 days before surgery compared to two applications of a 5% PI solution in each nostril within 2 h of surgical incision in patients undergoing arthroplasty or spine fusion surgery. Both groups also received CHG bath with 2% cloths the night before and the morning of surgery. In the per protocol analysis, *S. aureus* deep surgical site infections (SSIs) developed in 5 of 763 surgical procedures in the mupirocin group and 0 of 776 surgical procedures in the PI group ($p = 0.03$). In addition, if the preoperative nasal culture grew *S. aureus*, a second nasal culture was obtained within 1–3 days after surgery. The proportion of postoperative negative nasal cultures was 92% (78 of 85 patients) in the mupirocin group versus only 54% (45 of 84 patients) in the PI group. Unfortunately, the authors could not perform multivariate analysis due to small sample size, and patients were not followed after discharge to identify late infections [44].

In a second study, Bebko and colleagues recently published a preoperative decontamination protocol to reduce SSIs in orthopedic patients undergoing elective hardware implantations. This was a quasi-experimental, retrospective, nonrandomized trial comparing a bundle intervention to historical controls. The intervention consisted of application of 2% CHG and oral CHG the night before and morning of surgery plus intranasal PI solution the morning of surgery. Patients were followed for 30 days postoperatively for SSI. The SSI was significantly lower in the intervention group 1.1% versus 3.8% in the control group ($p = 0.02$). This was a retrospective quasi-experimental nonrandomized trial, patients were only followed for 30 days, and information regarding MRSA carrier status of patients before and after decontamination was not collected; therefore the study did not allow evaluation of the effect of nasal decolonization versus other interventions [45]. Although nasal PI may be a potential alternative to nasal mupirocin for prevention of SSIs, more studies are needed. The Mupirocin-Iodophor Swap Out Trial will directly evaluate the non-inferiority of universal ICU decolonization with CHG-iodophor compared to CHG-mupirocin for the outcomes of ICU-attributable *S. aureus* clinical cultures and all-cause bacteremia [46].

Steed et al. [47] published a double-blinded, placebo-controlled RCT testing the effectiveness of an alcohol-based nasal antiseptic in reducing *S. aureus* nasal colonization in colonized healthcare workers. Healthcare workers testing positive for nasal *S. aureus* colonization were treated three times during the day with a nasal alcohol-based antiseptic or placebo. Nasal *S. aureus* and total bacterial colonization levels were determined before and at the end of a 10-h shift. Antiseptic treatment reduced *S. aureus* colony-forming units from baseline by 82% (mean) and 99% (median) ($p = 0.001$) [47]. Mullen et al. [48] published a brief report using an alcohol-based nasal antiseptic decolonization to reduce *Staphylococcus* spp. SSIs. All patients scheduled for spine surgery were included in the study. Records from 1073 spine surgical patients undergoing inpatient or outpatient procedures (400 and 673 in the baseline and intervention periods, respectively) were part of the study. Investigators combined immediate presurgical application of an alcohol-based nasal antiseptic with existing CHG bath or wipes in a comprehensive pre- and postoperative decolonization protocol. After surgery, patients were expected to follow the regular three-times-daily cycle of staff-applied alcohol-based application in the postsurgical units until discharge, at which time the patient and family coach were instructed to continue applications for an addition of 5–7 days with the remaining antiseptic. Mean infection rates were significantly decreased by 81% from 1.76 to 0.33 per 100 surgeries during the 15-month trial, when compared with the prior 9-month baseline ($p = 0.036$) [48]. This is a small, single-center, quasi-experimental intervention that needs confirmation.

Chlorhexidine Bathing (Horizontal)

Chlorhexidine is a topical antiseptic solution that has been used worldwide since the 1950s. Chlorhexidine gluconate is a water-soluble, cationic biguanide that binds to the negatively charged bacterial cell wall, altering the bacterial cell

osmotic equilibrium. CHG has a broad-spectrum activity against gram-positive and gram-negative bacteria as well as yeast. CHG has an excellent safety record. Adverse events associated with CHG include mild skin irritation and rare serious allergic reactions.

CHG efficacy has been documented for diverse indications such as hand washing, procedure skin preparation, vaginal antisepsis, and oral care for prevention of VAP, treatment of gingivitis, and body washes to prevent infections. Chlorhexidine is commercially available at a variety of concentrations (0.5–4%) and formulations (with and without isopropyl alcohol or ethanol), and certain chlorhexidine-containing products are available over the counter. This section will focus on the use of CHG bathing to prevent MRSA HAIs.

Recently, multiple studies have evaluated CHG bathing to reduce bacterial skin burden among patients in the ICU in an effort to reduce HAIs. CHG bathing has been shown to decrease the bioburden of microorganisms on the patient, the environment, and the hands of healthcare personnel [49]. Bleasdale et al. observed a 60% reduction in BSI among MICU patients who were bathed with 2% CHG cloths daily versus soap and water [50]. Popovich et al. also compared CHG bathing with soap and water in another MICU and also reported a significant reduction in BSIs including *S. aureus* [51]. During 2013, four randomized cluster trials were published evaluating the effectiveness of CHG bathing in preventing HAIs or MDRO acquisition among ICU patients. Climo et al. performed a multicenter cluster-crossover study and reported that daily 2% CHG cloth bathing in the ICU resulted in a 23% reduction of VRE/MRSA acquisition and a 28% reduction in BSIs [13]. Using a similar study design, Milstone et al. reported that 2% CHG cloth bathing was associated with a significant reduction in bloodstream infections among pediatric ICU patients compared to standard bathing [52]. Huang et al. compared three approaches to MRSA prevention among patients in 74 adult ICUs (the REDUCE MRSA study): Arm 1 MRSA screening and isolation, Arm 2 targeted decolonization (screening, isolation, and decolonization of MRSA carriers with chlorhexidine bathing and nasal mupirocin), and Arm 3 universal decolonization (no screening, all patients decolonized with CHG cloth bathing and nasal mupirocin). The investigators found that universal decolonization of all ICU patients was associated with the largest reduction in all-cause bloodstream infection (44%; $p < 0.001$) and MRSA clinical culture rates (37%; $p = 0.01$) [23]. In a secondary analysis, CHG bathing was also shown to reduce blood culture contamination by 45% ($p = 0.02$) confirming earlier studies [53]. A European study demonstrated that improved hand hygiene plus universal CHG cloth bathing reduced acquisition of MDROs including MRSA and showed that in a setting where high levels of adherence to hand hygiene and CHG bathing were sustained, the addition of active surveillance testing (either rapid or conventional testing) and isolation of carriers did not further reduce MDRO acquisition rates [54]. There is very little evidence on the use of CHG bathing in non-critical settings. Kassakian et al. did study the effectiveness of daily CHG bathing in a non-ICU setting to reduce MRSA and VRE HAIs, compared with daily bathing with soap and water. This was a quasi-experimental before and after trial. Daily CHG bathing was associated with a reduced HAI risk, using a composite endpoint of MRSA and VRE HAIs, in a general medical inpatient population [55].

Decolonization Prior to Surgery

In the recent Vital Signs report, 44.4% of *S. aureus* SSIs were MRSA [7]. Decolonization has been found to reduce the incidence of gram-positive surgical site infections (SSIs) after some types of surgery [22]. This is because SSIs are often endogenous, spreading from one body site (e.g., nose, skin) to the surgical wound of the same patient. Multiple studies have demonstrated that the genotypes (via pulsed field gel electrophoresis [PFGE]) of *S. aureus* colonizing and infecting isolates are identical in 75–85% of surgical patients [29, 56]. There is strong evidence that nasal and skin decolonization (nasal mupirocin plus CHG bathing) prior to cardiac and orthopedic surgery is effective at preventing SSIs caused by gram-positive organisms. Two systemic literature reviews and meta-analyses of published studies found a protective effect of mupirocin decolonization against surgical site infections, especially among non-general surgery such as cardiac, orthopedic, and neurosurgery [33]. A meta-analysis of 17 randomized controlled trials or quasi-experimental studies that included cardiac and orthopedic surgery patients evaluated the effectiveness preoperative decolonization [22]. The meta-analysis found that decolonization was significantly protective against gram-positive surgical site infections (SSIs), specifically *S. aureus* SSIs. A recent pragmatic quasi-experimental study implemented a bundle in 20 hospitals in order to prevent complex *S. aureus* SSIs after cardiac surgery and hip and knee arthroplasty [57]. The bundle included CHG bathing for all patients, screening for MRSA and MSSA nasal colonization, nasal mupirocin decolonization for *S. aureus* carriers, and both vancomycin and cefazolin perioperative prophylaxis for MRSA carriers. The mean rate of complex *S. aureus* SSIs significantly decreased from 36 per 10,000 operations during the baseline period to 21 per 10,000 operations during the intervention period (rate ratio [RR] = 0.58; 95% CI, 0.37; 0.92).

Universal Decolonization Versus Targeted Decolonization

Both targeted decolonization and universal decolonization strategies have been shown to decrease cross-transmission and infection due to MRSA. Currently, there is a debate as to whether decolonization regimens should only be performed among patients who are colonized with pathogens that are sensitive to the decolonizing agents (e.g., *S. aureus* including MRSA) or if all high-risk patients should receive decolonizing agents without being screened for colonization. Universal decolonization, decolonizing all high-risk patients regardless of colonization status, only requires healthcare workers to provide the decolonizing agents to the patients without the labor and complexity of screening. Targeted decolonization requires the collection of a screening swab and laboratory testing before decolonization. This usually entails nasal screening for *S. aureus* colonization. Targeted decolonization is considered by some the preferred standard because antimicrobial agents would only be used in patients who need them, which may prevent antimicrobial resistance. However, this strategy would not identify patients who are *S. aureus* colonized at extranasal body sites, would not decolonize patients with false-negative results, and would not decolonize patients who are colonized with other pathogens such as the skin commensal organism CNS or other multidrug-resistant organisms.

Depending on the patient populations, different laboratory tests may be appropriate for screening. If fast results are needed, real-time polymerase chain reaction (PCR) can be used to test nasal swabs for both MRSA and MSSA within 1 h [58]. However, PCR is more costly than both chromogenic agar (test time at least 1–2 days) and standard culture (test time approximately 2–3 days) [59]. Fast results may be needed in the preoperative clinic, so that patients can be sent home with mupirocin and CHG as needed. Slower methods could be used for dialysis patient populations who have frequent contact with the healthcare system and thus could obtain their decolonizing agents at their next healthcare visit. However, any type of screening is likely to be more expensive and certainly utilizes more healthcare worker time compared with universal decolonization [60–62].

Meta-analyses of decolonization studies among surgical and non-surgical populations found that both universal and targeted decolonization strategies resulted in similar protection against *S. aureus* infections [22, 63]. The only multicenter study that compared universal and targeted decolonization head to head found that in the ICU, universal decolonization was superior to targeted decolonization at reducing the number of bloodstream infections caused by any pathogen including skin commensal organisms. The reduction in MRSA bloodstream infections was not significantly different between the universal and targeted decolonization groups; however, there was a trend toward a larger reduction among the universal decolonization group [23]. However, this study also found a 37% reduction in MRSA clinical cultures ($p = 0.01$). Universal decolonization has been shown to have other potential benefits, such as reducing rates of CLABSI, overall BSIs, and environmental contamination with and acquisition of VRE [49–51]. Thus, universal decolonization is effective at reducing the total number of positive cultures and infections including MRSA in both surgical and non-surgical patients.

The patient population must also be factored into the decision of targeted versus universal decolonization. Given the evolving epidemiology of MDROs and the complexity of managing epidemiologically important pathogens across the continuum of care, we must ensure reliable performance of basic infection prevention practices known to reduce transmission of all MDROs and the infections they cause. Applying evidence-based horizontal strategies such as universal decolonization in settings where benefits have been demonstrated and cost-effective should be implemented. Vertical approaches such as active surveillance testing should be considered when epidemiologically important pathogens are newly emerging or rare to a given institution or to control outbreaks. Universal decolonization may be preferred in ICU settings in which there is concern over both endogenous infection and exogenous patient-to-patient transmission. In the ICU setting, missed colonization sites or false-negative tests could result in the spread of pathogens from one patient to another. Conversely, targeted decolonization may be preferred for preoperative and dialysis settings where endogenous infections are the main concern. There are even differences in the preoperative setting. Targeted decolonization may be feasible for elective procedures but not for urgent procedures such as emergency coronary artery bypass graft. A compromise between the two types of decolonization prior to surgery would be to attempt targeted decolonization, but if a patient presented to surgery with unknown results, that patient could be treated as colonized and receives a dose of mupirocin and a CHG bath prior to surgery and finishes the 3–5 days of mupirocin after surgery [56]. Current guidelines suggest decolonization as a special approach during MRSA outbreak or to combat endemic MRSA when other strategies have failed. Decolonization can be targeted to MRSA-colonized persons or applied universally to populations deemed to be at high risk for infection [64].

The primary concern regarding universal decolonization is the emergence of resistance to the decolonizing agents. Mupirocin resistance has been reviewed earlier. Most studies of short-term, target mupirocin use have not seen significant emergence of mupirocin. Resistance to CHG has been rare. However, increased use of decolonizing agents could lead to

selection of resistant strains. One study found that patients with persistent *S. aureus* carriage after decolonization were statistically more likely to be colonized with *S. aureus* isolates with combined low-level mupirocin resistance and genotypic chlorhexidine resistance before decolonization compared with patients who were successfully decolonized [65]. Another study showed that decolonization with chlorhexidine in the ICU led to selection of a non-epidemic MRSA strain (ST239) that had reduced susceptibilities to chlorhexidine [66]. Finally, in a recent publication, Hetem and colleagues developed a mathematical model of mupirocin resistance comparing a targeted strategy of applying mupirocin and CHG in *S. aureus* carriers only versus universal decolonization in the prevention of SSIs. Based on their results, they conclude that there is a similar low risk of mupirocin resistance for *S. aureus* in the setting of targeted or universal decolonization and treating all surgical patients with mupirocin and CHG preoperatively eliminated the need for preoperative testing and simplifies implementation. The downside of this approach would be to expose 70% of patients who are not *S. aureus* carriers and are unlikely to benefit from this intervention [67]. Implementation of universal decolonization should be done with caution with monitoring for mupirocin and CHG resistance.

Lastly there are a limited studies looking at the cost-effective strategies to prevent MRSA infections. A series of economic computer models found that screening and nasal decolonization are cost-effective in some patient populations but not others. Murthy et al. evaluated a bundled intervention that included PCR screening for MRSA prior to surgery, decolonization of MRSA-positive patients with mupirocin and CHG, and contact isolation for MRSA-positive patients. They found that this was not strongly cost-effective, meaning that the costs avoided through reducing MRSA infections did not completely offset the costs of screening. However, this model was based on data from a hospital in Geneva, which is known for its low rates of MRSA [68]. Conversely, using data inputs from the United States, multiple studies found that MRSA screening and decolonization prior to cardiac, vascular, or orthopedic surgery or heart-lung transplant were cost-effective from both the third-party payer perspective and the hospital perspective [24, 60, 61, 69–71]. Additionally, other economic models have found MRSA screening and decolonization to be cost-effective among hemodialysis patients, ICU patients, and all hospitalized patients [62, 72–75]. Recently Robotham and colleagues evaluated the costs and benefits of universal MRSA screening in English National Health Service (NHS) hospitals. They found that at current MRSA prevalence, that screening of all admissions was not cost-effective [76]. However, screening of high-risk specialties might be an option such as admission to nephrology, hematology, and oncology and orthopedic and cardiac surgery. In contrast two different studies performed cost analyses of universal decolonization in the ICU setting and found it to be the most cost-effective strategy [75, 77]. One economic model compared seven different strategies to prevent MRSA transmission and infection in ICUs and found that the strategies that included decolonization were less expensive and more effective than other strategies [62]. Universal decolonization was found to be cost-effective by preventing 44% of cases of MRSA colonization and 45% of cases of MRSA infection.

Conclusion

Given the evolving epidemiology of MDROs and the complexity of managing the multiplicity of epidemiologically important pathogens across different healthcare settings including MRSA, ensuring adherence to evidence-based strategies to prevent HAIs is critical. Apply horizontal strategies such as universal decolonization in settings where benefits are likely and cost-effective, and use active surveillance testing (AST) for MDROs including MRSA and other vertical approaches selectively when epidemiologically important pathogens are newly emerging, to control outbreaks of specific pathogens, or preoperative screening in orthopedic and cardiovascular surgery and other high-risk populations.

There is growing evidence that in endemic settings in the ICU, vertical strategies that involve active surveillance testing for MRSA, isolation, and targeted decolonization are not as effective as horizontal approaches utilizing hand hygiene and universal decolonization using CHG bathing with or without intranasal mupirocin. In addition, several studies have shown this is also the most cost-effective strategy. Evidence for universal decolonization with CHG bathing in non-critical care has evolved. The results of the recently completed ABATE Trial (Active Bathing to Eliminate Infection Trial), a two-arm cluster-randomized trial in non-critical care comparing usual bathing with CHG bathing and intranasal mupirocin for MRSA-positive patients, found that non-ICU patients with medical devices had a significant 37% reduction in MRSA and VRE and a significant 32% reduction in all-cause bloodstream infections. Patients with medical devices constituted only 10% of the inpatient population but were responsible for 37% of MRSA and VRE cultures and 56% of all-cause bloodstream infections [78].

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Staphylococcal Decolonization in Surgery Patients

10

Andrew D. Ludwig and E. Patchen Dellinger

Introduction

Incidence and Sites of Colonization

Staphylococcus aureus is a commensal skin bacteria found on approximately 30% of adults in developed nations [1–3]. Its primary site of colonization is thought to be the keratinized epithelium of the anterior nares, from which it can seed additional external sites, such as the pharynx and the skin of the hands, axillae, and perineum [4]. When multiple sites are cultured, the anterior nares are most often colonized and carry 93% sensitivity in detecting colonization [5]. Decolonization of the anterior nares leads to a decrease in the rate of colonization of other external sites of colonization [6, 7].

Type of Carriage

Historically, nasal carriers of *S. aureus* have been divided into three classifications: persistent carriers of a single strain (20% of the population), intermittent carriers of changing strains (60%), and noncarriers (20%) [1, 4]. The determination of carriage type appears to be based on both host and pathogen factors. When inoculated with multiple strains, persistent carriers were recolonized by only their original strain while noncarriers eliminated all strains [8]. About 6% of individuals are carriers of multiple concomitant strains [9]. Based on cross-sectional surveys, the prevalence of nasal carriage in the community is about 35%, comprising both persistent and intermittent carriers [1, 10–12] Some populations of patients have a significantly higher carriage rate, such as those with insulin-dependent diabetes mellitus, chronic ambulatory peritoneal dialysis (CAPD), intravenous drug abuse, liver dysfunction, and HIV [1, 8].

Nasal carriage of *S. aureus* is an independent risk factor for clinically significant *S. aureus* infections of the bloodstream, skin and soft tissues, and surgical wounds [1, 13–16]. Carriage of methicillin-resistant *S. aureus* (MRSA) bears a higher risk than methicillin-sensitive *S. aureus* (MSSA) for nosocomial infection and a higher rate of morbidity and mortality in ICU patients [17, 18]. The association between nasal carriage of *S. aureus* and surgical site infection (SSI) has been studied extensively among general, thoracic, and orthopedic surgery patients. These efforts have determined that preoperative colonization with *S. aureus* carries an increased risk of surgical site infection (SSI) [13, 19]. Prospective studies have determined that the same strain colonizing the nares is found in infected surgical sites 75% to 85% of the time [16, 20, 21]. This association has led to the hypothesis that nasal decolonization of *S. aureus* may present an opportunity to decrease the rates of SSI.

Incidence of Surgical Site Infection (SSI), *S. aureus* SSI, and Association with Colonization

Based on a recent Centers for Disease Control and Prevention (CDC) survey, SSIs account for 21.8% of all nosocomial infections, and among surgical patients, SSIs are the most common nosocomial infection, accounting for 38% of hospital-acquired infections in this group [22]. A recent systematic review of SSI in the literature found an overall incidence of 3.7%, among operated patients with *S. aureus* implicated in 49% of cases [23], making it the most common cause of SSI. This finding is shared by many other large databases. *S. aureus* is responsible for 20% of SSI among hospitals that report to the CDC NNIS system [24] and up to 37% of community hospitals [25].

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_10

The CDC have published criteria for defining SSI which classifies infections as superficial incisional, deep incisional, and organ space infections. According to these criteria, superficial incisional SSI involves the skin and subcutaneous tissue, deep incisional SSI involves the deep soft tissue, including fascia and muscle, while organ space infections involve anatomy deep to the incision that was manipulated during surgery [26]. Regardless of classification, an infection is attributed to surgical intervention if it is related to the incision and occurs within 30 days of surgery if no implant was placed or within 90 days if an implant was placed.

Burden and Cost of Treating SSI

Surgical site infections portend a worse prognosis for patients, a longer duration of hospitalization, and a greater financial cost. Each SSI increases length of stay by 7 to 10 days, increases cost by $3000 to $29,000 per patient, and increases mortality risk 2- to 11-fold [25, 27, 28]. Even compared to other types of infection, patients who undergo invasive surgery and have an *S. aureus* infection suffer additional burdens. An analysis of the Nationwide Inpatient Sample database revealed an additional 7.3 hospital days, $22,000 in charges, and 1.7-fold increased absolute risk of in-hospital mortality for those surgical patients with an *S. aureus* infection compared to those with other types of infections [29]. Antibiotic resistance increases these figures further. Patients who develop an MRSA SSI accrue an additional $14,000 in hospital costs and 3.4 times higher 90-day mortality rates compared to those with an MSSA SSI [30]. Because of the significant clinical and financial impact of *S. aureus* surgical site infection, the high rate of nasal colonization, and the literature supporting the link between colonization and infection, a large amount of research has been devoted to developing effective screening and decolonization programs.

Screening

Screening for *S. aureus* nasal colonization has traditionally involved nasal swab and culture technique. Those that screen positive are then treated with topical intranasal medication to eradicate colonization prior to surgery, and eradication may be demonstrated with repeat testing prior to operating. Another strategy involves universal treatment of all patients without screening. When considering methods of decolonization, there are several important factors. The method must be safe, effective, rapid, cost-effective, and produce prolonged decolonization. Given these principles, several agents have been proposed and studied in the literature.

Methods of Decolonization

Mupirocin

Mupirocin (pseudomonic acid) has been used as a topical agent for nasal decolonization of *S. aureus* since the 1980s [31]. It is a potent and rapid agent for decolonization, clearing >80% of patients immediately after application [6, 32, 33]. Long-term efficacy is persistent clearance rates of 50% at 6 months and 1 year [6, 33]. When healthcare workers were treated with mupirocin, it was found to decrease the rate of *S. aureus* hand colonization from 58% in placebo-treated participants to 3% in mupirocin-treated individuals [33].

Historic Controls

Initial investigations into the effectiveness of mupirocin to reduce the rate of SSI used historic control groups. In one of the largest such studies, Kluytmans et al. compared 983 cardiac surgery patients receiving preoperative mupirocin with 1003 historic controls and found a reduction in SSI from 7.3% to 2.8% [34]. It should be noted that the control group also experienced a decrease in the rate of SSI, indicating that there were unmeasured variables responsible for at least some of the reduction seen in both groups. In a study of consecutive cardiac surgery patients before and after the introduction of intranasal mupirocin treatment, Cimochowski et al. found that decolonization significantly decreased wound sternal infection rate by 66%, from 2.7% to 0.9% [35]. This outcome is shared by a more recent study of nasal decolonization with mupirocin among a cohort of >17,000 cardiac surgery patients which found a significant reduction in sternal wound infection after implementing a universal decolonization protocol, though nasal carriage of *S. aureus* remained a risk factor for SSI even following the intervention [36]. A smaller-scale prospective before-and-after study among patients undergoing aortoiliac surgery found a similar result with a screen-and-treat approach, demonstrating significantly reduced *S. aureus* SSI, 30-day mortality rate, and reintervention rate among those colonized patients treated with mupirocin and chlorhexidine gluconate (CHG) body wash [37].

Randomized Controlled Trials

Despite the findings in these early studies, randomized controlled trials in unselected patient populations have failed to demonstrate a statistically significant decrease in SSI among patients preoperatively receiving mupirocin compared to placebo.

In the Mupirocin And Risk of *S. aureus* (MARS) study, Perl et al. investigated the effect of intranasal mupirocin in a randomized, placebo-controlled study of over 4000 elective

general, cardiothoracic, oncologic-gynecologic, and neurosurgical patients [20]. The authors found that twice-daily mupirocin up to five days before surgery eliminated *S. aureus* colonization in 83% of carriers and significantly reduced *S. aureus* nosocomial infections in nasal carriers. Overall nosocomial infections, overall SSI rate, and *S. aureus* SSI rate were all reduced following mupirocin treatment, though not to a statistically significant degree. However, among patients who were colonized preoperatively, *S. aureus* infections were reduced by 51% ($p = 0.02$). Among those carriers who developed *S. aureus* infections, 85% had identical strains in their nares, and their infected sites and rates of MRSA and mupirocin resistance were low (less than 1%).

In a randomized controlled trial of 614 orthopedic surgical patients, Kalmeijer et al. found a carriage rate of about 30%. Similar to the MARS study, mupirocin eradicated colonization in 83% of carriers. Among carriers who developed an *S. aureus* infection, the same strain was found in the nares and infected area of 84% of patients. Also like the MARS study, mupirocin lowered but did not significantly reduce the rate of overall SSI or *S. aureus* SSI [21]. In a pooled analysis of these two studies, Kluytmans et al. found a nearly significant reduction in *S. aureus* SSI among carriers ($p = 0.06$, pooled OR = 0.58, 95% CI 0.33–1.02) and a significant reduction in overall nosocomial infections in carriers ($p = 0.01$, RR 0.49, 95% CI 0.29–0.83) [7]. This analysis also revealed that 26 carriers would need to be treated to prevent one nosocomial *S. aureus* infection.

The prior two studies randomized both carriers and noncarriers to receive mupirocin treatment and, as expected, a significant reduction in infections was seen only in the *S. aureus* carriers. Konvalinka et al. conducted a randomized controlled trial on the effect of mupirocin on cardiac surgery patients who were *S. aureus* carriers. The patients were screened by nasal swab and culture, and then carriers were randomized to receive intranasal mupirocin or placebo. A total of 263 patients were enrolled after positive screening by nasal swab. Treatment with mupirocin eliminated *S. aureus* carriage in 81.5% of patients compared to a reduction of 46.5% in those treated with placebo ($p < 0.0001$). The authors found an overall wound infection rate of 13.8% in the treatment arm and 8.6% in the placebo arm ($p = 0.27$) with 3.8% of mupirocin-treated patients developing an *S. aureus* infection compared to 3.2% of patients treated with placebo ($p = 1.0$) [32]. So despite a significant reduction in nasal carriage, this patient population did not experience a significant reduction in overall SSI, *S. aureus* SSI, or nosocomial *S. aureus* infection. Furthermore, *S. aureus* colonization at the time of surgery was not found to be an independent predictor of SSI in multivariate regression analysis. Subgroup analysis of superficial and deep space infections was too limited for meaningful conclusions to be drawn. The authors concluded that due to the low rate of SSI in their patient population, the study size was too low to detect a difference in SSI rates, which is a common theme among randomized controlled trials on this topic.

In a Cochrane review and meta-analysis of nine randomized controlled trials encompassing 3396 patients, van Rijen et al. found a statistically significant reduction in the rate of *S. aureus* infection in patients treated with intranasal mupirocin (RR 0.55, 95% CI 0.43–0.70). A subgroup analysis of surgical trials found a significant reduction in the rate of nosocomial *S. aureus* infection associated with mupirocin use (RR 0.55, 95% CI 0.34–0.89). When looking specifically at surgical site infections caused by *S. aureus*, no significant reduction in infection rate was found (RR 0.63, 95% CI 0.38–1.04) likely due to low numbers [38]. This conclusion is echoed by a previous meta-analysis of 4 randomized controlled trials consisting of 686 mupirocin-treated surgical patients with *S. aureus* nasal carriage. This analysis did find a statistically significant reduction in the rate of overall *S. aureus* infection (RR 0.55, 95% CI 0.34–0.89, $p = 0.02$), but no such difference was found when examining *S. aureus* SSI (RR 0.64, 95% CI 0.38–1.06) [39]. All four of these trials were included in the later Cochrane analysis.

In another focused review of mupirocin prophylaxis in surgical patients, Kallen et al. conducted a meta-analysis of three RCTs and four single-institution before-and-after trials including both general surgery patients and cardiothoracic, orthopedic, and neurosurgery patients [40]. These authors found a significant reduction in the risk of overall surgical site infections in both RCTs (7.6% vs. 6.0%, RR 0.80, 95% CI 0.58–1.10) and in before-and-after trials (4.1% vs. 1.7%, RR 0.40, 95% CI 0.29–0.56) but only in the "nongeneral" surgery patient populations. Combining these two types of studies resulted in a population too heterogeneous for meaningful results. Because of the analyses conducted by the primary studies, no summary statistics could be performed on the rate of *S. aureus* infections as opposed to overall SSI.

More recently, a randomized controlled trial was conducted in the Netherlands by Bode et al. using PCR to rapidly screen and identify *S. aureus* nasal carriers at hospital admission [41]. Carriers were then treated with twice-daily mupirocin ointment and daily CHG soap for 5 days, and treatment was continued even if surgery was performed during the initial treatment timeframe. The screening was carried out on 6771 patients from 2005 to 2007 and identified 1251 nasal carriers (18.4%), of whom 917 were included in an intent-to-treat analysis and 808 underwent surgery. If still hospitalized, inpatients were retreated at 3 and 6 weeks after initial treatment, and the patients were followed until 6 weeks after hospital discharge. All *S. aureus* in this study were MSSA. The effect of combined nasal and skin decontamination resulted in a decrease in *S. aureus* surgical site infection from 7.7% to 3.4% (RR 0.42, 95% CI 0.23–0.75) and reduced the risk of deep space infection from 4.4% to 0.9% (RR 0.21,

95% CI 0.07–0.62). Superficial surgical site infections were also reduced in the study population, though not to a statistically significant degree (3.5% vs. 1.6%, RR 0.45, 95% CI 0.18–1.11). A comparison of *S. aureus* strains obtained from the nasal passages with those isolated from surgical site infections revealed that endogenous *S. aureus* infection was significantly less likely in the treatment population, though there was no effect seen in the risk of exogenous *S. aureus* infections or in overall hospital-acquired *S. aureus* infection.

Taken together, the high-quality studies that have been published to date on the use of intranasal mupirocin with or without CHG body wash as a means of *S. aureus* SSI prophylaxis do not reveal consistent findings of mupirocin treatment reducing the risk of SSI. However, some conclusions can be drawn from these analyses. First, as expected, mupirocin treatment only benefits those with nasal colonization. Second, it appears that cardiac and orthopedic surgical patients benefit more from preoperative *S. aureus* decolonization than general surgery patients. This may be attributable to the difference in the likelihood that *S. aureus* is the causative organism when an SSI occurs. Cardiac and orthopedic surgeries are commonly clean operations compared to general surgery cases which are more likely to be clean-contaminated or contaminated due to involvement of the enteric tract. In clean cases, skin flora like *S. aureus* may be one of the most common causative pathogens for an SSI. Whereas in clean-contaminated cases, Gram negative bacteria may be more common and therefore staphylococcal decolonization affects a smaller proportion of potential SSIs. An example of this may be seen in a recent study by Zhu et al. in which screening and decolonization in patients undergoing arthroplasties significantly reduced SSI due to *S. aureus* but not infections due to other organisms [42].

Mupirocin Resistance

In some institutions, mupirocin resistance, particularly among MRSA isolates, has emerged as a significant problem and has been correlated with an increased use of mupirocin [43, 44]. In a review of intranasal mupirocin use for MRSA decolonization in multiple healthcare settings, Poovelikunnel et al. concluded that indiscriminate use of mupirocin in both colonized and uncolonized patients could lead to an increasing prevalence of mupirocin resistance [45]. This hypothesis is supported by a more recent single-center study demonstrating that use of mupirocin above 25 defined daily doses (DDD)/1000 patient-days resulted in increased resistance compared to use at 25 DDD/1000 patient-days or less [46]. In the studies reviewed above, resistance was found to be low in elective surgical patients who received short preoperative courses of mupirocin [20, 34, 35]. In a four-year study of routine empiric mupirocin prophylaxis in orthopedic and vascular surgical patients, Fawley et al. found no trend toward increasing prevalence of mupirocin resistance [47]. A recent systematic review and meta-analysis found a worldwide resistance to mupirocin of 7.6% in MSSA isolates and 13.8% in MRSA isolates. The resistance patterns were variable depending on region, but tended to be higher in Asia than in Europe or the United States [48].

Povidone-Iodine

Because of the risk of mupirocin resistance, alternative treatments for nasal decolonization have been proposed. One such agent is povidone-iodine (PI), which produces a bactericidal effect by disrupting protein and nucleic acid structure and synthesis. In a study of universal decontamination among elective orthopedic patients undergoing hardware implantation, Bebko et al. found a significant reduction in overall SSI using CHG washcloths and oral rinse along with intranasal PI as compared to historical controls who received no decontamination [49]. Interestingly, the nasal treatment was applied only on the morning of the surgery, and therefore, compliance could be assured. Patient-reported compliance does appear to be a reliable indicator of preoperative decolonization protocol adherence. A prospective study of *S. aureus*-colonized cardiac surgery patients in France found that declared compliance with a decolonization regimen of nasal mupirocin, CHG shower, and mouthwash was associated with decolonization success while those who reported low compliance were unlikely to be decolonized [50]. Reported compliance was highly correlated with mupirocin concentrations in the nose and of a mupirocin metabolite in the urine. As expected, postoperative carriage was associated with an increased risk of *S. aureus* SSI.

In a randomized open-label comparison between nasal mupirocin and nasal povidone-iodine of over 1800 orthopedic patients undergoing arthroplasty or spine fusion, Phillips et al. found a reduced rate of deep SSI with PI use in their per-protocol analysis, which excluded those participants who did not receive the full course of their prescribed prophylaxis [51]. The difference in rates of deep SSI did not reach statistical significance in the intent-to-treat analysis, however. Importantly, in this study the control participants received mupirocin twice daily for 5 days before the operation, whereas the treatment group received two applications of PI within 2 hours of the surgical incision. As in the prior study, the implication of receiving a short course of monitored prophylaxis has clear advantages with respect to patient compliance, even if the two treatments are equivalent in their prevention of SSI. In fact, in this randomized trial, about three times as many patients failed to complete at least seven doses of mupirocin as failed to receive the two doses of PI. Regarding the role of mupirocin resistance, the authors detected resistance in 4 of 219 (1.8%) preoperative *S. aureus*

isolates, but no deep *S. aureus* SSI occurred in these subjects. The authors also found that mupirocin was more effective than PI at clearing nasal *S. aureus* colonization based on postoperative nasal cultures and *spa* typing. This is most likely due to the ability of mupirocin to eradicate colonization, while PI probably suppresses *S. aureus* activity only for the duration of the surgery.

Another advantage of PI over mupirocin is the significant cost savings associated with intranasal treatment because of both the reduced cost per dose and the reduced number of doses needed. Torres et al. compared a screen-and-treat algorithm targeted at eradicating MRSA colonization with a universal PI prophylaxis strategy [52]. In this retrospective analysis of 1853 patients undergoing total hip or knee arthroplasty, the authors studied a cohort of patients screened for MRSA—and treated with 5 days of mupirocin if colonization was found—compared to a cohort of patients universally treated with one dose of PI immediately before surgery. The authors found no significant difference in SSI rates between the cohorts. The screened population had a 4.8% incidence MRSA colonization, while the unscreened population had a 4.7% incidence of prior documented MRSA colonization or infection. However, there was a significant difference in out-of-pocket cost, with MRSA screening and mupirocin treatment costing a mean of $110.47 per patient, whereas the universal PI treatment cost a mean of $16.42 per patient.

Despite the cost savings of PI over mupirocin, some authors have suggested a difference in efficacy between generic PI solutions and commercial products developed specifically for intranasal use. In a randomized, prospective, placebo-controlled study of nearly 500 patients undergoing major orthopedic procedures, Rezapoor et al. observed successful removal of *S. aureus* cultures in 48% of patients with off the shelf PI, 79% with the nasal-specific PI, and 41% with saline (p = 0.003) [53]. Importantly, this study also found a significant rebound of colonization by 24 hours after application in all study groups, which resulted in no statistical difference in decolonization between treatment groups at this time point. The authors also did not investigate the effect of this differential decolonization at 4 hours on the rate of SSI. This study highlights the difference in efficacy among products using the same active ingredient as well as the potential to develop formulations with superior effectiveness for decolonization based on factors independent of the active ingredient.

Nasal Chlorhexidine

Chlorhexidine gluconate has been used extensively for topical decolonization of the skin in surgical patients; however, it has also been used for nasal and oropharyngeal decolonization as well. In a randomized controlled trial of 991 elective cardiac surgery patients conducted in the Netherlands from 2003 to 2005, Segers et al. studied the effect of four-times-daily nasal and oropharyngeal CHG treatment from hospital admission until the day after surgery [54]. The authors found a significant reduction in the risk of overall nosocomial infection in CHG-treated patients (26.2% vs. 19.8%, ARR 6.4%, $p = 0.002$). On subgroup analysis, the risk of both deep and deep sternal infections was also significantly reduced (5.1% vs. 1.9%, $p = 0.002$; 3.0% vs. 1.0%, $p = 0.001$, respectively). Interestingly, lower respiratory tract infection rates and bacteremia rates were also lower in the group treated with CHG. However, neither overall SSI nor superficial SSI rates were significantly reduced in the treatment group, a finding that is shared with many studies of mupirocin decolonization. The authors also found a significant reduction in the length of hospital stay among those treated with CHG, from 10.3 days to 9.5 days (ARR 0.8 days, 95% CI 0.24–1.88).

Photodisinfection

Photodisinfection of the nares is another approach that has been studied for decolonization. In combination with CHG wipes, photodisinfection in the preoperative area was found to decrease surgical site infection among 3068 elective cardiac, orthopedic, spinal, vascular, thoracic, and neurosurgical patients. However, this study was limited by the use of a single-center observational study design, historic control population, and a significant lag time between control and experimental groups [55]. Clearly, further study is needed to determine the utility and efficacy of photodisinfection for *S. aureus* decolonization in surgical patients.

Perioperative Antibiotics

Timing and dose of perioperative systemic prophylactic antibiotic are critical and reduce the risk of SSI [56–58]. As discussed above, despite correct timing and dosage of perioperative antibiotics, nasal carriers of *S. aureus* still retain a higher risk of *S. aureus* SSI over noncarriers. Specific systemic antibiotic treatments have been studied prospectively for their ability to decolonize nasal *S. aureus* carriers. In particular, rifampin, either alone or in combination with novobiocin or trimethoprim-sulfamethoxazole, has been studied in randomized controlled fashion and found to be effective at decolonization [59, 60]. However, emerging resistance to rifampin limits its usefulness for large-scale decolonization programs. Combining topical agents with systemic antibiotics has also been attempted. In a randomized trial of hemodialysis patients, Yu et al. found that

rifampin and intranasal bacitracin was more effective at nasal decolonization than rifampin alone. In the same study, the authors determined the combination was also more effective than vancomycin, which itself was no more effective at nasal decolonization than no treatment [61]. Unfortunately, no published studies have looked specifically at nasal decolonization with systemic antibiotics in surgical patients.

Body Wash

Because *S. aureus*, as well as many other commensal and potentially pathogenic bacteria colonize the skin of surgical patients, the use of preoperative antimicrobial body washes is an appealing strategy to decrease SSI. In fact, showering or bathing with antiseptic agents such as chlorhexidine, povidone-iodine, or triclosan soap has been shown to decrease the burden of endogenous flora on the skin [62, 63]. Unfortunately, large randomized trials, specifically of chlorhexidine preparations for all surgical patients, have failed to demonstrate a reduction in SSI rates when compared to perioperative bathing with detergent alone [64–68].

Timing of Decolonization

If decolonization is chosen for surgical cases, it is important that it be done in close conjunction with the operative procedure. Mody has shown that recolonization is common at 90 days [69]. In another prospective study of decolonization for MRSA before orthopedic procedures, the authors confirmed decolonization and then patients were "admitted for operation within three months of a negative screen." Intravenous prophylaxis was cefuroxime. MRSA SSIs were statistically significantly more frequent in patients with a history of MRSA colonization who had been decolonized [70]. This presumably occurred because those patients had become recolonized with MRSA during the interval between decolonization and operation and were treated with an ineffective prophylactic antibiotic.

Cost-Effectiveness of Decolonization

The cost-effectiveness of treating *S. aureus* colonization depends on the cost of the prophylactic treatment, the cost of the prevented infection (both in-patient and out-patient costs), indirect costs, the costs of screening, if implemented, and the frequency of both colonization and infection. Because the cost associated with the most common decolonization treatments is low and the cost of a nosocomial infection is so high, most studies have determined that decolonization is cost-effective. Bloom et al. examined the cost-effectiveness of two treatment strategies in hemodialysis patients—a screen-and-treat program and a universal treatment program without screening. Assuming that 75% of *S. aureus* infections are attributable to nasal colonization and that eliminating colonization will reduce the number of infections by about 50%, the authors found an annual savings of $784,000 per thousand dialysis patients if patients were screened by culture and only carriers were treated. This saving was improved to $1,117,000 per thousand patients if all patients are treated for 3 days without screening [71].

Regarding surgical patients and prevention of surgical site infections, Vandenbergh et al. studied the cost-effectiveness of universal perioperative mupirocin in cardiothoracic surgery patients based on a prior intervention study using historical controls. As expected, postoperative costs were dramatically higher in patients with an SSI. Given an incidence of SSI of 7.3% in the control group and 2.8% in the mupirocin group, the use of mupirocin resulted in a cost savings of $16,633 per infection prevented [72].

A more recent study from the Netherlands found a similarly significant reduction in costs among cardiothoracic and orthopedic patients. The authors examined a subgroup of surgical patients who participated in a multicenter randomized controlled trial of hospitalized patients with *S. aureus* nasal carriage. This trial was discussed above and had previously shown a significant decrease in healthcare-associated *S. aureus* infections in patients receiving mupirocin nasal ointment and CHG-medicated soap compared to placebo [41]. In the analysis of cost-effectiveness, the authors found that mupirocin and CHG treatment of nasal carriers resulted in an average savings of €1911 per patient, with cardiac patients saving €2841 and orthopedic patients saving €955 [73]. The number of patients needed to screen to prevent an SSI was 250, while the number of carriers needed to treat was 23. Although the colonized patients were treated with 5 days of nasal mupirocin, in one of the busiest hospitals in the study, 90% of the surgical patients were admitted the day before operation and received only one or two decolonization treatments before the operation (Jan Kluytmans, personal communication, September 2011).

A population-based cohort study of the economic burden of SSI among hip and knee arthroplasty patients in Alberta, Canada, demonstrated a mean 12-month cost of CAD$95,321 [US$68,150] per patient in patients who developed a complex SSI vs. CAD$19,893 [US$14,223] among those who did not. The most commonly identified organism in SSI was *S. aureus,* and the cost associated with treatment of infection with this organism was higher than with all other pathogens. The authors indicated that, given this cost burden, decolonization protocols can be cost-effective even on a large scale [74].

An analysis of cost-effectiveness based on a culture-and-treat strategy in surgical patients found a savings of about

$1.5 million per 10,000 patients screened based on a carriage rate of 31% and a risk reduction of 48% [75]. These rate estimates are in line with those derived in the above studies and systematic reviews in surgical patients.

As suggested by Blooms' study in dialysis patients discussed above, there is evidence of decreased hospital costs among surgery patients using a universal decolonization protocol as compared to a screen-and-treat algorithm. In a before-and-after study of over 4000 patients undergoing primary total joint arthroplasty, Stambough et al. studied the effect of a newly-introduced universal intranasal mupirocin and CHG body wash protocol [76]. The authors found a significant reduction in both the overall SSI rate (5 vs. 15 cases; 0.2% vs. 0.8%; $p = 0.013$) and SSIs caused by *S. aureus* organisms (2 vs. 10; 0.09% vs. 0.5%; $p = 0.01$) compared to a previously implemented screen-and-treat program. Because the net cost of a total joint arthroplasty in this study increased by 462% in the setting of a prosthetic joint infection, even a small reduction in the rate of SSI resulted in a significant overall cost savings in the universal treatment group. In addition, the cost per patient for administering the universal treatment program was less than in the screen-and-treat era with an incidence of 20% *S. aureus* colonization in their patient population. As the authors acknowledge, the cost analysis does not account for the potential increased risk of mupirocin resistance among *S. aureus* carriers and the concomitant increase in SSI rates over time that may result.

MRSA Screening and Decolonization

Methicillin-resistant *S. aureus* colonization represents a special consideration when determining screening and decolonization methods. In the United States, a national survey from 2001 to 2004 demonstrated a decrease in the prevalence of MSSA colonization and an increase in the prevalence of MRSA colonization [3]. As mentioned above, MRSA colonization bears a higher risk than MSSA for nosocomial infection and a higher rate of morbidity and mortality in ICU patients [17, 18]. In addition, patients who develop an MRSA SSI have both a higher 90-day mortality rate and higher hospital costs compared to those with an MSSA SSI [30]. This risk is further heightened in patients who undergo hardware implantation. However, methods of decolonization have shown less success among MRSA carriers than MSSA carriers.

A randomized controlled trial of combined intranasal mupirocin, CHG body wash, and rifampin and doxycycline systemic treatment for MRSA colonization decolonized 74% of patient at 3 months and 54% at 8 months compared to no treatment. Mupirocin resistance appeared in 5% of follow-up isolates [77]. In a retrospective cohort analysis of MRSA carriers decolonized with mupirocin and CHG or PI nasal and body wash, only 39% of patients were successfully decolonized. The nosocomial infection rate was significantly lower among those successfully decolonized [78]. A systematic review of randomized controlled trials of MRSA decolonization methods found insufficient evidence to support any topical or systemic antimicrobial treatment for eradicating MRSA carriage [79]. When looking only at surgical patients, the effect of MRSA decolonization is similarly contentious. In a prospective interventional cohort study of universal MRSA real-time PCR (RT-PCR) screening and 5 days of intranasal mupirocin and CHG body wash among surgical patients, there was no significant decrease in nosocomial or surgical site infections. There was, however, a low level of MRSA colonization at admission (5.1%) and a low overall rate of surgical site infection (0.6%) in this study population [80].

When deciding whether to screen and decolonize, especially for major clean operations where the primary pathogen is *S. aureus*, it makes the most sense to target both MSSA and MRSA. Infection with either for an arthroplasty, spinal fusion, open heart procedure, or vascular prosthesis is disastrous complication. The Bode trial showed benefit when MSSA was the only *S. aureus* type found on screening [41]. In a multi-institutional study of patients having cardiac or orthopedic surgery performed in 20 hospitals in 9 U.S. states, the investigators followed an algorithm that attempted to screen all patients. If no *S. aureus* were found, then standard protocols were followed. If either MSSA or MRSA were found, then decolonization was performed. Patients with MSSA received standard intravenous prophylaxis, while those with MRSA received both vancomycin and a cephalosporin. Patients who could not be screened were treated as MRSA-positive. Those patients who were unscreened or whose screening results were unknown at the time of surgery received decolonization treatment and were assumed to be MRSA-positive. Mupirocin was continued until screening results were known, and mupirocin was discontinued for those with negative results. If sites were analyzed according to adherence to the protocol, *S. aureus* infection rates were three times lower when the protocol was adhered to than when it was partially adhered to or not adhered to [81].

In addition to topical treatment for MRSA decolonization, patients known to be colonized with MRSA prior to surgery should receive perioperative antibiotic prophylaxis directed at MRSA. Perioperative antibiotic selection for patients colonized by *S. aureus* is especially important and should be based on whether MRSA or MSSA colonization is present. In a report of perioperative prophylaxis among cardiac surgery patients, MSSA SSIs were more common among those who received vancomycin compared to cefazolin prophylaxis [82]. This finding was echoed in a retrospective study of vancomycin or beta-lactam prophylaxis in nearly 23,000 clean cardiac and orthopedic surgery

procedures from the Australian Surveillance Data (VICNISS). For these procedures, the risk of SSI with MSSA was nearly 3-fold higher if vancomycin prophylaxis was administered, whereas the risk of MRSA SSI was doubled if beta-lactam prophylaxis was used instead [83]. These two studies highlight the importance of accurately determining *S. aureus* carriage (MRSA or MSSA) and administering appropriate prophylaxis. Clinical practice guidelines further support this conclusion. A joint committee consisting of members of the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) recommends vancomycin plus a cephalosporin for SSI prophylaxis among patients known to be colonized with MRSA undergoing cardiac, thoracic, general, and neurosurgical procedures [84].

Conclusion and Summary of Recommendations

Patients colonized with *S. aureus* carry an increased risk of nosocomial and surgical site infections with the same organism. Carriage of MRSA is more difficult to eradicate, further increases the risk of infection, and makes treatment of infection more difficult, but MSSA is not benign. Programs aimed at screening and decolonizing patients prior to surgery have had varying degrees of success, depending on the endemic incidence of colonization, the type of organism, and the type of surgery. The benefit of decolonization has been most conclusively demonstrated in cardiothoracic and orthopedic surgery patients where surgical site and hardware infection are more problematic but are likely beneficial in other clean operations with placement of prostheses such as spinal operations and incisional hernia repairs with mesh. Results from trials of decolonization in general surgery patients have had variable success, largely due to limited sample size and an overall low incidence of Staphylococcal SSI. In general, decolonization has a greater effect on the prevention of deep space surgical site infection compared to superficial or wound infections.

Strategies for decolonization have focused on universal treatment for all patients or screen-and-treat programs aimed at rapid detection of colonization and treatment of carriers. This latter approach also affords the opportunity to demonstrate decolonization prior to surgery, if necessary. Both methods have proven to be cost-effective in a variety of surgical patient populations given the relatively low cost of preoperative decolonization compared to the burden of treating a surgical site infection.

The optimal decolonization strategy depends on the incidence of colonization in the patient population, the speed and cost of detection of carriage, and the cost and compliance associated with treatment. As the cost and delay for RT-PCR decrease over time, this will likely be the best method for rapid detection. Conceivably, this screening could be accomplished at the outpatient preoperative clinic visit and a decolonization regimen prescribed at the end of the visit for those patients who are found to be colonized.

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The Surgical Care Improvement Project Redux: Should CMS Revive Process of Care Measures for Prevention of Surgical Site Infections?

11

Deborah S. Yokoe

The Genesis of the Surgical Care Improvement Project

Many surgical procedures are performed each day in the United States; in 2014 approximately 14 million operative procedures were performed in inpatient hospital settings [1], and an additional 48 million were performed in ambulatory settings [2]. Surgical site infections (SSIs) are currently one of the most common types of infections associated with care that patients receive in healthcare facilities [3]. Approximately 110,000 SSIs occur each year in the United States [3] although this is likely to be an underestimate because of challenges around complete ascertainment of these infections, especially for SSI that are diagnosed after hospital discharge or are sequelae of procedures performed in the ambulatory setting. Estimates of average attributable costs of SSI range from $10,433 to $25,546 per infection (2005 and 2002 dollars, respectively), with considerably higher costs associated with some types of surgery. SSI have a substantial impact on national healthcare expenditures and are associated with an estimated annual cost in the United States of $3.3 billion and nearly 1 million additional inpatient days [4–7].

In August of 2002, the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) established the Surgical Infection Project (SIP) with the goal of improving SSI outcomes by increasing adherence to evidence-based use of perioperative antimicrobial prophylaxis (AMP) [8]. A SIP multidisciplinary expert panel selected these three performance measures for national surveillance and quality improvement:

1. The proportion of patients who have parenteral antimicrobial prophylaxis initiated within 1 h before the surgical incision.
2. The proportion of patients who are provided a prophylactic antimicrobial agent that is consistent with currently published guidelines.
3. The proportion of patients whose prophylactic antimicrobial therapy is discontinued within 24 h after the end of surgery.

The SIP expert panel chose to focus on subgroups of surgical procedures with clear evidence-based benefits of AMP including coronary artery bypass graft and other cardiac surgery excluding transplantation, vascular surgery, colorectal surgery, hip and knee arthroplasty, and abdominal and vaginal hysterectomy. In 2003, this national initiative evolved into the Surgical Care Improvement Project (SCIP) [9, 10], an extension of SIP supported by multiple agencies and organizations that continued to focus on the three AMP measures described above as well as three additional SSI prevention processes:

1. No hair removal or hair removal with clippers or a depilatory agent (i.e., avoidance of shaving) at the surgical site
2. Control of blood glucose during the immediate postoperative period for patients undergoing cardiac surgery (i.e., glucose of ≤200 mg/dL at 6 a.m. on postoperative days 1 and 2)
3. Maintenance of perioperative normothermia among patients with anesthesia duration of at least 60 min

Because the overall goal of the SCIP was to reduce preventable surgical morbidity and mortality, some additional process measures focused on improving non-SSI outcomes were also included:

1. Surgery patients on beta-blocker therapy prior to arrival who received a beta-blocker during the perioperative period.
2. Surgery patients who received appropriate venous thromboembolism prophylaxis within 24 h prior to surgery to 24 h after surgery.

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_11

Table 11.1 Surgical Care Improvement Project (SCIP) measures

SCIP performance measure	Performance measure description
SCIP Inf-1	Prophylactic antibiotic started within 1 h prior to surgical incision
SCIP Inf-2	Received prophylactic antibiotic consistent with recommendations
SCIP Inf-3	Prophylactic antibiotics discontinued within 24 h after surgery end time
SCIP Inf-4	Cardiac surgery patients with controlled postoperative blood glucose
SCIP Inf-6	Surgery patients with appropriate hair removal
SCIP Inf-9	Urinary catheter removed on postoperative day 1 or postoperative day 2 with day of surgery being day zero
SCIP Inf-10	Surgery patients with perioperative temperature management
SCIP Card-2	Surgery patients on beta-blocker therapy prior to arrival who received a beta-blocker during the perioperative period
SCIP VTE-2	Surgery patients who received appropriate venous thromboembolism prophylaxis within 24 h prior to surgery to 24 h after surgery

3. Surgery patients with urinary catheters removed on postoperative day 1 or postoperative day 2.

These SCIP measures (Table 11.1) were supported by a number of quality improvement organizations and endorsed by the National Quality Forum.

CMS and The Joint Commission provided the infrastructure for voluntary reporting of SCIP measures by hospitals. As part of the Deficit Reduction Act of 2005, CMS was required to collect hospital reported performance measures and to make this information available to the public [11]. Although reporting of SCIP measure adherence by hospitals to CMS continued to be voluntary, hospitals that did not report these process measures did not receive their annual 2% CMS market basket reimbursement updates. Hospital-specific SCIP adherence rates were also made accessible to the public on the CMS Hospital Compare website [12]. The Patient Protection and Affordable Care Act in 2010 further accelerated implementation of the CMS Value-Based Purchasing (VBP) and Hospital Acquired Conditions (HAC) Reduction programs, pay-for-performance programs with substantial potential to impact hospitals' Medicare reimbursement levels [13, 14]. Adherence to the SCIP measures along with other quality metrics was used to determine hospitals' VBP scores starting in 2013.

Evidence to Support the SCIP Measures

Perioperative Antimicrobial Prophylaxis

The evidence to support the impact of appropriate choice of antimicrobial agent(s) used for antimicrobial prophylaxis (AMP) and the importance of the timing of the start of AMP administration have been summarized in other publications including the "Clinical practice guidelines for antimicrobial prophylaxis in surgery" that was jointly developed by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA) [15].

1. Choice of AMP Agent(s)

The antimicrobial agent(s) selected for SSI prophylaxis should have activity against the most common SSI organisms associated with the specific surgical procedure. In addition, fundamental AMP principles include using an antimicrobial agent with the narrowest spectrum of activity required for SSI prevention in order to minimize the risk of adverse consequences resulting from impact on the patient's native microbial flora, including the emergence of multidrug-resistant organisms and infection due to *Clostridium difficile*. Overall, the most common organism associated with SSI following clean procedures continues to be *Staphylococcus aureus* [16] and therefore recommended AMP regimens for most surgical procedures include an anti-staphylococcal agent such as cefazolin. Because organisms that lead to SSI are those that are likely to contaminate the operative bed during the course of the procedure, procedure-specific AMP regimens recommended by SCIP also include agents with activity against other organisms that most commonly contaminate the operative field (e.g., anti-staphylococcal, Gram negative and anaerobic coverage for colon surgery to cover bowel flora) [15].

2. Timing of the Start of AMP Administration

In order to optimize the impact of AMP, serum and tissue concentrations exceeding the minimal inhibitory concentrations of the agent(s) being used should be achieved prior to the initial surgical incision (i.e., before contamination occurs). Support for the importance of the SCIP recommendation to begin administering the first dose of the AMP agent(s) within 60 min prior to the initial surgical incision (or within 120 min before incision for antimicrobial agents with longer infusion times such as vancomycin and fluoroquinolones) is mainly based on observational study data, including the study by Classen et al. that assessed SSI outcomes for patients who underwent a variety of surgical procedures and found SSI rates to be significantly lower for patients who received AMP starting within 2 h before surgical incision compared to any time after incision (0.59% vs. 3.3%) [17]. When the results were stratified according to the timing of the start of prophylaxis administration in relation to incision time, a statistically significant trend was observed demonstrating increasing risk of SSI with each successive hour that the start of AMP was delayed. Although some studies have

demonstrated lower SSI rates associated with shorter time intervals between the start of AMP and start of surgery (e.g., within 30 min prior to incision) [18, 19], the generalizability of those results is unresolved.

3. Minimize the Duration of AMP

Studies assessing the impact of varying durations of AMP strongly indicate that continuation of AMP after incision closure is not associated with added benefit compared with receipt of AMP limited to the procedure duration. Prolonged AMP administration, however, has been associated with adverse consequences including the emergence of resistant organisms [20] and increased risk for *Clostridium difficile* infection [21]. Although minimizing the duration of AMP is unlikely to impact patients' SSI risk, adherence to this antimicrobial stewardship-focused recommendation is important to reduce the risk of unintended adverse consequences associated with unnecessary exposure to antimicrobial agents.

Hair Removal Technique

There is limited high quality data addressing the impact of hair removal or hair removal techniques on SSI risk. Theoretically, shaving using razors may lead to microabrasions of the skin that can increase the bioburden of microorganisms and therefore the risk for subsequent development of SSI. A Cochrane systematic review [22] demonstrated no significant difference in SSI risk between patients who were shaved versus those who had no hair removal (relative risk of 1.75, 95% confidence interval 0.93–3.28) but did find a significantly higher risk of SSI associated with shaving compared with hair removal using clippers (relative risk of 2.03, 95% confidence interval 1.14–3.61). Although the evidence is limited, these results have been used to support the SCIP recommendation for no hair removal or, if hair removal is needed to perform the procedure, to avoid use of razors.

Perioperative Glucose Control

Although SCIP measures focused on blood glucose control in patients undergoing cardiac surgery during the immediate postoperative period [23, 24], beneficial impact of glucose control has also been demonstrated for patients undergoing other types of operative procedures [25–29]. The SHEA/IDSA "Strategies to prevent surgical site infections in acute care hospitals: 2014 update" [30], the Healthcare Infection Control Practices Advisory Committee (HICPAC) "Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017" [31], and the World Health Organization's (WHO) "Global guidelines for the prevention of surgical site infection" [32] recommend perioperative glycemic control for diabetic and nondiabetic patients undergoing cardiac and noncardiac procedures. Guideline recommendations regarding blood glucose target levels typically range from <180 to <200. Studies comparing these blood glucose targets to stricter glucose targets (e.g., 80–100 mg/dL or 80–130 mg/dL) suggest that tighter glucose control does not significantly improve SSI risk compared to standard glucose control [33, 34]. However, a systematic review and meta-analysis of studies comparing intensive (i.e., maintaining glucose ≤150 mg/dL) versus conventional glucose control protocols concluded that based on generally low quality evidence, intensive protocols were associated with reduced SSI risk [35].

Normothermia

High quality, randomized controlled trial results suggest that maintenance of perioperative normothermia reduces SSI risk for a variety of surgical procedures [36, 37]. The most effective strategies and temperature targets needed to optimize benefit are unclear based on existing literature, although some practice guidelines [30, 38] recommend maintaining a temperature of ≥36° or ≥35.5°.

Did the SCIP Improve SSI Outcomes?

Despite evidence-based support for the beneficial impact of individual SCIP measures on SSI risk and despite national data demonstrating improved adherence to SCIP measures over time, a clear association between adherence to SCIP measures and improvements in SSI outcomes has been difficult to demonstrate [39, 40]. A retrospective cohort study from an inpatient administrative database (Premier, Inc's Perspective Database) that included information from discharges between July 1, 2006, and March 31, 2008, for over 400,000 patients used administrative data to identify surgical patients with probable SSI using an algorithm based on discharge diagnosis codes. The investigators assessed the association between risk of SSI and adherence to individual and composite SCIP measures [41]. Although adherence measured through a global all-or-none composite infection-prevention score was associated with a lower probability of developing a postoperative infection, adherence to individual SCIP measures was not significantly associated with SSI risk. Limitations of this study included dependence on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify patients with SSI and restriction of these discharge codes to the hospitalizations when the surgical procedures took place (i.e., no readmission data); this may have substantially limited SSI ascertainment since many SSIs are diagnosed after

hospital discharge [42]. A retrospective cohort study by Hawn et al. used National Veteran's Affairs SCIP adherence data and SSI outcomes collected through the Veteran's Affairs Surgical Quality Improvement Program to assess the relationship between SCIP adherence and SSI risk. They found that although adherence to all SCIP measures significantly improved between 2006 and 2009, risk-adjusted SSI rates remained unchanged and SCIP adherence was not associated with lower SSI risk at the hospital level [43].

Why Is It So Challenging to Demonstrate a Significant Impact on SSI Risk?

There are a number of possible reasons for the apparent limited impact of improvements in adherence to SCIP measures on national SSI rates.

1. Some SCIP measures were not designed to impact SSI risk.

As discussed, the goal of the SCIP program was to improve postoperative outcomes and several of the SCIP measures are focused on non-SSI complications. For example, limiting the duration of AMP would not be expected to reduce an individual patient's SSI risk. The goal was instead to prevent the emergence of multidrug-resistant organisms and other complications of unnecessary exposure to antimicrobial agents through improved antimicrobial stewardship. Other SCIP measures are focused on preventing cardiac and venous thromboembolism-associated complications and catheter-associated urinary tract infections.

2. Adherence to many of the SCIP measures quickly became "topped off".

Hospitals attained high adherence to many of the SCIP measures shortly after SCIP implementation, and by 2009 national adherence rates exceeded 90% for all SCIP measures [12]. Because of this, further incremental improvements in adherence rates were unlikely to result in substantial improvements in SSI outcomes [44].

3. Reported adherence may not always reflect true practice.

Because CMS relied on self-reporting of SCIP adherence rates by hospitals with minimal data validation and because of pressure on hospitals to demonstrate good performance on publicly reported measures, the potential exists for "gaming" the system by inflating self-reported adherence rates.

4. SCIP recommendations may not be nuanced enough to impact outcomes.

Although AMP has been shown to reduce SSI risk for a wide variety of surgical procedures, it is possible that the specific aspects of AMP that are highlighted by SCIP were not nuanced enough to optimize impact. For example, although a menu of AMP choices for procedure categories were provided by the SCIP [45], a hospital's specific distribution of antimicrobial resistance (i.e., the hospital's "antibiogram") may suggest the need for broader or differing coverage than that recommended by the SCIP technical expert panel.

The effectiveness of AMP also depends on achieving adequate antimicrobial concentrations throughout the period of risk when the surgical incision is open. In order to achieve this, weight-based dosing may be required for some antimicrobial agents, including commonly used antimicrobials such as cefazolin and vancomycin. In addition, re-dosing of AMP agents for long surgical procedures is likely to be important for sustaining the protective effect of AMP during the period of risk [15]. Data from some studies suggest that repeat dosing of AMP agents for procedures lasting more than approximately two half-lives of the agent(s) is associated with lower SSI risk compared to procedures without redosing [18].

5. SCIP recommendations may constitute minimal requirements but additional SSI prevention strategies may be needed for further improvements in outcomes.

The practices highlighted by SCIP may reflect minimum requirements for SSI prevention but optimizing SSI prevention may require adherence to one or more additional interventions. Some of these interventions are discussed below (Table 11.2).

Preoperative Skin Preparation Using a Long-Acting Antiseptic Agent Plus Alcohol

A systematic review by Kamel et al. [46] included data from five randomized controlled trials, two cohort studies and two case-control studies, including a randomized controlled trial [47] that compared the impact of chlorhexidine-alcohol

Table 11.2 Examples of supplemental surgical site infection prevention strategies

Use an antiseptic that includes a long-acting agent plus alcohol for preoperative skin preparation
Administer preoperative oral antimicrobial prophylaxis to patients undergoing colorectal surgery
Use hemodynamic goal-directed therapy
Use supplemental oxygenation for patients with normal pulmonary function who undergo general anesthesia with endotracheal intubation
Screen patients for *Staphylococcus aureus* (SA) carriage and decolonize SA carriers for selected surgical procedures
Implement surgical site infection prevention bundles

versus povidone-iodine for preoperative skin preparation prior to clean-contaminated surgical procedures and demonstrated significantly lower SSI risk for patients randomized to receive skin preparation with chlorhexidine-alcohol. The overall conclusion of this systematic review was that conclusive evidence demonstrating the benefit of one skin preparation agent over another was lacking but that this should be a high priority topic for further research. A Cochrane systematic review and meta-analysis evaluating the impact of preoperative skin antiseptics on SSI prevention following clean procedures also concluded that there was insufficient evidence to recommend the use of one preoperative skin preparation agent over another but in a mixed treatment comparison meta-analysis found that alcohol-containing products had the highest probability of being effective [48].

Administering Preoperative Oral Antimicrobial Prophylaxis to Patients Undergoing Colorectal Surgery

For patients undergoing colorectal surgery, the utility of preoperative oral antimicrobial agents with or without preoperative mechanical bowel preparation remains controversial. Interpreting the results of studies on this topic is challenging because of lack of clarity around the impact of the interaction between mechanical bowel preparation and oral antimicrobial prophylaxis on SSI risk. The results of a Cochrane systematic review and meta-analysis showed no significant difference in SSI risk between patients who did and did not receive mechanical bowel preparation prior to colorectal surgery [49], supporting the NICE surgical site infection guideline recommendation to not use mechanical bowel preparation routinely as a strategy to reduce the risk of surgical site infection for colorectal surgery [38]. Despite this, preoperative mechanical bowel preparation is still commonly favored by colorectal surgeons [50]. Among patients who undergo mechanical bowel preparation, receipt of preoperative oral antimicrobial agents, usually consisting of oral neomycin plus erythromycin or metronidazole given two or three times during the day prior to surgery, has been associated with significant reductions in SSI risk following colorectal surgery [51, 52]. Most studies demonstrating improved SSI outcomes associated with oral antimicrobial prophylaxis also utilized mechanical bowel preparations, making it difficult to extrapolate results to patients who receive oral AMP without mechanical bowel preparation prior to colorectal surgery. Overall, study results suggest a benefit to preoperative oral antimicrobial prophylaxis when provided in conjunction with mechanical bowel preparation.

Hemodynamic Goal-Directed Fluid Therapy

A systematic review and meta-analysis by Dalfino et al. [53] evaluated the impact of hemodynamic goal-directed fluid therapy on SSI risk. Goal-directed fluid therapy was defined as perioperative monitoring and manipulation of hemodynamic parameters to reach normal or supraoptimal values by fluid infusion alone or in combination with inotropic therapy within 8 h after surgery. In this meta-analysis of 18 randomized controlled trials, standard therapy was associated with significantly higher SSI risk compared with goal-directed fluid therapy (odds ratio of 5.8, 95% confidence interval 0.46–0.74). Hemodynamic goal-direct fluid therapy is a component of "Enhanced Recovery After Surgery" protocols (see below) and is included as a conditional recommendation in the WHO SSI prevention guidance [32].

Supplemental Oxygenation

Although studies evaluating the impact of supplemental oxygenation on SSI risk have had varying results, overall they provide support for the benefit of administering increased fraction of inspired oxygen (FiO_2) both intraoperatively and post-extubation in the immediate postoperative period for patients with normal pulmonary function who undergo general anesthesia with endotracheal intubation [54]. Benefit was seen in studies in which normothermia and adequate volume replacement were monitored and maintained [55–57], suggesting the importance of optimizing parameters needed to ensure tissue oxygen delivery in order to maximize the impact of supplemental oxygenation on SSI prevention.

Preoperative *Staphylococcus aureus* Screening and Decolonization

A number of recent studies have assessed the impact of a variety of strategies that include *Staphylococcus aureus* (SA) decolonization, including a randomized controlled trial performed in the Netherlands in which patients were screened for SA carriage on hospital admission and patients found to be SA carriers were then randomized to receive either 5 days of intranasal mupirocin and chlorhexidine bathing or placebo. In this study, SA carriers who received intranasal mupirocin and chlorhexidine bathing had significantly lower SSI risk [58]. A systematic review and meta-analysis evaluating studies that assessed the effectiveness of nasal SA decolonization and inclusion of a glycopeptide for AMP on SSI risk for patients undergoing cardiac surgery and orthopedic total joint replacement surgery concluded that a bundled intervention including nasal decolonization for all SA carriers and glycopeptide prophylaxis for methicillin-resistant SA (MRSA) carriers may decrease rates of SSI caused by SA or other Gram positive bacteria [59]. A prospective, observational multicenter study involving patients who underwent cardiac surgery and hip or knee replacement procedures demonstrated that a bundled intervention that included preoperative SA screening, decolonization of SA carriers with intranasal mupirocin and topical chlorhexidine, and targeted addition of vancomycin to cefazolin or cefuroxime AMP for MRSA carriers was associated with a

significantly lower deep incisional and organ/space SSI risk (rate ratio 0.58, 95% confidence interval 0.37–0.92) [60].

SSI Prevention Bundles

During recent years, there has been increasing interest in using bundled protocols to prevent healthcare-associated infections. A "bundle" is usually defined as a grouping of evidence-based practices that individually improve care. Central line-associated infection (CLABSI) prevention bundles, for example, have been shown to result in significant improvements in CLABSI outcomes [61]. Some examples of SSI prevention bundles that merit attention are discussed below.

1. Surgical Safety Checklist

Haynes et al. in collaboration with the World Health Organization evaluated a Surgical Safety Checklist in a multinational, multicenter observational study. Their checklist consisted of questions assessing adherence to practices aimed at preventing surgical complications. The checklist questions were administered at three perioperative time points (before induction of anesthesia, before skin incision, and before patient left the operating room). Implementation of the checklist was associated with significant improvements in SSI and mortality rates in a before-after comparison [62].

2. Other SSI Prevention Bundles

A variety of other SSI prevention bundles have been evaluated. These typically include SCIP-recommended practices in addition to varying combinations of supplemental practices including many of those discussed above. A systematic review and meta-analysis by Tanner et al. assessed the impact of SSI prevention bundles for colorectal surgery using results from 13 studies and concluded that use of evidence-based surgical care bundles significantly reduced the risk of SSI compared with standard care (risk ratio of 0.55, 95% confidence interval of 0.39–0.77) [63].

3. Enhanced Recovery After Surgery

Use of a bundle of perioperative practices aimed at improving surgical recovery following colorectal procedures referred to as Enhanced Recovery After Surgery (ERAS) has gained support in the surgical community based on a growing body of literature suggesting beneficial impact of ERAS bundles on postoperative outcomes, including SSI [64–67]. ERAS protocols typically include administration of a carbohydrate beverage prior to surgery, avoidance of sedatives, goal-directed fluid administration, multimodal pain control minimizing use of narcotics, and postoperative immediate diet and mobilization. ERAS protocols have been implemented with and without additional bundles of practices specifically aimed at SSI prevention. For example, a study by Keenan et al. evaluated sequential implementation of an ERAS pathway followed by a SSI prevention bundle and found that introduction of the ERAS pathway alone resulted in reduced length of stay and improved superficial and organ/space SSI rates while subsequent addition of an SSI bundle that included mechanical bowel preparation with oral antibiotics, preoperative chlorhexidine cleansing of patient, chlorhexidine-alcohol preoperative skin preparation, standardized AMP, maintenance of euglycemia and normothermia, fascial wound protectors, gown and glove change prior to fascial and skin closure, and a dedicated wound closure tray led to further significant reductions in SSI and sepsis rates [68].

The impact of SSI bundles likely depends on adherence to bundle elements, and some studies demonstrated that the number of bundle processes that were adhered to correlated with patients' SSI risk, suggesting an additive effect for each SSI prevention element [69].

Change of Focus from Process to Outcomes Measures Used for Pay-for-Performance

Over the past several years, CMS's approach to assessing the quality of care provided by hospitals has undergone a major shift in focus from process to outcome measures. In the area of SSI prevention, the shift towards focus on SSI outcomes was reflected by a change in CMS reimbursement practices implemented in October of 2008, in which CMS ceased additional payment for Hospital-Acquired Conditions not present on admission (POA), including some specific types of SSI [70]. Beginning in 2012, acute care hospitals were required to either report SSI outcomes following abdominal hysterectomy and colon surgery in addition to other healthcare-associated infection outcomes to CMS as part of the Hospital Inpatient Quality Reporting Program or receive a 2% penalty on Medicare reimbursement. As part of the CMS HAC Reduction program, beginning in fiscal year 2016 CMS reimbursement was tied to hospital performance around SSI and other healthcare-associated infection outcomes. Hospitals with HAC scores that fall within the lowest performing quartile are subject to a 1% loss in total Medicare inpatient prospective payment system (IPPS) reimbursement [71].

Metrics used to determine a hospital's VBP score are divided into domains that include clinical process of care (including the SCIP measures), patient experience, and outcome measures (including SSI outcomes following colon surgery and abdominal hysterectomy procedures). In fiscal year 2013, process of care measures accounted for 70% of a hospital's VBP score but by fiscal year 2016, process of care

measures accounted for only 20% of VBP scores compared to a 40% weight for outcome measures. Starting in fiscal year 2017, VBP no longer included SCIP process of care measures.

Limitations of SSI Outcome Measures for Pay-for-Performance

Although judging the performance of hospitals based on SSI outcomes makes intuitive sense since the goal of quality improvement efforts is ultimately to prevent postoperative complications, utilizing SSI outcomes as pay-for-performance metrics has led to a number of major challenges.

SSI Surveillance Relies on Subjective Interpretation of Medical Information and Is Vulnerable to Gaming

There are a number of studies that demonstrate substantial variation in the completeness of SSI data reported by hospitals [72, 73]. Even when using standardized CDC National Healthcare Safety Network (NHSN) surveillance definitions [74], application of SSI surveillance definitions requires some subjective interpretation of clinical information. For example, assessing the presence of "purulent drainage", a criterion for both deep incisional and organ/space SSI, requires both highly subjective interpretation of the quality of drainage material and documentation in the medical record. Some SSI criteria also depend on provider practices that may vary between hospitals; for example, facilities that are more aggressive about aspirating and culturing postoperative intraabdominal fluid collections are more likely to fulfill microbiology-based SSI criteria.

Ascertainment of SSI diagnosed after hospital discharge can be particularly challenging, especially for postoperative infections diagnosed and treated solely in the ambulatory setting or SSI diagnosed and treated at healthcare facilities other than the hospital where the original surgical procedure took place. The proportion of patients with SSI who are readmitted to the same hospital where the index surgery took place can vary considerably among healthcare facilities, and this can impact the completeness of SSI ascertainment and relative ranking of hospitals based on SSI outcomes [75, 76].

Surveillance Bias and Accessibility to Data

The completeness of hospitals' SSI ascertainment is highly dependent on the intensity of resources focused on SSI surveillance. Healthcare facilities with robust electronic health records or surveillance processes that effectively utilize automated medical data will be more likely to capture information that can be used to determine the presence of postoperative infections. These hospitals are therefore likely to report more SSI events than healthcare facilities with limited access to electronic health data and can be erroneously characterized and penalized as poor performers. Variability in infection preventionist access to electronic surveillance systems is reflected in the finding by Stone et al. that only 34.3% of NHSN facilities reported using an electronic surveillance system for identifying healthcare-associated infections [77]. In addition, SSI surveillance is resource-intensive, requiring review of a broad range of clinical information in order to apply surveillance definitions, and the effort available for surveillance can vary substantially between facilities, affecting the completeness of SSI ascertainment [78].

Using SSI Outcomes to Judge the Performance of Hospitals Requires Adequate Risk Adjustment

In order to meaningfully compare hospitals' SSI outcomes, adequate risk adjustment is critically important in order to take account of intrinsic differences in patient risk factors that are not modifiable through improvements in hospitals' practices. Currently, the standardized infection ratio for complex SSI used for CMS submission utilizes only a small number of variables for SSI risk adjustment. For example, for patients undergoing abdominal hysterectomy procedures, only a limited number of variables (i.e., age, American Society of Anesthesiologists (ASA) score, diabetes status, body mass index, and whether the healthcare facility is considered an oncology hospital) are included in the logistic regression model used for risk adjustment [79]. Other potentially important risk factors including medical comorbidities that increase SSI risk (e.g., active malignancies, renal failure) are not currently taken into account [80], and hospitals with more complex patient populations at higher intrinsic risk for SSI may be more likely to receive lower performance rankings and to incur financial penalties. The possibility of inadequate risk adjustment was highlighted in a study examining Medicare fiscal year 2015 payments that found that major teaching hospitals were four times more likely to receive the HAC Reduction penalty compared to nonteaching hospitals [81].

Outcome Measures Are Challenging to Apply to Small Volume Hospitals

Because SSIs are relatively rare events and because of limitations in the stability and reliability of SSI outcome measures for hospitals that perform relatively few surgical

procedures, SSI data for all hospitals with <1 expected SSI per year based on procedure volume are excluded from metrics contributing to that hospital's HAC score and ranking. Based on CMS Hospital Compare data, this meant that SSI outcome measures from over 30% of hospitals performing colon surgery and over 60% of hospitals performing abdominal hysterectomy procedures were excluded from metrics used to determine those hospitals' HAC scores during the performance period of April 2014 through March 2015 [82]. This is problematic for a number of reasons. First, it means absence of SSI performance measures for a large proportion of hospitals that perform the targeted surgical procedures. Secondly, there is evidence that hospitals that perform a lower volume of surgical procedures may have higher postoperative complication rates [83–85]; this means that the hospitals that are most likely to benefit from SSI-related quality improvement efforts are excluded from submitting SSI metrics and that some larger volume hospitals may consequently receive undeserved financial penalties. The study by Kahn et al. described above found that hospitals with 400 or more beds were almost twice as likely to receive the HAC penalty and more than twice as likely to be penalized under VBP compared to hospitals with fewer than 100 beds [81].

The limitations of using SSI outcome measures for interhospital comparisons are underscored by studies that suggest that hospitals' performance around healthcare-associated infection metrics may not adequately reflect the quality of care provided. A study by Rajaram et al. evaluated hospitals that were penalized based on HAC Reduction Program performance data used for fiscal year 2015 assessments and examined the association between those hospitals' HAC scores and other quality metrics. The investigators found that hospitals that were penalized under the HAC program were more likely to have quality accreditations, to offer advanced services, to be major teaching institutions, and to have better performance on other process and outcome measures, suggesting a disconnect between hospitals' HAC scores and the quality of care provided [86].

Going Forward—Back to the Future?

CMS incentives and penalties have the potential to exert powerful motivating forces on hospital decision makers and can result in major changes in prioritization of hospital resources. For this reason, thoughtful alignment of incentives and penalties with performance metrics that are likely to promote adherence to processes that result in improved patient outcomes is critically important. As discussed above, CMS has transitioned from using process measures to outcome measures as pay-for-performance SSI metrics. Limitations around the ability to standardize application of SSI surveillance definitions and methods and to adequately risk adjust SSI outcomes may unfairly penalize some high performing hospitals with robust surveillance processes or complex, intrinsically high-risk patients and excludes low volume hospitals from evaluation. For these reasons, investing research into improving our ability to perform adequate SSI outcome risk adjustment is essential.

Until these challenges are resolved, it may also be worth considering shifting the focus of pay-for-performance programs at least partially back towards SSI process measures. In order to optimize the impact of SSI process of care measures, it will be important to choose processes that are evidence-based and that augment fundamental SSI prevention practices already in place at most hospitals, to consider procedure-specific modifications of recommendations, and to take into consideration the additive effects of bundled approaches to SSI prevention.

Importantly, our ability to prevent SSI is limited by gaps in our understanding about which perioperative practices, individually or in combination, are most likely to impact SSI risk. We also have limited insight into about how best to implement and sustain adherence to those practices that have been shown to be effective. In order to optimize national efforts to improve surgical outcomes, it will be essential to allocate adequate financial resources to support high quality SSI prevention research.

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Healthcare Worker Apparel and Infection Prevention

12

Salma Muhammad Abbas and Gonzalo Bearman

Healthcare Worker (HCW) Apparel and Infection Prevention

HCW attire is considered an important component of professionalism [1]. Traditionally, items of clothing such as lab coats and scrubs have been worn by HCWs for identification by hospital staff and patients. These garments also provide protection against infections caused by organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae*, *Acinetobacter* spp., Ebola, respiratory viruses, as well as blood-borne viruses such as HIV, hepatitis B, and hepatitis C by preventing exposure to blood and body fluids [2]. According to one study, nasal carriage rates of MRSA among HCWs may range from 0.3% to 12%, and colonized individuals may spread these infections to others [3]. While the role of HCW apparel as a vehicle for the spread of infections is not completely understood, a growing body of evidence suggests that contaminated soft surfaces, such as curtains, upholstery, and apparel, are implicated in the transmission of infectious diseases [2, 4].

Hospital Policies Regarding HCW Attire

Hospital policies pertaining to HCW attire address the general appearance of employees and provide guidelines for dress code appropriate for settings such as procedure areas and operating rooms [1]. Most of these outline detailed instructions regarding the use of items such as masks, head covers, scrubs, footwear, and jewelry and are in agreement with the Association of Perioperative Nursing (AORN) standards [1]. Attire outside sterile procedure areas is not as well-defined at most facilities and practices vary across centers. Several facilities support the use of white coats, while others adopt measures such as "bare below the elbows" (BBE).

White Coats, Scrubs, and Uniforms

Some institutions mandate the use of lab coats and uniforms for certain HCWs in favor of projecting a professional image. Over recent years, these have been linked to the spread of multidrug-resistant organisms (MDROs). Microorganisms are capable of surviving in moisture and protein-rich soil or dirt that contaminates HCW apparel [2]. According to one study, 23% of lab coats were found to be contaminated with methicillin-sensitive *S. aureus* (MSSA) and 18% with MRSA [5]. In another study, samples were collected from uniforms of 135 HCWs including nurses and physicians, 58% of whom had reported changing uniforms every day. Potentially pathogenic bacteria were cultured from 60% of the uniforms [6]. In a study carried out by Munoz-Price and colleagues, cultures were obtained from the hands and apparel of HCWs working in five intensive care units. Microorganisms were isolated from 103 hands which constituted 86% of the total number cultured. These included *Staphylococcus aureus*, *Acinetobacter* spp., enterococci, and skin flora. Bacterial growth on hands was more likely to be associated with contamination of lab coats when compared to growth on scrubs [7]. Krueger et al. compared the bacterial profile of 30 pairs of scrubs worn continuously by on-call residents with unworn scrubs. Eighty-nine percent of post-call samples tested positive compared to 41% of unworn scrubs. Coagulase-negative *Staphylococcus* (CoNS), *Micrococcus*, MSSA, and gram-positive rods were isolated from post-call scrubs, while CoNS, gram-positive rods, and *Streptococcus viridans* were cultured from unworn scrubs [8].

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_12

Neckties

Multiple studies examined the potential for neckties to be contaminated with bacteria during patient interactions. Organisms such as *Staphylococcus aureus*, bacillus, and gram-negative bacilli have been isolated from ties [9, 10]. According to a study, 20% of doctors' ties were colonized with *Staphylococcus aureus* and 70% admitted to have never washed the ties [9]. In a recent systematic review, Pace-Asciak et al. concluded that neckties may be contaminated during patient encounters; however, there was no evidence to support the role of neckties in infection transmission [11].

Bare Below the Elbows (BBE) Strategy

The Society for Healthcare Epidemiology of America (SHEA) defines BBE as wearing short sleeves and eliminating jewelry, wristwatches, and neckties from the attire of HCWs in an attempt to minimize the risk of transmitting infections [1]. This strategy has been implemented by multiple centers in the USA and nationwide in the UK. Multiple studies have been conducted to determine the effectiveness of this strategy for infection prevention, with conflicting results. According to a prospective, randomized controlled trial, the rates of *Staphylococcus aureus* contamination of garments and skin at wrists were similar among physicians wearing white coats or short-sleeved apparel following an 8-h work shift [12]. In addition, two other studies were unable to establish a significant difference in bacterial contamination when comparing the BBE attire with controls [13, 14]. A study conducted by Farrington et al. reported an advantage of this strategy while examining wrist disinfection rates after use of an alcohol handwash when compared to non-BBE apparel [15]. Similarly, in a randomized clinical trial, healthcare workers wearing long-sleeved lab coats while examining a mannequin contaminated with cauliflower mosaic virus DNA were more likely to get their sleeves and wrists contaminated compared to those wearing short-sleeved lab coats. Twenty percent of those wearing long-sleeved lab coats transmitted the DNA on to a second mannequin [16].

Laundering

Laundering practices for HCW apparel vary across institutions. Some offer laundering facilities for lab coats, scrubs, and uniforms on-site. HCWs may use these or opt to launder items of clothing themselves. It is crucial for industrial laundering setups to clean as well as disinfect textiles contaminated with microorganisms [17]. These facilities are generally considered sufficient to render garments bacteria-free, but several studies have indicated that clean laundry may be recontaminated due to improper handling. In a study conducted by Fijan and colleagues, rotavirus RNA was isolated from hospital laundry rinse water, laundered garments, environmental textiles, and hands of laundry workers following standard washing. Regular education of workers regarding hygiene and regulation of disinfecting procedures with special focus on areas such as sorting, ironing, folding, and packing of laundered textiles can help prevent the transmission of infections through industrial laundering [17]. The results of two other studies revealed that *Klebsiella oxytoca* and *Clostridioides difficile* spores can survive through washer extractors, highlighting the need to monitor laundering facilities [18, 19].

While these facilities have been linked to the transmission of infections, washing clothes at home may also be associated with the spread of infections. According to one study, artificially contaminated apparel was not free of bacteria at the end of a wash at home [20]. This is supported by other studies whereby *Staphylococcus aureus*, *Acinetobacter*, and *Gordonia bronchialis* were isolated from domestically laundered apparel [21, 22]. Of note, studies evaluating the process of domestic washing or comparing this with professional hospital laundering are limited.

Outbreaks Related to HCW Apparel

A recent study linked an outbreak of *Gordonia bronchialis* sternal infections to an anesthesia nurse's scrubs. Four different strains of *G. bronchialis* were isolated from her hands, scrubs, and axillae as well as her roommate. Following disposal of the washing machine used for laundry at home, repeat cultures from her scrubs, axillae, and hands were negative, and no further *G. bronchialis* sternal infections were identified [22].

Innovations in Textiles

Textiles impregnated with antimicrobials and those with fluid-repellant properties have been on the market for a long time, but their use has not been widely implemented in infection control programs [2]. In a crossover trial to assess the effectiveness of antimicrobial scrubs, a four to seven mean log reduction in MRSA carriage was noted in the antimicrobial scrub group, but no differences were noted for the burden of vancomycin-resistant enterococci or gram-negative rods [23]. Combining hydrophobic repellency with this technology may be beneficial [2]. Data on textile innovations and infection prevention remain limited [24]. Further studies are warranted to assess the impact of this novel technology on infection prevention.

Patients' Perceptions Regarding HCW Attire

Several studies have been carried out to determine the perceptions and preferences of patients regarding HCW attire. Most studies revealed an inclination toward formal apparel when compared to casual dressing or wearing scrubs, and some of these indicated that attire preferences were unlikely to impact clinical encounters in terms of patient satisfaction [25, 26, 27, 28, 29, 30, 31, 32, 33]. In contrast, multiple studies assessing perceptions regarding white coats revealed a patient preference for these with some studies indicating a higher level of trust in physicians wearing white coats [25, 27, 34, 35, 36, 33]. With regard to BBE, most studies have indicated that patients do not favor this policy [25, 26, 31, 37, 38]. Following education, older patients were found to have a predilection for short-sleeved shirts, while younger patients preferred scrubs for choice of BBE attire [25]. Several studies addressing the inclusion of neckties in HCW attire revealed that these items were not considered a necessary component of physicians' apparel, and patients did not expect physicians to wear them [9, 38, 39]. According to a cross-sectional descriptive study, patients indicated daily laundering of clothes as the most important feature of HCW attire [34]. Patient perceptions are crucial in clinical interactions and must be taken into account when formulating policies pertaining to HCW apparel. Patient education is of paramount importance when changes such as BBE or mandating white coats are considered.

Proposed Approach for HCW Attire

The best choice for HCW attire is one that promotes a professional image while minimizing the transmission of infections [1]. Several studies have been conducted to determine the optimal approach to HCW apparel, but no consensus has been reached, and this remains an area of ongoing debate. Current SHEA guidelines for HCW attire have been summarized in Table 12.1 [1]. Some experts recommend augmenting infection control strategies such as handwashing with introduction of strategies such as Bare below the elbows (BBE) attire in view of biological plausibility. The role of this approach has not been established in the realm of infection prevention, but it is a cost-effective measure, unlikely to cause harm and may be considered for these reasons [1]. For facilities that opt for white coats, HCWs must be provided with two or more coats. Experts recommend laundering of such items of clothing daily if possible and at least once a weak. On-site professional laundering should ideally be available to employees at minimal cost. If domestically washed, the use of hot water and bleach is recommended. Additionally, institutions should make arrangements for hooks to enable HCWs to remove white coats prior to patient encounters to minimize contamination of these. With reference to items of clothing such as neckties, there is evidence to suggest that contamination may occur during patient interactions, and if worn, these must not come in contact with patients or their surroundings. There is, however, paucity of data to support elimination of neckties from HCW attire. Some studies support the use of a plastic apron to prevent bacterial contamination of the front of apparel worn by HCWs, and this may be a consideration for those wearing neckties [40]. Similarly, items such as jewelry, watches, cell phones, and pagers should be secured to prevent contact with patients and their surroundings; if contaminated, these must be disinfected. Items such as stethoscopes must be disinfected after use and patients in contact isolation must have designated medical equipment. The use of identification badges is strongly recommended and these must be clearly visible when worn [1]. In terms of protecting feet from contamination with blood and hazardous materials and preventing falls among HCWs, footwear with closed toes, low heels, and nonskid soles is recommended. Individual centers may differ in preferences, and therefore, consultation with HCWs and patients to determine their perceptions is critical in the process of formulating policies. HCW attire remains as area of scrutiny in the realm of infection prevention, and further studies are required to better characterize the best approach in this regard.

Table 12.1 Current guidelines for HCW attire [1]

Component of HCW attire	Recommendations
White coats	HCWs must be provided with two or more coats
	Hooks should be available in areas close to patients' rooms to enable physicians to remove white coats prior to contact with patients or their surroundings
Neckties	Must be secured to prevent contact with patients or their surroundings
BBE	Use supported by biologic plausibility
	Exact impact on infection prevention unknown
	May be used as an adjunct to other infection control measures such as handwashing
	Scrubs or short-sleeved shirts may be used
Laundering	Ideally, items of daily wear should be laundered daily or at least once a week
	May be laundered at on-site facilities or at home
	If washed at home, hot water and bleach must be used
Footwear	Closed toes with small heels and nonskid soles
Personal items such as jewelry and pagers	Must be disinfected if contaminated

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Antimicrobial Textiles and Infection Prevention—Clothes and Inanimate Environment

13

Rachel H. McQueen and Briana L. Ehnes

Introduction

Textiles are ubiquitous and an essential part of human society. Within the hospital environment, textiles have many functions, such as the clothing worn by patients and healthcare workers, the towels and cloths used to contain and mop up fluids, drapes used to isolate and maintain sterility during surgery, furnishings such as upholstered chairs as well as curtains, carpets, and also bedding. As part of the inanimate environment, textiles could act as a potential source of infection [1, 2]. This is because microorganisms can be transferred from an infected patient, a healthcare worker, or some environmental source, and persist within the textile only to be transferred to a susceptible individual. Frequent and effective laundering is the most common and most effective strategy for reducing microbial burden on textiles [3]. However, not all textiles in the hospital setting are frequently laundered (e.g., privacy curtains) or easily laundered (e.g., upholstery on chairs). As well, within a typical work shift (8–12 hours), the microbial load on a healthcare workers' clothing could become significant [4], and thus the transmission of pathogenic microorganisms may be possible. A possible solution to the problem of relying solely on cleaning involves integrating biocidal textiles into the hospital environment in order to reduce the microbial burden to levels low enough to reduce the rate of healthcare-associated infections (HAIs) [1]. The purpose of this chapter is to review the literature pertaining to contamination of hospital textiles by potentially pathogenic microorganisms and the related transmission of HAIs, describe the antimicrobial agents incorporated in textiles, describe the in vitro standard test methods used to assess antimicrobial efficacy, and evaluate the effectiveness of antimicrobial-treated textiles in the hospital environment.

Textiles in Healthcare

Many textiles are utilized in a healthcare setting, including bedding (pillows, bed linens, and blankets), patient gowns, towels, surgical gowns, scrub suits, lab coats, splash aprons, and privacy drapes. Healthcare-related textiles are functional and intended to provide some or all of the following functions: a protective function (e.g., surgical gowns), to ensure privacy (e.g., drapes, patient gowns), be absorbent (e.g., towels), or add a level of comfort (e.g., bedding). Hospital textiles fall under two broad categories, reusable and disposable. Reusable or multiple-use textiles tend to be woven structures composed of cotton or polyester or blends of these fibers. Other fibers and fabric structures can be present as well, for example, in compression garments knitted fabrics composed of nylon/spandex, and liquid impermeable aprons, which are typically a composite material with a polyurethane or PVC laminate film over a knit backing. Disposable or single-use textiles tend to be nonwoven structures, which may include cellulose fibers (i.e., wood pulp) or synthetic fibers such as polypropylene, polyester, and nylon. Disposable textiles vary widely in their functions and properties, but the majority are intended to be single-use items. They also tend to be less durable than reusable textiles, although some types of synthetic nonwovens can have high tensile strength. Multiple-use hospital textiles should be durable to the high wash/dry temperatures and chemical treatments (e.g., bleach) necessary to ensure removal of human-based soils and eradication of microorganisms. Any treatments that have been applied to the textile during or after construction in order to have specific (or more desirable) properties (e.g., stain repellency, antimicrobial) must also remain durable during use and to laundering.

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_13

The Role of Textiles in Healthcare-Associated Infections (HAIs)

Among the many routes of exposure to infectious agents, with the person-to-person route for transmission of HAI being the most common [5, 6], the inanimate environment, which includes textiles, plays a significant role. Clothing, worn by healthcare workers such as scrubs, white coats, and gowns have been shown to harbor potentially pathogenic bacteria [7–11]; both the person's own microflora could become a source of transmission [12], but more concerning is the transmission of infected patient via healthcare workers clothing to other patients [2]. As well, hospital privacy curtains, bedding, towels, and drapes have been identified as textiles that have the potential to harbor harmful bacteria [13–16].

Privacy curtains have been found to frequently be contaminated with potential hospital pathogens such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile* [13, 16]. Since curtains are touched by health care personnel before, during, and after performing patient care, often before the worker has had time to wash their hands, contaminated curtains can be a source of transmission of infectious agents [13, 17]. Furthermore, compared with many other hospital textiles, privacy curtains are infrequently changed, difficult to clean, and often only dealt with when visibly soiled [13]. Even after only one week of use, 92.3% of new curtains had evidence of contamination [13]. In an in vitro study, polyester fabric (used privacy curtains) was found to harbor harmful bacteria such as staphylococci and enterococci, which could survive for days and even months after drying on commonly used hospital fabrics. The authors reported that the viability of the enterococci on the fabrics tended to be much longer than on other common hospital surfaces [18].

Within the hospital ward, the process of making beds can release considerable amounts of microorganisms into the air which could be breathed in by staff or patients, as well as contaminate surrounding surfaces which may be transmitted later. For example, in one study, high levels of MRSA were detected during and immediately after bed-making in the air as well as the floor, on bed sheets, over-bed tables, and clothing [19].

Hospital linens and clothing have reportedly become contaminated due to poor quality hygiene practices within hospital laundry facilities, as "clean" linen trolleys were not being cleaned frequently enough. Coagulase-negative staphylococci (human origin), and *Bacillus* spp., molds (environmental origin) were found to have transferred to the freshly laundered linens [5]. Other cases where "clean" laundry has been implicated in transmission of infection are: an infection among infants connected to the presence of *Streptococcus pyogenes* on hospital laundry and in particular, the vests given to new-borns after birth [20]; an outbreak of *Bacillus cereus* in Japan in which laundered towels were the suspected source of contamination [14]; and another *Bacillus cereus* infection in which hospital linens and the washing machine were both highly contaminated with bacteria [21]. In these cases, the contamination likely came from the washing machine itself, all from hospital laundries. Another case, reported that a washing machine located in the home of a nurse anesthetist was the cause of *Gordonia bronchialis* infections within three patients following open heart surgery [22].

In one hospital in the Netherlands, a case study was reported where pillows were implicated in the spread of HAIs as *Acinetobacter* spp. were allowed to flourish as a result of the lower washing temperature required of the feather pillows [15]. Replacing feather pillows with synthetic pillows that could be washed and dried at a higher temperature controlled the outbreak. Another study examined a mucormycosis outbreak at a Louisiana hospital following the death of five pediatric patients. It was suspected the outbreak was caused by hospital linen that had been contaminated after the laundering process [23]. An increase in the presence of *Bacillus cereus* in blood cultures on a pediatric ward at a Malaysian hospital was linked to hospital linens that became contaminated during storage and transportation from the laundry facility [24]. These studies recognize the importance of proper laundering techniques in preventing outbreaks and HAIs as "clean" linen may still carry some microbial burden [25, 26]. Although the risk of infection is considered to be quite small for the majority of patients, the risk lies in the fact that many patients in these studies were already immunocompromised, increasing the opportunity for a HAI to take hold [23].

Hospital textiles being traced to HAIs occurring within hospital staff as a result of contaminated laundry has been suggested as the likely route of contamination in many case studies [3]. For example, transmission of scabies among laundry employees was traced to improper handling of infected hospital bed linens [27]; one house-keeping staff member likely acquired *Microsporum canis* through handling contaminated bed linens [28]; in another, following an outbreak of *Salmonella hadar* food-poisoning occurring to patients in a nursing home, a subsequent outbreak 7 to 10 days later occurred within laundry workers infected via soiled bed linens [29]. Following standard precautions such as wearing protective clothing (gloves, apron) while handling dirty linen and hand washing is therefore vital for laundry workers.

Patient's clothing could also be viewed as a potential source of carriage for MRSA within acute- and long-term healthcare facilities. One study found that patients colonized with MRSA had the organisms transfer to their clothing,

which could then transfer to gloves and wheelchairs [30]. Patients who changed their clothing daily had significantly lower quantities of MRSA on them than those who changed them 2 to 3 days [30], highlighting the need for patients known to be carriers to change into clean clothing frequently.

Healthcare worker's uniforms have also been postulated as a source of microbial contamination and spread of infection [31]. One study showed that the white coats of attendees on wards resulted in a significant proportion of *Staphylococcus aureus* being present [9], and in another the white coats of medical students showed high levels of bacterial contamination in sites of frequent contact (i.e., sleeve cuff and pockets) [32]. These studies suggest that the white coat could be an important vector for patient-to-patient transmission. Other clothing, such as hospital gowns, surgical scrubs, and nurses' uniforms have been shown to pick up bacteria during patient contact [2, 4, 33–35], with certain high-contact patient care duties resulting in higher microbial loading on clothing than others [8, 36].

In a survey of 160 healthcare professionals [31], even though 90% of respondents were aware that their uniforms (including scrubs and/or a white coat) were potentially contaminated with hospital pathogens, white coats were not laundered regularly. As well, not all uniforms were laundered using hot water (which is more effective at reducing microbial burden than laundering at low-temperatures). These findings suggest that personal practices of healthcare workers in maintaining the cleanliness of their uniforms may impact the transmission of pathogens within a hospital setting. Furthermore, home laundering, while still commonly employed for nonoperative garments, is not recommended by AORN due to the potential for contamination to occur from home washing machines. Also, the laundering conditions at home may not meet the necessary "mechanical, thermal, or chemical measures" to reduce antimicrobial levels in soiled surgical attire [37].

Despite the hypothesis that contaminated uniforms become a vector for the transmission of pathogens, a literature review by Wilson, Loveday, Hoffman, and Pratt concluded that no studies demonstrated the transfer of microorganisms from uniforms to patients in the clinical setting [38]. Nonetheless, the fact remains that potentially pathogenic microorganisms can survive within textiles for a considerable length of time in a dry state [18, 39]. The best course of action is to regularly launder uniforms and other hospital textiles following recommended practices and preferably in a health care accredited laundry facility [40]. Furthermore, healthcare worker uniforms (such as scrubs and white coats) should not be treated as personal protective equipment (PPE), and that proper PPE (such as gloves and gowns) should be donned whenever possible [38]. Due to the fact that textiles can harbor microorganisms and the imperfect nature of personal and industrial hygiene practices, incorporating antimicrobials into hospital textiles is one suggested solution to reduce HAIs.

Antimicrobials in Textiles

Antimicrobials incorporated into textiles and other inanimate objects (e.g., plastics, foams, etc.) work as a biocide (i.e., killing microorganisms or inhibiting their growth within the object). Most antimicrobial agents act by either damaging the cell wall, altering the cell membrane permeability, denaturing proteins or inhibiting or altering essential functions of the microorganisms' metabolic pathways [41]. Antimicrobials are typically added to a textile product or other inanimate product to (i) protect the product from degradation, staining, or odor during its useful life, and (ii) to reduce microbiological colonization with human pathogens. However, the US Environmental Protection Agency (EPA) and other regulatory bodies in many other countries consider the reduction of pathogens to be a health-related claim and as such no antimicrobials in textiles can specifically be marketed as reducing human pathogens. This does not, however, preclude antimicrobials from being incorporated into healthcare-related textiles. If an antimicrobial textile is intended for healthcare applications, a number of requirements need to be met: it should be wide spectrum against bacteria, fungi, and viruses; effective against antibiotic resistant strains of bacteria; not enable development of resistance microorganisms; remain effective for the duration of the textile's lifetime; and be durable to commercial launderings. As well, they should not cause skin irritation or be hazardous for humans following dermal exposure [42].

For synthetic textile fibers and plastics, the antimicrobial active agent can be imbedded into the fiber in the liquid polymer stage prior to fiber spinning. Synthetic (e.g., polyester) and natural fibers (e.g., cotton) can also have antimicrobial agents added at the fabric finishing stage. The former process typically denotes better durability of the antimicrobial into the textiles. Common antimicrobial agents used in textiles are triclosan, noble metals (e.g., silver, copper) and their ions, metal oxides, polyhexamethylene biguanides (PHMB), quaternary ammonium compounds (QAC), and N-halamines.

Triclosan

For decades, triclosan (5-chloro-2-(2,4-dichlorophenoxy)-phenol) has been added to a number of consumer products such as hand soap, toothpaste, mouthwash, food storage containers, toys, and clothing. Triclosan inhibits an enzyme necessary for synthesizing fatty acids needed for building cell membranes and for cell division within microorganisms

[43], and thus there has been concern that due to the similarity in its mode of action to antibiotics that it may induce antibiotic resistant strains [44]. Indeed, resistant strains have been noted under laboratory conditions [45, 46].

Triclosan has been widely used in synthetic textiles and other products such as plastics as it can be incorporated in the polymer melt stage leading to better durability over the lifetime of the product. Windler et al. [47] estimated that about 5% to 15% of the total global production of triclosan is used for textiles, which they calculated to be about 75 to 210 metric tonnes. In comparison to other common antimicrobials used in textiles (i.e., silver, QAC, zinc-pyrithione), a much higher proportion of triclosan is used due to the higher concentration needed for sustained antimicrobial activity [47]. Recently, triclosan is coming under increased scrutiny as it has been shown to accumulate within the environment and have adverse effects on aquatic life, as well as a potential risk as an endocrine disrupter and found to be distributed in human tissues [47, 48]. The bioaccumulation in the Great Lakes led to it being banned from soap in Minnesota in 2017 and recommendations that it also be banned in consumer products in Canada labeled as a chemical of "high concern" [49]. In a comprehensive review of five most common textile antimicrobials, Windler et al. [47] ranked triclosan to have the highest potential for a negative impact on the environment and human health.

Metallic Compounds

Metallic compounds such as silver and copper have been used for their bactericidal properties for centuries. Both silver and copper coins have been used in ancient times to purify water [50], and are still used today in water purification. Silver has been used in medicine in treatment of wound infections and incorporated into medical devices, such as catheters, due to the broad spectrum antimicrobial activity. It may have potential to control biofilms [51]. The metals must be in their ionized form (e.g., Ag^{+}, Cu^{2+}) to be effective against microbes, with the metal ions binding to intracellular proteins and subsequently inactivating them [41].

Silver and silver ions are the most common type of antimicrobial active agent utilized in textiles [52]. The forms of silver incorporated into textiles can differ and range from metallic silver, silver salts, silver-polymer composites, silver-impregnated zeolites, or silver nanoparticles [48]. The concentration of silver in textiles can also vary considerably with concentrations ranging from as low as 1 to ~3000 mg/kg (ppm) [53]. The wide application rate relates to the different forms silver can take. For example, application rates for nanosilver metal are considerably lower than application rates for silver zeolites [47]. Commercial textile products which had silver nanoparticles were found to exhibit much higher in vitro antimicrobial activity than other products where the silver was present in other forms (e.g., silver wires) [53].

Compared with silver, copper is used far less extensively as an antimicrobial in textiles. Copper oxide is the main active agent for any antimicrobial-treated copper textile and can be applied to cellulose and synthetic fibers [54]. Notably, copper alloys and polymeric surfaces containing copper oxide are the only antimicrobial solid surface that has gained EPA registration to make public health claims [55]. To receive this registration, manufacturers of copper products must show that their product kills 99.9% of Gram-positive and Gram-negative bacteria within two hours of inoculation and continuously kills 99.9% of bacteria after multiple reinoculations as well as wet and dry abrasion "wear" cycles [55]. Therefore, in many hospitals copper is replacing stainless steel in applications such as bed rails, door handles and other frequently touched hard surfaces. No copper-impregnated textiles have received such EPA registration, so public health claims about copper textiles cannot yet be made. There is compelling evidence that copper-treated textiles would also be beneficial in healthcare settings as various strains of bacteria, viruses and fungi have been found to be reduced by 99.9% within relatively short time frames (i.e., ranging from 20 minutes to 4 hours) by copper oxide-treated textiles [54].

Titanium dioxide is a strong photocatalytic material as it is comes into contact with UV light "the active oxygen species are released following the relaxation of electrons to the ground state from the excited singlet state, resulting in an antimicrobial effect due to the emission of light" [56]. In one study, the outermost layer of a surgical facemask was treated with a mixture of silver nitrate and TiO_2 nanoparticles and evaluated for antimicrobial resistance against a strain of *Escherichia coli* and a strain of *Staphylococcus aureus*. The authors reported in vitro antimicrobial activity of 100% reduction with no viable colony counts present after 48 hours incubation. Prior to antimicrobial testing, the facemasks were activated under UV radiation [57]. TiO_2-treated textiles have been found to not exhibit any antimicrobial activity without UV radiation and may potentially degrade the textile under UV radiation [58]. Therefore, with the exception of drapes and bedding in wards exposed to natural sunlight through windows, the suitability of using TiO_2 as the active agent in indoor applications such as most healthcare settings is questionable.

Quaternary Ammonium Compounds

Quaternary ammonium compounds (QACs) are cationic surfactants that are useful disinfectants in healthcare for both clinical use on skin and mucous membranes and for

disinfecting hard surfaces [59]. As a hospital disinfectant, QACs are used and registered with the EPA as being tuberculocides (i.e., kills *Mycobacterium tuberculosis*) [60]. QACs are membrane active agents and damage the cell membrane, denature proteins, and disrupt the cell structure [59]. In antimicrobial-treated textiles, the main type of QAC used are long-chained (12–18 carbon atoms) with a dominant compound being a linear alkyl ammonium QAC based on silane quaternary ammonium compounds [47]. The estimated metric tons of QAC used in antimicrobial-treated textiles is greater than other common textile antimicrobial products (i.e., silver, triclosan, zinc pyrithione) but overall, antimicrobial textiles make up a small component compared to the total consumption of QACs [47]. Durability of a QAC applied to 65% polyester/35% cotton fabrics (typical of that worn by healthcare workers) in an in vitro study was poor following multiple washings, as efficacy against *S. aureus* became less notable as washing increased and no activity against *Klebsiella pneumonia* was evident by about 10 washes [61].

Polybiguanides

Polyhexamethylene biguanide (PHMB) is a polymeric antimicrobial compound that can have 8 to 15 biguanide units per molecule with an average of 11 [41, 62]. It is a broad-spectrum antimicrobial with low toxicity and as such has been used as a disinfectant for years. PHMB has been applied in the food industry, as swimming pool sanitizers, and contact lens solutions [41, 59]. In textile applications, it is usually bound to cellulose fibers. In health care, it has been successfully used in wound dressings in order to lower microbial burden [63, 64]. It kills microbes as the positively-charged biguanide groups are attracted to the negatively-charged bacterial cell wall and causing cell lysis by destroying the integrity of the bacterial cell [59, 63]. In vitro activity of PHMB was shown to be high (i.e., 94.11%–99.9% reduction in *Staphylococcus aureus* and *Klebsiella pneumoniae*) up to 25 laundering cycles in polyester/cotton clothing typical of that worn by health care workers [61]. However, the antimicrobial efficacy of PHMB has been found to be inhibited when cotton fabrics are dyed with anionic reactive dyes [65].

N-halamines

N-halamines are compounds that contain amine, amide and imide bonds and are well known to be potent broad-spectrum biocides. N-halamines have been used in water disinfection for swimming pools. Of the types of antimicrobials which can be incorporated into textiles, N-halamines are able to rapidly kill a wide range of microorganisms without causing resistant strains [66]. The mechanism of N-halamines is described as "the direct transfer of oxidative halogen (Cl+ or Br+) from the N-halamine nitrogen to the cell wall of the organism by direct contact followed by oxidation, rather than dissociation of X+ into water followed by diffusion over to the cell" [67]. N-halamines have been incorporated to many textile fibers, including cotton, polyester, polypropylene, acrylic, and nylon [66, 68–71]. Along with the rapid kill times [72], another advantage of N-halamines for their application in healthcare is their ability to be regenerated with chlorine bleach since the bleaching process is a routine part when laundering hospital linens. Although despite its success in the laboratory the commercial applications of N-halamine-treated textiles are limited. This may result in part due to the undesirable residual chlorine on the surface resulting in staining and odor [41].

Test Methods for Assessing Antimicrobial Efficacy

Various standard test methods set by specific testing groups exist which assess the antimicrobial activity of textiles. These methods can be described as qualitative (where visual assessment of bacterial growth on agar are made) or quantitative test methods (where colony forming units are counted). Diffusion tests, such as the AATCC 147 and JIS L 1902 "halo method," are qualitative test methods that are similar to the disk diffusion antibiotic sensitivity tests. A strip of fabric is placed in contact with agar that has been streaked with test microorganisms. Following incubation growth is examined underneath and surrounding the fabric. The size of the no growth area can be an indication of the potency of the antimicrobial or the rate at which the active agent is released from the fabric [41]. Several limitations exist, such as the inability to compare across different products, and that the high nutrient component and presence of moisture are not realistic conditions for most textile applications [73]. Nonetheless, the qualitative methods are generally quick to administer and are useful for screening antimicrobial activity before quantitative tests are undertaken.

Quantitative methods range from absorption tests where a set amount of inoculum is directly applied to a test and control fabric (i.e., AATCC 100), or the control and test fabrics are individually placed directly in flasks of bacterial suspensions and shaken (i.e., ASTM E2149). Antimicrobial activity is expressed as percentage of reduction (i.e., AATCC 100) or a log-reduction (i.e., ISO 20743). Appropriate controls are included where possible, which typically include a fabric that has gone through the same finishing processes to ensure activity is due to the active agent rather than any other

finishing process. A blank control of just inoculum is also recommended as per the ASTM E2149 test.

Within the ISO 20743 standard three different methods can be conducted: the absorption method, the transfer method and the printing method [74]. The absorption method is similar to the AATCC 100 test method in that the bacterial suspension is pipetted directly onto the fabric to be sorbed by the textile. The transfer method involves fabric specimens being pressed against inoculated agar for 60 seconds before being placed in an empty flask and incubated fabric face up at 37 °C in a humidity chamber for 24 hours. The transfer method is less commonly used but is useful for fabrics which resist wetting [75]. The printing method requires specialized equipment in which bacteria are collected onto a membrane filter which is then used to "print" the bacteria onto a test specimen. Incubation at 20 °C and 70% relative humidity is carried out for up to 4 hours.

Many limitations of the current in vitro test methods exist, such as they tend not to be realistic of real-life circumstances, where reinoculation of microorganisms onto textiles would occur constantly. The length of time it takes for the antimicrobial textile to kill microorganisms is much longer in vitro than required for inherently sterile textile products. The ASTM E2149 test method in particular has been described as being nonrealistic and typically shows no correlation between it and other quantitative tests [76]. The ISO 20743 printing method more closely represents conditions of use as humidity and nutrient requirements are much less than those in the other standard methods. As well, incubation time is shorter and incubation temperature is lower which reflects conditions more likely to be encountered in a hospital environment for airborne contamination or transfer (e.g., contaminated hands onto clothing). Despite it being more realistic it has not been commonly used which might be due to the complexity of the method and equipment required for the procedure. The development of new test methods that may address some of the limitations of standard test methods are being undertaken. For example, Nicoloro et al. [77] developed a method where an inoculum containing multiple organisms and various artificial soils were placed in contact with fabric swatches for 15 minutes of contact time.

Evidence of Antimicrobial Activity in Hospital Textiles

For many commercial products there is no certainty that the antimicrobial will indeed offer the protection it purports to have during use. This may be due to poor quality control at the site of manufacturing resulting in poor retention of the antimicrobial agent on the fabric or the concentration of the antimicrobial applied to the fabric is below the minimum inhibitory concentration (MIC) for the challenge microorganisms. Many in vitro studies evaluating commercially available antimicrobial-treated textiles found that antimicrobial activity may not always be evident [53, 78, 79]. Of four reportedly antimicrobial-treated commercial products (QAC, silver, triclosan and one unknown antimicrobial), only two exhibited any antimicrobial activity against a strain of *S. aureus* (i.e., silver and the unknown) [78]. Variability in the efficacy of silver within eight commercially available textiles (socks, t-shirts, trousers) was noted against Gram-negative *Klebsiella pneumoniae*. This related to both variabilities in the quantity of silver present on the textile items, and the form (e.g., silver wires throughout) [53]. Similar variability has been noted in other studies as well (e.g., [79]).

Even when in vitro testing shows the antimicrobial to be effective this may not correspond to antimicrobial efficacy in vivo [80]. This may be due to the conditions in use being quite different from in vitro laboratory tests (i.e., much higher moisture and nutrient content in vitro). This lack of certainty about whether an antimicrobial will actually inhibit growth of microorganisms during use raises important concerns for the use of antimicrobial textiles in healthcare where antimicrobial activity may be assumed. This concern has also been raised by Alvarez et al. [81] who argue that when public health claims can be made on the product label based on in vitro efficacy against human pathogens (as is the case with EPA approval of many copper products) this may create a public health concern as the public may believe the products reduce cross-contamination of microorganisms. Therefore, clinical data showing a reduction of HAIs due to antimicrobial-treated products are needed.

Bacterial Contamination of Antimicrobial-Treated Textiles Compared to a Control

Very few in situ studies have been conducted evaluating the effectiveness of an antimicrobial-treated product in reducing bacterial colonization [82–88], and still fewer with a focus on evaluating the effect of antimicrobial treatments on HAIs [89–91]. Furthermore, where studies have been implemented in this area, then a reduction from control garments/products has not always been shown [82, 84, 85, 88].

A randomized controlled double-blind study evaluating antimicrobial-treated hospital curtains was carried out in ICU units within an Iowa hospital. The antimicrobial treatment was by PurThread Technologies and described as a "complex element compound" (CEC) in which the active agent was a silver compound integrated into the fiber during fiber spinning. Although both types of curtains (standard and CEC experimental curtains) were found to be contaminated with potentially pathogenic microorganisms during the

study, the CEC curtains were significantly lower in contamination than the standard curtains up to 10 days. After 10 days (up to four weeks) the CEC curtains did not differ from the standard curtains [86].

In another study, two outpatient units of a major NHS hospital in the UK were refurbished with either multiple products treated with the BioCote® silver technology (e.g., door furniture/safety rails, wall tiling, electrical switches, cubical curtains, water taps, furniture fabric) (Suite A) or non-BioCote® treated materials (Suite B) [87]. The trial involved swabbing surfaces for total aerobic bacterial counts four times during a four-month period (12 months following refurbishment). Surfaces in the treated Suite A ranged from 62% to 98% lower than surfaces in the nontreated Suite B. The fabric samples included in the study typically had lower levels of bacterial contamination than many of the other surfaces. This was likely due to these items being less frequently touched (e.g., curtains) compared with other objects (e.g., door handles, light switches), as well as being drier (e.g., compared with tiles near sinks). But the difference between bacterial contamination of the textile products in the treated suite compared with the untreated suite was less at a 70% reduction than for the untreated/treated hard surface objects. The authors also found that untreated surfaces within the treated suite were on average 43% lower than similar surfaces in the untreated suite, concluding that lower bacterial burden on many surfaces due to the treated objects resulted in lower levels of cross-contamination to untreated surfaces. This study is unique in that multiple objects and surfaces were impregnated with a bioactive agent and shows promise for reducing the likelihood of cross-contamination and the spread of infection. However, the authors did not state whether the research personnel swabbing samples were blinded to the suite treatment, nor did they indicate when environmental swabbing occurred in relation to room cleaning.

Another study evaluated the performance of antimicrobial-treated polyester fibers blended with untreated cotton. The treatment was described as "sodium aluminosilicate associated with silver and copper according to the BactiSTOP® process" [92], and the study included a regular cotton fabric with no antimicrobial finish as the control. A treated and control swatch (20 cm × 20 cm) were sewn onto either the left or right side of nurses' uniforms ($n = 12$). The garments were sterilized before wear and then worn for 8 to 12 hours in ICU or surgical units. The authors found that for heavily contaminated garments (i.e., >75 CFU/25 m^2) there was a 50% reduction in bacterial counts per 25 cm^2 on the treated fabric compared with the untreated. However, since a complete reduction of bacteria did not occur, then cross-infection from the treated textile to a patient could still potentially occur.

Two trials evaluating the bacterial colonization of healthcare workers uniforms did not find the antimicrobial treatments to reduce colony counts. One prospective, randomized controlled trial was conducted comparing two antimicrobial-treated hospital scrubs with a control to determine whether there was a reduction in bacterial colony counts on the scrubs and wrists of health care workers after an 8-hour shift [85]. A total of 105 health care workers were enlisted in the study with 35 participants in each group (Scrub A: polyester fabric with an unknown antimicrobial; Scrub B: polyester/cotton fabric finished with two unknown antimicrobials and silver; Control scrub: polyester/cotton blend with no antimicrobial finish). The authors found no significant differences in the contamination of uniforms among all three types of scrubs [85]. In another study, Anderson et al. [82] conducted a three-arm randomized controlled study to evaluate the efficacy of two different antimicrobial-treated scrubs against the standard cotton/polyester surgical scrubs worn by nurses ($n = 40$) in an ICU during 12-hour shifts. Scrub 1 included a "complex element compound with a silver-alloy embedded in its fibres" and Scrub 2 an "organosilane-based quarternary ammonium and a hydrophobic fluoroacrylate copolymer emulsion." Cultures from the nurses' scrubs were taken at the beginning and end of a shift from locations on the sleeve, abdomen and pocket. No significant differences in the total contamination of bacteria identified from the control scrub or either of the two antimicrobial-treated scrubs were found, indicating that neither of the two antimicrobials were effective in limiting that growth of bacteria [82].

Similar findings were found by Boutin et al. [84] in a blinded, randomized crossover study design with 90 health care workers who were assigned an antimicrobial-treated scrub and a control scrub to wear during a hospital shift. Sampling of bacteria and frequency of pathogenic bacteria (i.e., *Staphylococcus aureus, Enterococcus,* or gram-negative rods) was taken between 8 and 12 hours after the beginning of the shift. No difference in aerobic bacterial counts was found between the control scrub and the antimicrobial-treated scrub. The authors stated the antimicrobial was proprietary but that chitosan was one of the active ingredients [84].

Evidence of Antimicrobial-Treated Textiles Effect on HAIs

Few clinical trials have been conducted evaluating the effect of antimicrobial-treated textiles. Of those carried out, most have involved copper oxide-impregnated hospital linens on patient HAIs [89–91, 93, 94, 95]. Lazary et al. [89] evaluated the effect of copper oxide-impregnated linens on patient HAIs in a long-term care ward. The protocol involved

comparing the number of HAIs, fever days and administration of antibiotics over two parallel six-month periods (i.e., in the first six month period December 2010–June 2011, regular hospital linens were used; in the second six month period December 2011–June 2012, copper oxide-treated sheets, pillowcases, and patients' clothing were used). Data were collected from patient medical records and healthcare workers directly caring for patients were not involved in the data collection, although treated linens did look noticeably different from regular hospital linens. The authors stated that 108 patients were involved in the study (57 in the first period and 51 in the second period), but it was not clear whether any of these patients were present in both periods. A significant reduction in HAIs associated with the eyes and gastrointestinal tract, as well as significantly fewer numbers of fever days and days of antibiotic use was observed. The study has been reviewed as having "very low quality of evidence" under the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system for critiquing clinical trials [96]. Since then, other clinical trials have been published on the use of copper oxide-impregnated textiles in hospital facilities. Bulter [94] examined the effect of switching the regular hospital linens with copper-impregnated linens (i.e., patient gowns, pillow-cases, sheets, washcloths, towels and blankets) on HAIs within six small to medium-sized hospitals in the US. Data were collected prior to implementation of the antimicrobial-treated textiles that began on May 2016. Data were collected for the control 90, 180, and 240 days post the beginning of the trial. The intervention with antimicrobial-treated linens began on May 2017, and again data were collected 90, 180, and 240 days post implementation of the treated linens. The study found a significant reduction of about 43% in *Clostridium difficile* infections per 10,000 patient-days in hospital. A reduction in the number of infections due to multidrug resistant organisms between the control and treatment periods was also found; however, it was not statistically significant. This was suspected to be due to the relatively low number of infections due to multidrug resistant organisms in the study hospitals [94]. This reduction supported findings in a previous study [91] where a significant reduction in *Clostridium difficile* infections were found in an acute care unit of a renovated hospital wing where copper oxide-impregnated hard surfaces and patient linens were used, in comparison to units in the old hospital wing.

A meta-analysis of six studies [97] examining the effectiveness on copper-impregnated linen in reducing HAIs concluded that results from the studies are conflicting. The complexity associated with patient factors and basic infection control practices may impact the outcomes of the different studies. Nonetheless, despite the conclusions of Fan et al. [97] and the poor evaluation using the GRADE system for the Lazary et al. [89] study, these studies suggest some potential for copper oxide-treated textiles in a holistic approach to reduction in HAIs. However, the combination of copper oxide-impregnated hard surfaces would be necessary, rather than just implementation of copper oxide-impregnated hospital linens alone [95].

Conclusion

As part of the inanimate environment, clothing and textiles used in hospitals can harbor potentially pathogenic microorganisms. As a result they may be implicated in the transmission of HAIs. Many of the published cases where textiles have been recognized as the source of an infectious outbreak, or an isolated case of infection, inadequate hygiene practices while handling dirty laundry or contamination occurring during or following laundering has been identified as the issue. These studies highlight how important it is to follow recommended procedures for laundering hospital textiles. Antimicrobial efficacy can be highly variable even with some commercially acquired antimicrobial textiles not exhibiting any efficacy at all, despite being labeled as antimicrobial. The conditions under which an antimicrobial textile may be used can vary considerably from the conditions under which most in vitro standard tests for antimicrobial efficacy occur. Unfortunately, the research evaluating how antimicrobial-treated textiles perform in reducing microbial load within a healthcare setting is minimal, with even fewer examining their impact on HAIs. Therefore, the evidence showing that antimicrobial-treated textiles are beneficial in reducing HAIs is negligible.

Nonetheless, in theory, antimicrobial-treated textiles have considerable potential to contribute to reducing HAIs, but must be used in conjunction with well-established, thorough hygiene practices (e.g., hand washing, hospital cleaning, and laundering), and certainly not in replacement of such practices. Two antimicrobials showing good potential are copper oxide and N-halamine, both of which have rapid kill times. Many copper products already have EPA approval to allow public health claims to be made, and in situ studies of treated textiles have shown reduction in microbial loads, with some published clinical trials finding when hospital linens were replaced with copper oxide-treated textiles a reduction in some types of HAIs occurred [89, 94]. N-halamine-impregnated textiles have shown astoundingly rapid and effective broad-spectrum antimicrobial activity in the laboratory [72], although there is limited availability of the textiles commercially. The ability of N-halamine-treated textiles to be recharged through chlorine bleaching compatible with hospital laundering processes, although may not be suitable for all types of textiles. Nonetheless, it is clear that considerably more research examining antimicrobial-treated textiles within a clinical setting, including their cost-effectiveness, is still required.

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14 Multidrug-Resistant Gram-Negative Bacilli: Infection Prevention Considerations

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Introduction

Gram-negative bacilli (GNB) pathogens cause a variety of serious infections. Their role as causative offending pathogens increased in the past decades, and in many regions, they are considered the most common human bacterial pathogens [1, 2]. Emergence of resistance to antimicrobials among GNB has become a worldwide threat in both healthcare settings and the community, including among previously healthy and young individuals [3–5].

In 2008, the Infectious Diseases Society of America (IDSA) had established a definition called "ESKAPE," in order to designate the pathogens that cause the majority of US hospital infections while effectively "escaping" the activities of the commonly used antimicrobials (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) [6, 7]. "ESKAPE" changed later on into "ESCAPE," in order to include the "C" for *Clostridiodes difficile* and "E" for *Enterobacterales* as a group (as opposed to the "K" of *Klebsiella* and "E" of *Enterobacter*) [8]. Among the ESCAPE group, GNBs are the pathogens that pose the highest epidemiological threat, due to extreme shortage of effective therapeutics [9]. In a large point-prevalence analysis conducted among 13,796 intensive care unit (ICU) patients from all over the world, GNB accounted for 62% of ICU infections [2, 10].

The epidemiology of GNB has evolved dramatically over the years in several aspects, such as the incidence of infections increased, the distribution of resistant isolates changed (in terms of geographic locations, facilities involved, unit composition, and populations affected), new mechanisms of resistance emerged, and moreover the definitions and detection rates changed, enabling more efficient monitoring and analysis of multidrug-resistant (MDR) GNBs [9]. Although the extent and diversity of antimicrobial resistance among GNB is very broad, non-susceptibility to beta-lactam agents, particularly to carbapenems and to extended-spectrum cephalosporins, frequently defines the epidemiological significance of the GNB pathogen [11]. Therefore, control of beta-lactam-resistant pathogens is commonly central to most infection control programs [11–13]. The use of beta-lactams as the backbone of treatment for serious GNB-related infections (being the oldest, safest, frequently the least expensive with established efficacy per post-marketing controlled trials) [5, 14] contributed to the development and spread of resistance mechanisms. This chapter will focus primarily on infection control measures aimed at curbing the emergence and spread of four phenotypic resistance traits among the ESCAPE GNBs: (1) carbapenem-resistant *Enterobacterales* (CRE), (2) carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), (3) *Acinetobacter baumannii* (including but not solely limited to carbapenem-resistant *A. baumannii* [CRAB]), and (4) *Enterobacterales* resistant to extended-spectrum cephalosporins. This latter group will include pathogens expressing various types of beta-lactamases, including the Ambler-A extended-spectrum beta-lactamases (ESBL) and the Ambler-C bla_{AmpC} (AmpC).

In general, there are two major approaches for limiting the emergence and spread of multidrug-resistant organisms (MDROs). One is to address the spread of resistant organisms from one patient to the next (e.g., via healthcare staff, patient environment, and shared equipment). Alternatively, one may try to attenuate the emergence of resistance among susceptible strains of the patient microbiota. The possible infection control measures and interventions that address patient-to-patient transmission include (1) hand hygiene (HH), (2) contact isolation precautions (CIP), (3) cohorting with or without dedicated staff, (4) environmental cleaning, (5) surveillance programs to identify asymptomatic carriers,

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_14

and (6) decolonization protocols [15–20]. In contrast, attenuating emergence of resistance currently requires enforcing adherence to antimicrobial stewardship policies [21]. In this chapter, we will review the role and available scientific data for each one of those measures, for each one of the aforementioned four groups of pathogens. When no conclusive controlled data are available, we will state our recommendations based on expert opinion.

Carbapenem-Resistant *Enterobacterales* (CRE)

Epidemiology and Microbiology

The first carbapenem-resistant case of *Klebsiella pneumoniae*, through bla_{KPC} production, was reported from North Carolina in 2001 [22]. A few years later, it was identified in New York and spread to the south and west parts of the USA, eventually involving almost every US state [23–25]. Data from the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) indicated that by 2014, 2.8–12% of the *Enterobacterales* healthcare-associated infections (HAIs) were CRE [26]. There was also an increase of CRE in Europe. The European Antimicrobial Resistance Surveillance Network (EARS-Net) reported in 2019 a mean of 7.9% CREs among *K. pneumoniae* (with rates of 60% in Greece) and 0.3% among *Escherichia coli* [27].

CREs were once considered exclusively nosocomial pathogens [28]; however, over the last decade, the boundaries between hospitals and long-term care facilities (LTCFs) including skilled nursing facilities and long-term acute-care hospitals (LTACHs) changed [29]. In a 2011 point-prevalence survey in an LTACH in Chicago, CRE was detected among 30% of residents [30, 31]. Today, every infection control program in an acute-care hospital must involve its surrounding LTCFs, in order to be successful [29]. Another area of concern is international travel and the associated spread of antimicrobial resistance, including CRE [32]. Studies had reported CRE colonization among 0.4–3.4% of returned international travelers who had no CRE colonization prior to their leave [32–34].

The main resistance mechanism of CRE is by hydrolyzing the carbapenem by carbapenemase enzymes often carried on mobile genetic elements (i.e., CP-CRE) [22, 35]. The current major carbapenemase in the USA and worldwide is the Ambler-A bla_{KPC} [36], but Ambler-B (bla_{NDM}, bla_{VIM}, bla_{IMP}) and Ambler-D (bla_{OXA-48}) are additional carbapenemases reported in various frequencies from various parts of the world [37]. Non-carbapenemase-producing CRE (non-CP-CRE) are becoming increasingly prevalent worldwide [35], particularly since the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) lowered the breakpoints defining non-susceptibility to carbapenems among *Enterobacterales* [38, 39]. The proportion of non-CP-CRE among CRE isolates is variable across different geographic areas (10–61%) and highly depends on the study design and state's policy with regard to CRE surveillance definitions [40]. Not much is known about the epidemiology of non-CP-CRE. It is speculated that this group of pathogens is heterogenic, consisting of various mechanisms of resistance, including unidentified (or misdiagnosed) carbapenemases and non-carbapenemase beta-lactamases (e.g., ESBL, AmpC) coupled with the loss of expression of outer membrane proteins and reduced outer membrane permeability and/or expression of efflux pumps [41]. Clinical outcomes of patients with non-CP-CRE infection appear to be better than patients with CP-CRE [42]. In a small retrospective observational cohort of 83 patients with CRE bloodstream infection (BSI), 14-day mortality was higher among patients who had CP-CRE BSI compared to non-CP-CRE BSI (adjusted OR 4.92, 95% CI 1.01, 24.81). In a matched case-case-control investigation, involving 109 non-CP-CRE carriers and 327 patients overall, recent exposure to antibiotics (but not specifically to carbapenems), prior ICU stay, and chronic skin ulcers were all independent predictors for non-CP-CRE acquisition [43]. Acquisitions were almost exclusively associated with asymptomatic carriage, and despite strong associations per univariable analyses, none were independently associated with worse outcomes. The genomic analyses of 13 representative isolates from this study revealed polyclonality and not only confirmed the absence of carbapenemases but also confirmed the coexistence of multiple other genes contributing to carbapenem-resistant phenotype (multiple beta-lactamases and efflux pumps) [43].

The epidemiological implications of CP-CRE versus non-CP-CRE are controversial [40, 42], and tests for resistance mechanisms are utilized differently in various geographic areas [44]. For instance, while the Israeli Ministry of Health advocates to test every CRE for carbapenemase production, preferably through molecular methods, and implements different infection control measures guided by carbapenemase production results, the US CDC does not require mandatory testing for carbapenemase production for the definition of CRE. Whether differential infection control measures should be implemented for non-CP-CRE and CP-CRE carriers is an unresolved issue that should be addressed in well-designed studies [25, 45]. However, in uncontrolled observational studies, non-CP-CRE potential endemicity is reduced in comparison to CP-CRE, and its emergence is less affected by infection control barrier precaution measures. It is reasonable to assume that stewardship interventions might impact more effectively non-CP-CRE acquisitions. Therapeutically

wise, CREs (whether CP or non-CP) are extensively drug-resistant organisms (XDRO) [46], with very few therapeutic options available [47].

Measures to Decrease CRE Patient-to-Patient Transmission

Hand Hygiene

Hand hygiene (HH) is considered one of the important interventions and measures to prevent patient-to-patient transmission of CRE. HH is a vital part of standard precautions and of contact isolation precautions (CIP); however, data demonstrating the impact of HH as a stand-alone intervention are lacking. Nevertheless, it is simple and considered the most efficacious intervention [25, 48]. Unfortunately, compliance with this simple and basic practice is inadequate [49]. A mathematical model estimated the impact of HH on CRE transmission in a surgical unit with low HH compliance (21%). The authors demonstrated that an increase in HH compliance to a rate of 60% succeeded in containing CRE transmission and was the most important and effective intervention in curbing CRE spread [50]. HH must serve as the cornerstone for every CRE prevention plan, and resources should be allocated accordingly. HH adherence should be monitored and reported to staff and managers accompanied by systematic education to care providers.

Active Surveillance

Active surveillance has become one of the central measures used in infection control programs. Active screening cultures (ASC) of asymptomatic patients reflect colonization pressure better than clinical specimens [51, 52] and identify patients who serve as a reservoir for potential MDRO transmission. When accompanied by pre-emptive CIP [23, 53], ASC was shown to reduce colonization pressure [54] and limit the spread of MDROs, including CRE [52]. In addition, since CRE colonization is a risk factor for CRE infection [55], ASC may lead to improved outcomes for patients infected with CRE, by reducing the delay in instituting appropriate antimicrobial therapy, which is the strongest independent predictor for mortality in severe sepsis [56, 57].

ASC is now recommended for CRE prevention by the leading international societies in Europe and North America [12, 25, 58–60]. Cultures for screening should be taken from the rectum (samples should contain stool), and the perirectal area should be sampled only in specified populations (e.g., neutropenic patients, premature neonates) [56]. The methods used for processing surveillance samples are varied and include culture-based and molecular techniques to identify CRE and relevant carbapenemase genes [45]. Local policies for CRE screening should be developed to target certain populations based on risk stratification in any given facility. Major risks to be considered include patients who were recently hospitalized (i.e., within the past 6–12 months), patients with a previous CRE infection and/or colonization in the past 12 months, LTCF residents, elderly incontinent individuals with reduced cognition, cancer patients, patients who received chemotherapy in the past 12 months, patients who are treated with maintenance dialysis within the last 12 months, and people who have recently received healthcare in endemic countries (i.e., "medial tourism") [25, 61, 62]. The WHO recommended ASC of asymptomatic patients in both outbreak situation and in endemic settings [59]. Both the CDC and ESCMID recommend that patients being treated at cancer centers, in an ICU, and/or in endemic units/floors should be periodically (i.e., weekly) screened to further reduce the colonization pressure [12, 25]. In addition, in the case of new acquisition, contacts should be re-screened.

Clinical laboratories should have an established protocol for timely notification of clinical and/or infection prevention personnel when CREs are identified by clinical or surveillance culture. Facilities should also establish a flagging system to point to staff of CRE carriage status upon future admissions or whenever the patient is transferred between locations inside the institution [12, 25, 53]. In Israel, a national registry governed by the Ministry of Health assists in improving inter-facility communications on the national level and may have contributed to the containment of a huge outbreak in 2006–2009 [52, 63]. In a model-based study conducted in an ICU in Brazil [64], ASC was used along with predefined goals for HH and CIP compliance rates. This intervention was effective in reducing CRE transmission and prevalence in the ICU and prevented another ICU closure.

Contact Isolation Precautions (CIP)

Contact precaution is an established infection prevention intervention to reduce CRE transmission [59, 65]. Contact isolation precautions (CIP) include several components:

1. Appropriate patient placement in a single-patient room, preferably with designated toilets. In low-income countries, where only multi-bedded patient rooms are available, CIP is sometimes implemented in a room occupied by other patients who are not on CIP, but the patient's unit still must be distinct and separated by hard partitions, and toileting should be dedicated. Regardless, CIP in multi - MDRO - bedded room is *never recommended* for CRE carriers (see section Patient Cohorting and Dedicated Staff).
2. HH before donning a gown and gloves.
3. Donning a gown and gloves before entering the patient's room.
4. Removing gown and gloves and performing HH before leaving the patient's room.
5. Dedicated equipment for isolated patients (e.g., stethoscopes, blood pressure cuffs; see specified section below).

6. Limiting transport of carriers in the facility [25, 59, 66].

   Our recommendation is that CRE carriers (both CP-CRE and non-CP-CRE) should always be subjected to CIP, in every facility (including LTCF), in both epidemic and endemic situations [25, 59].

Several studies demonstrated that CIP may limit the spread of CRE [63, 67]. A national intervention program in Israel reduced the incidence of CRE detected in clinical cultures from 55.5 to 11.7 per 100,000 patient-days [63]. In an ICU in a New York City hospital, the incidence of CRE detected in clinical cultures decreased from 9.7 to 3.7 per 1000 patient-days following implementation of CIP as part of a prevention bundle [63, 68]. Other examples for bundles implemented to reduce CRE spread were described worldwide, all including CIP as the pivotal measure.

There is no consensus as for the duration of CIP for CRE carriers [60]. In one study, the duration of carriage was found to be prolonged; specifically, the mean duration of carriage was 387 days (95% CI 312–463 days), and 39% of the patients were positive for at least 12 months [69, 70]. Predictors of CRE persistence or recrudesce include antimicrobial use, subsequent admission to an institution or another hospital, and a time interval less than or equal to 3 months since the first positive CRE culture. It was shown that having one of the predictors was associated with a 50% chance of having a positive result [71]. Other factors associated with prolonged CRE carriage were the presence of an indwelling device, immunosuppression, poor functional status, and high comorbidity index [60]. In an Israeli study, risk factors for recurrent carriage in patients who were predefined as "CRE-free" (i.e., two negative cultures collected on different days) included short time between the last positive culture, re-admission to a healthcare facility, and the presence of foreign devices [72]. We believe that the duration of CIP should be at least 6 months, only when no reported predictor for recrudesce (as depicted above) is present. Moreover, as long as the patient is incontinent, we advocate not to remove the patient from CIP, though this recommendation is not scientifically supported. CIP, just like HH, depends on healthcare worker (HCW) compliance; therefore, adherence to correct CIP should be monitored closely, followed by adequate education and feedback.

Patient Cohorting and Dedicated Staff

Cohorting refers to placing patients with the same pathogen or mechanism of resistance together, preferably cared by dedicating staff who do not care for additional patients during the same shift. In the Israeli national CP-CRE epidemic, the outbreak was further curbed and contained only following the institution of a set of regulations that mandated every institution in the country to designate a specified cohort unit for CP-CRE carriers, treated by dedicated nursing staff [52, 63]. In a study from a tertiary hospital in Israel, where infection control interventions were implemented gradually between 2007 and 2016, it was only after implementing cohorting with dedicated staff that CRE incidence had begun to decrease significantly [73].

"United cohort units" containing several types of carriers (i.e., CRE, CRAB, CRPA) are strongly *discouraged* given the risk of transferring mobile genetic elements containing resistance traits that could cross the inter-species barriers [74], resulting from pan-resistant isolates. In a multicenter trial, co-carriage of CP-CRE along with *A. baumannii* or *P. aeruginosa* was associated with increased overall mortality and with emergence of colistin-resistant CP-CRE. This was evident in a united cohort unit (for all carbapenem-resistant GNBs) located in one of the ICUs [74, 75]. Currently, the CDC recommends cohorting of patients with CRE in both hospitals and LTCFs [25]. The WHO recommends patient isolation in single rooms, while cohorting is reserved for situations where single rooms are unavailable. Although dedicated staff was not evaluated as a single infection prevention intervention, it is always recommended as part of cohorting.

Environmental Cleaning and Disinfection

Surface disinfection in healthcare environments has been shown to be important for controlling infections caused by MRSA, VRE, and *C. difficile* [76]. Studies demonstrate that carrier's immediate environment becomes colonized with the same MDR-GNB relatively fast [77] and for prolonged periods [78, 79]. In a report from a tertiary facility, two environmental sampling methods were used, i.e., direct CHROMagar KPC contact plates and eSWAB. Direct CHROMagar contact plates were more sensitive than eSWAB for detecting environmental CRE on flat surfaces (e.g., bedside table/tray), and the eSWAB was superior on non-flat surfaces (e.g., pillows) [77, 80]. The areas closest to the patient had the highest pathogen recovery. In another study, the areas with the highest contamination rate were the toilet and the floor near the toilet [81]. In another report of an ICU outbreak, sinks were shown to be an important reservoir for CRE contamination in the room [82].

Evidence from controlled CRE outbreak investigations demonstrated that cleaning the patient environment, specifically high-touch surfaces, can assist in reducing potential transmission [23, 77, 83, 84]. Even though evidence evaluating the sole impact of cleaning on CRE acquisitions is lacking, maintaining a clean environment must be perceived as fundamental for all hygienic measures in preventing CRE infections [76]. Rooms occupied by patients with CRE should be cleaned and disinfected thoroughly at least once per day. Moreover, we advocate cleaning the high-touch surfaces (e.g., bedrails, bedside tables or trays, infusion pumps, feeding pumps, monitors [including its wires], respirators, charts hung on beds, nurse call-on buttons, light switches of

night lights, door handles, toilet, sinks) every shift, i.e., multiple times a day. Following patient discharge, any facility should establish an internal "terminal cleaning" protocol, which details the measures that should be applied specifically for this indication. Training is important, the process of terminal cleaning should be monitored, and results should be distributed to all involved personnel. CDC encourages institutions to optimize their policies and procedures related to environmental disinfection in both CRE endemic and epidemic settings [85].

New methods for disinfection of the patient's environment after discharge were evaluated in recent years, including ultra-violet (UV)-C-emitted light and hydrogen peroxide vapor systems. These methods were not tested specifically for CRE„ but they were tested for *P. aeruginosa* and *A. baumannii* [86, 87] and are recommended as part of the terminal cleaning protocol following the discharge of CRE carriers as well. Given the potential role of cleaning in the control of CRE outbreaks, monitoring the adherence to cleaning policies and the efficacy of cleaning are now considered fundamental additives for prevention [85]. In some cases, a visual inspection does not suffice, and culturing methods on routine basis (i.e., in non-outbreak settings) yield unsatisfactory recovery rates [77]. Monitoring cleanliness may be accomplished using invisible fluorescent markers or adenosine triphosphate (ATP) bioluminescence measurements. Utilizing ATP bioluminometers has provided quantitative evidence of improved cleanliness in terms of Gram-positive pathogens from high-touch surfaces [88, 89]. In a study that used fluorescent markers to objectively evaluate the thoroughness of terminal cleaning before and after implementing an educational intervention for environmental services personnel, cleaning improved from 49.5% to 82% (of surfaces cleaned) and helped increase compliance with proper procedures [90]. However, the impact of evaluating the quality and compliance of cleaning practices on clinical outcomes, including acquisitions of CRE, is lacking.

Shared Equipment

Shared equipment refers to objects used by more than one patient or physician, which can potentially be contaminated with MDRO (including CRE) and provide a vector of fomites for transmission. CRE was isolated from ambu bags, phones, toys, pens, keyboards, blood pressure cuffs, and stethoscopes [91]. Protocols for cleaning, disinfection, and sterilizing shared equipment should be established and followed closely. The importance of equipment disinfection with regard to CRE was recently highlighted following an outbreak of CRE serious infections associated with the use of duodenoscopes (2012–2015) [92–94]. In about 65% of medical centers who participated in the investigation, positive CRE cultures of the duodenoscopes were evident even after proper reprocessing per manufacturer's instructions. The complex design of the duodenoscopes limited access to parts of the scopes, which were then found to be contaminated with CRE [92, 93, 95].

Decolonization for CRE

As a concept, because *Enterobacterales*, including CRE, colonize the human gastrointestinal tract (GIT), one of the proposed solutions to stop CRE transmission is to eradicate GIT carriage [96].

Selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) involve administration of antibiotics (mainly oral non-absorbable agents), to eradicate gastrointestinal (GI) carriage of MDR-GNB, in order to reduce the risk of progressing from colonization to infection. This measure was mainly studied in preventing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [97, 98]. Several randomized controlled trials evaluated the impact of anti-CRE decolonization on CRE carriage eradication and CRE infection prevention, with conflicting results. Saidel-Odes et al. demonstrated a decrease in *K. pneumoniae* CRE (CRKP) carriage following 7 days of SDD and SOD using polymyxin and gentamicin (compared to a placebo-controlled group), but recrudesce rate increased after 6 weeks [99]. In another study, the use of colistin and/or gentamicin for SDD was associated with significant eradication of CRE as well as decreased mortality [100]. However, in the same study, 26% of the patients treated with gentamicin were later colonized with gentamicin-resistant CRE. Lubbert C et al. used colistin and gentamicin as SDD and SOD and did not observe a significant difference in the eradication rate compared to control group. Moreover, at the 48-day stool culture follow-up, there was a 19% increase in colistin resistance and a 45% increase in gentamicin resistance among CRKP isolates, whereas no emergence of resistance was detected among the control group [101]. In an international, multicenter randomized controlled trial (RCT), conducted in settings with moderate to high levels of antibiotic resistance [102], using either SDD, SOD, or CHG mouth washing, failed to demonstrate any effect with regard to MDR Gram-negative bloodstream infection (BSI) reduction.

Since CRE is an XDRO with very limited therapeutic options [46], we do not recommend using a potentially therapeutic agent (e.g., colistin) for CRE prevention or for decolonization of asymptomatic carriers. SDD could be considered for unique indications only (e.g., candidates for transplant or for intensive chemotherapy) [53, 103].

One potential intervention to eradicate CRE colonization in the GI tract is by fecal microbiota transplantation (FMT). FMT is now used for recurrent *C. difficile* infection and was recently reported to have success in eradication of GI ESBL *K. pneumoniae* in immunocompromised patients. Retrospective studies of FMT for decolonization of CRE

reported variable results with regard to the impact on CRE infection and colonization [104, 105]. A recent randomized controlled trial of 5-day oral antibiotics followed by FMT was terminated early and failed to demonstrate efficacy of FMT on ESBL or CRE colonization [106]. Efficacy and safety data from larger cohorts of carriers are needed in order to advocate specific and clear recommendations.

Antimicrobial Stewardship

Antibiotic stewardship program (ASP) has an important role in curbing the emergence of antimicrobial resistance and should be incorporated into every CRE prevention program [25, 107]. There is no antibiotic found consistently to be associated with CRE acquisition, not even carbapenems [21]. However, exposure to antibiotics in general was the strongest independent predictor associated with CRE acquisition in many trials [47]. An ecological study conducted in India has shown that an antimicrobial stewardship program that included routine shortening of the duration of antibiotics administration was associated with reduction of CRE isolation [108, 109]. In an Israeli study, restricting the use of carbapenems showed remarkable success in lowering CRE rates, but that was part of a bundle that included, among others, ASC and cohorting [110]. The impact of ASP on non-CP-CRE rates could potentially be even more substantial [43].

Acinetobacter baumannii

Epidemiology and Microbiology

A. baumannii is a major cause of nosocomial infections. The ability to survive in the environment of hospital settings and on surfaces and the rapid emergence of antimicrobial resistance among offending strains have made *A. baumannii* one of the most prevalent causes of outbreaks in ICUs [111]. The prevalence of carbapenem-resistant *A. baumannii* (CRAB) has increased dramatically worldwide. Rates of CRAB increased from 1% in the 1990s to over 80% in many developing and developed countries [112–115]. *A. baumannii* outbreaks were initially restricted to ICUs. Over time, *A. baumannii* became a pathogen found in other departments (i.e., internal medicine wards), as well as among patients from LTCF and LTACHs [26, 116–118]. In a recent NHSN report of hospital-acquired infections (HAIs) among patients who were admitted in various settings, 43% of the device-associated HAI caused by *A. baumannii* were carbapenem-resistant, and of patients with *A. baumannii* CLABSI, the highest proportion of carbapenem resistance was detected among patients who arrived from LTACH (75.4% compared to 33.1% among patients inform other hospital wards) [119]. CRAB identified in the community usually reflects previous exposure to health system, to procedures, or to broad-spectrum antibiotics [116].

It is yet to be determined whether CRAB deserves a greater focus in terms of infection control measures than carbapenem-susceptible *A. baumannii* (CSAB). Since certain mechanisms of resistance to carbapenem are chromosomally encoded, CSAB may become CRAB in the same patient under certain stressors (i.e., exposures to antibiotics) [120]. A recent controlled study has shown similar outcomes between patients with CRAB and CSAB bloodstream infections after controlling for confounders, including the delay in initiating appropriate therapy [11]. Based on this analysis and available data, we propose that infection control measures should focus on reducing patient-to-patient transmission among all *A. baumannii* carriers, not only CRAB. *A. baumannii* which is resistant to colistin has also been reported from multiple countries worldwide [121], resulting practically pan-resistant strains. Some patients with colistin-resistant CRAB came from the "community," which highlights the importance of limiting transmission in acute-care hospitals of pan-resistant isolates, from patients admitted from certain LTCFs and LTACHs [29]. During the COVID-19 pandemic and the hospitalization conditions that were implemented in many cohort units, *A. baumannii* outbreaks were reported from multiple units [122, 123].

Measures to Decrease *A. baumannii* Patient-to-Patient Transmission

Hand Hygiene

In detailed and robustly conducted analyses, which aimed to quantify all transmission opportunities between *A. baumannii* carriers, it was shown repeatedly that patient-to-patient transmission is the major mode for *A. baumannii* acquisition in acute-care hospitals, compared to emergence of resistance [124, 125]. Colonized patients may serve as reservoirs, and HCW hands, shared equipment, and/or contaminated high-touch surfaces can all serve as vectors for transmission. A study that evaluated the transmission of MDR organisms in the ICU showed that HCW hands were contaminated (before entry into patient rooms) twice as more often with *A. baumannii* (5.1%) compared to other MDROs (0.6%–3.6%) [126]. This same study also demonstrated that after glove removal and before HH was performed, hands and gloves were contaminated with MDR *A. baumannii* in 4.2% and 29.3%, respectively. Gowns were also significantly contaminated after patient care. In a Spanish ICU, the contamination rate by MDR *A. baumannii* was 12–20% among HCWs [127]. Several studies have evaluated HH as a multimodal infection prevention intervention and reported reduction in CRAB infection and/or colonization [128–130]. HH should

be implemented as part of every infection control intervention to reduce transmission of *A. baumannii*. Data from experimentally contaminated hands show that alcohol-based hand rub could reduce *A. baumannii* counts by 98% [131].

Active Surveillance

The role of *A. baumannii* screening is still under debate. Early identification accompanied by pre-emptive CIP has the potential to limit patient-to-patient transmission [132, 133]. This is important since patient-to-patient transmission has a pivotal role in *A. baumannii* spread [124, 125]. In addition, patients colonized with *A. baumannii* are at higher risk for *A. baumannii* infection than patients without colonization [134, 135], and appropriate antimicrobial therapy in *A. baumannii* infections is frequently delayed [136]. All these factors theoretically support the use of active surveillance cultures (ASC) in order to prevent *A. baumannii* acquisitions.

In a recent study conducted in Florida among trauma ICU patients, rectal swabs and respiratory cultures were obtained upon admission and weekly thereafter. In this surveillance, 13.5% of the patients had CRAB on surveillance cultures, and the risk of having subsequent CRAB infection was higher by 8.4-fold among patients who had positive surveillance cultures compared to those who had negative surveillance cultures [135].

There are, however, limitations to ASC in the field of *A. baumannii*. First, the sensitivity of surveillance cultures using traditional methods was found to be low and varied between studies, ranging between 55% and 85% [137, 138], even when multiple body sites were concurrently sampled. Second, the optimal body site to screen has not been determined, as opposed to the rectum for CRE and VRE screening or the nares for MRSA. Studies that evaluated screening sensitivity for different body sites using different sampling techniques (e.g., swab versus sponge), and different microbiological processing methodologies, have yielded various results. The only clear recommendation is to obtain respiratory specimens for ASC obtained through deep suction in mechanically ventilated patients [137].

However, improved culture media and skin sampling technique using a premoistened sponge have increased test sensitivity. In a study published in 2020, Nutman et al. compared the yield of culture of different body sites for *A. baumannii* carriage. In their study, there was a 91.9% sensitivity of skin culture from a single site. The buccal mucosa, tracheal aspirate, and rectum showed lower sensitivity (between 47% and 65%). The combination of buccal mucosa and skin sampling reached a 99.3% sensitivity [139].

In a Monte Carlo simulation analysis with three possible carriage prevalence of *A. baumannii* (2%, 4%, and 6%) in a theoretical acute-care hospital settings, significant decreases in transmission, infection, and mortality rates were associated with *A. baumannii* ASC intervention, even when the sensitivity rate of the test was as low as 55% [140]. This study also demonstrated the cost-effectiveness of *A. baumannii* ASC, with cost reductions of 19–53%, unless the prevalence of *A. baumannii* was lower than 2% *and* the sensitivity of the test was lower than 55% [140]. In a study conducted in Thailand, a bundle that included ASC, CIP, cohorting, and enhanced environmental cleaning, the acquisition rate was reduced by 76% [141]. The ESCMID guidelines recommend ASC for *A. baumannii* during outbreaks, coupled with CIP and cohorting, whereas the WHO guidelines do not yet recommend ASC for CRAB. Our recommendation is to establish a good *A. baumannii* ASC methodology [139] in the facility and then initiate ASC in high-risk units (specifically ICUs).

Contact Isolation Precautions (CIP)

The efficacy of CIP in controlling *A. baumannii* outbreaks (irrespective of resistance pattern) has repeatedly been demonstrated [142]. In one study, the incidence rates of *A. baumannii* colonization and infections decreased during CIP and increased again when CIP was discontinued [142]. Another study demonstrated the efficacy of CIP as part of a bundle in an endemic setting [127]. In this study, an additional marked and sustained decrease in MDR *A. baumannii* infections was demonstrated, including BSI episodes. The success of containing outbreaks by implementing CIP depends on adherence to HH recommendations [131], proper environmental cleaning (e.g., appropriate disposal of contaminated equipment) [127], and pre-emptive isolation, while cultures of suspected carriers are being processed [142]. Although the APIC and the WHO recommend CIP for patients with MDR *A. baumannii* in acute-care hospitals [59, 143], CIP should be considered for all patients with *A. baumannii* strains (not related to *Acinetobacter* of non-*baumannii* complex). In LTCFs, APIC recommends that the individual patient's clinical condition, as well as the incidence of MDR *A. baumannii* in the facility, and the type of LTCF, should determine whether CIP should be implemented [143].

Patient Cohorting and Dedicated Staff

Patient cohorting and dedicating staff have not been evaluated independently for *A. baumannii* prevention, although it is appropriately recommended by several professional societies and guidelines. In a trial that instituted cohorting along with CIP as part of the infection prevention bundle, the acquisition of CRAB decreased by 77% [130, 142]. Cohorting patients (preferably with dedicated staff and always accompanied with CIP) should be implemented whenever patient isolation in a private room is not feasible and with the guidance of infection control programs.

Environmental Cleaning and Disinfection

Environmental contamination of dry and moist areas is an established mechanism for *A. baumannii* dissemination. Colonized and infected patients shed *A. baumannii* for prolonged periods, which can contaminate hospital surfaces and medical devices [111, 144–146]. In several studies, *A. baumannii* was cultured from various surfaces and devices (e.g., ventilators, suctioning equipment, resuscitation equipment, bed rails, bedside tables, sinks, pillows, and radiology machines) for up to 5 months [147]. In an ICU that evaluated transmission of various MDROs between HCWs, patients, and the environment, *A. baumannii* was present in 78% of rooms hosting known carriers. The authors estimated that one-third of occurrences where HCW enters a room of a patient with *A. baumannii* results in contamination of their gowns and gloves [126]. Most of the data pertaining to the efficacy of environmental cleaning in controlling outbreaks of GNBs are derived from *A. baumannii* outbreak investigations [148–150]. Several outbreak reports from general ICU, neurosurgery, and pediatric burn units were controlled only after initiating and implementing environmental screening and cleaning interventions [12]. A recent study from a tertiary center in Israel demonstrated high contamination rates in multi-patient rooms, particularly in step-up rooms (which host also mechanically ventilated patients), even after the cleaning personnel were educated and re-trained [151].

A. baumannii is more resistant to some products commonly used for cleaning and disinfecting the hospital's environment [152]. Persistent contamination by *A. baumannii* was demonstrated even after four routine cleaning and disinfecting sessions [153]. In that study, the addition of hydrogen peroxide vapor (HPV) improved the reduction of site contamination. Novel methods, such as HPV and UV-C light, have been shown to be significantly more effective in reducing contamination rates [154]. However, clinical efficacy, on actual infectious clinical outcomes studied in controlled design, is lacking, and these disinfection interventions should always be coupled with prior thorough cleaning procedures of all surfaces. In addition, current high turnaround time in many acute-care hospitals may hinder their implementation in hospitals [30, 87]. In the future, enabling the institution of these disinfecting devices in occupied rooms (with yet undetermined concentrations and proved efficacy) may alleviate this aspect of *A. baumannii* prevention. As discussed in other sections, infection control programs for curbing *A. baumannii* spread should always include specified policies that address cleaning techniques, products, and responsibilities at all levels. Both cleaning procedures while the patient is in the room and after the patient is discharged should be established. Audits and monitoring of cleanliness should be performed not only to evaluate the effectiveness of cleaning but also as a tool for education and feedback to the team. There may be a discordance in the cleaning effectiveness measured by environmental CRAB cultures compared to fluorescence marker. One study demonstrated that fluorescence marker was negative in 42% of positive environmental CRAB cultures. Using ATP bioluminescence assay may be used to assess organic material remaining on surfaces after cleaning and may have better concordance with culture results [155].

Decolonization for *A. baumannii*

Though polymyxins have been evaluated in decolonization protocols for CRE (as discussed above), and typically these agents are active against *A. baumannii* (including CRAB) [66], there are no clinical data to support this practice. When weighing the potential for the emergence of resistance to colistin [156], decolonization is strongly discouraged.

Antimicrobial Stewardship

Numerous controlled studies investigated the independent predictors for colonization and infection with *A. baumannii* [157, 158]. In a case-control study that evaluated predictors for CRAB versus CSAB, carbapenem use was found to be associated with CRAB colonization and infection [159]. In a systematic review of risk factors for MDR *A. baumannii*, antimicrobial exposures, including to carbapenems, were reported as independent predictors for MDR *A. baumannii* in 11/20 of the studies [160]. The relation between colistin exposure and pan-resistant colistin-resistant *A. baumannii* acquisition is also clearly evident [74, 156]. These studies highlight the importance of both mechanisms of CRAB spread, i.e., patient-to-patient transmission and the emergence of resistance among susceptible strains.

Several uncontrolled studies have demonstrated lower incidence of CRAB infection when antibiotic stewardship interventions were implemented and restricted carbapenem consumption [161–163]. The association between *A. baumannii* emergence and antimicrobial exposure mandates implementing a strong stewardship program (ASP). The ASP should address all aspect of stewardship, including (1) early detection of CRAB infection [164], (2) institutional guidelines based on local antibiogram that would assist in the selection of appropriate empiric treatment and (3) provide guidance on de-escalation and discontinuation of unnecessary broad-spectrum antibiotics [165]. The epidemiology of *A. baumannii* acquisitions should be one of the measurable elements for the ASP program. As in CRE cases, restricting and monitoring antimicrobial use in general, and not only carbapenems, may impact the rates of *A. baumannii* and CRAB, as well as other MDROs [21, 161].

Carbapenem-Resistant *Pseudomonas aeruginosa*

Epidemiology and Microbiology

Pseudomonas aeruginosa is the worldwide most prevalent GNB causing pneumonia among hospitalized patients [166]. It is also the fourth most common pathogen leading to hospital-acquired infections (HAI) overall [119]. CRPA infections have been associated with increased mortality, length of hospitalization, and costs [167, 168]. According to the SENTRY antimicrobial surveillance program, from 1997 to 2016, 20–30% of *P. aeruginosa* causing HAP were carbapenem-resistant, and the proportion increased over the years (with variations according to geographic regions). A lower rate of carbapenem resistance is evident among *P. aeruginosa* strains associated with infections from other sources, i.e., BSI (10.3%) and UTI (11.7%) [166].

P. aeruginosa possesses and expresses in certain conditions numerous resistance mechanisms to carbapenems. Efflux pumps, encoded both chromosomally and on numerous plasmids, confer resistance to multiple classes of drugs (except polymyxins) and are the predominant mechanism of multidrug resistance among *P. aeruginosa*, along with beta-lactamases (including carbapenemases) production [169].

Apart from the resistance issues, *P. aeruginosa* is also known for its ability to produce biofilm, which contributes to its resistance and survival on environmental surfaces, medical devices, and the airways of patients with chronic lung diseases [170]. These features highlight the role of both infection control and antibiotic stewardship measures in curbing the continued emergence and spread of CRPA.

Outbreaks associated with CRPA are typically described in ICU settings and among immunocompromised patients. Patients with cystic fibrosis (CF) are another prone population [171]. Other risk factors include exposures to invasive devices, being bedridden, and exposure to antimicrobials [172, 173]. Several recent CRPA outbreak investigations have also emphasized the possible role of endoscopes in patient-to-patient transmission [174]. The transmission modes vary, and the contribution of patient-to-patient (via staff, shared equipment, or directly) versus environment-to-patient transmission is not entirely clear. Studies estimated that the proportion of patient-to-patient transmission resulting in CRPA acquisition is 18% in hospital wards, 36–64% in ICUs [175], and over 70% in LTCFs [15].

Measures to Decrease CRPA Patient-to-Patient Transmission

Hand Hygiene

Colonization of the hands with *P. aeruginosa* was detected among 15% of ICU personnel and was demonstrated to persist on staff's hands for up to 4 weeks [175]. An outbreak investigation in a neonatal ICU (NICU) at Oklahoma City found an exact similarity between offending patients' strains and the isolate recovered from long artificial nails of one of the staff [176]. Improving HH and instituting restrictions pertaining to staff's nails had terminated the outbreak [176]. In a different study, the rate of CRPA infections was negatively correlated to the volume of alcohol being consumed by hand sanitizers, implying the role and impact of performing HH in terms of CRPA infections [177].

Active Surveillance

Since patients colonized with CRPA exert colonization pressure, and patient-to-patient transmission is important in CRPA spread [178], it would be reasonable to screen patients. However, current data to support the practice of ASC on CRPA spread are scarce. Several studies demonstrated prior colonization in 56.5–100% of ICU patients who had *P. aeruginosa* infection [175, 179, 180]. A study that screened ICU patients demonstrated an increased risk for infection in patients who were colonized on admission compared to non-colonized patients (14.65-fold) [181]. Rectal colonization was consistently reported to have the highest yield of screening cultures, followed by pharyngeal or other respiratory cultures [175, 181, 182]. In mechanically ventilated patients or patients with chronic lung diseases (e.g., CF), deep respiratory surveillances are preferable [56]. Overall, colonization rates are high in the ICU setting and range between 18% and 43% [180, 181, 183], but currently there is no evidence supporting routine screening (in endemic settings) as a measure for reducing CRPA acquisition rates [68]. A recent quasi-experimental study in an ICU has demonstrated significant reduction in resistance of *P. aeruginosa* to imipenem and meropenem (69.8% to 39%, $p = 0.008$, 62.9% to 37.2%. $p = 0.005$, respectively) when ASC was implemented as the second phase of a more extensive infection control intervention [183]. We recommend implementing ASC for CRPA prevention, only in ICUs during outbreaks or if significant increases in basal endemic rates are observed.

Contact Isolation Precautions (CIP)

A CRPA outbreak investigation carried out in a German surgical ICU showed that the most likely mode of transmission was cross-transmission between patients during postoperative

wound care with abdominal and/or thoracic drains. After implementation of CIP, no further clusters of CRPA cases were observed [184]. In a different study, strict CIP, together with removal of urinary collection machine urine, stopped a CRPA outbreak in a hemato-oncological unit [185].

Other studies, however, demonstrated failure of HH and/or CIP to limit the rate of CRPA infections [64, 68]. Since the pathways of transmissions vary and the contributions of patient-to-patient transmission in endemic settings varies as well, the rationale behind recommending CIP to limit the spread of CRPA is based primarily on extrapolations from other better-designed studies pertaining to other MDRO acquisitions [19].

Whereas the ESCMID guidelines recommend the use of CIP in cases of MDR-PA (i.e., *P. aeruginosa* resistant to ≥3 classes of agents [46] in both epidemic and endemic settings, CDC recommendations defer, as with other MDROs, to the clinical and epidemiological judgment of the attending personnel at any given site [12]. Most facilities are subjecting only patients with CRPA to CIP, since resistance to carbapenems is the marker for the epidemiological significance and threat of the pathogen [9]. In this context, it is important to note that CIP in general has been associated with less attention and personal contact from HCW because of the additional effort required in adhering to CIP [186]. CIP may be stressful for patients and their families, and isolated patients are prone to higher rates of dis-satisfaction with care, anxiety, depression, preventable adverse events, and medical errors [187]. Moreover, applying CIP measures can be challenging due to variable access to isolation facilities, understaff, or lack of educational programs [188–190]. However, CIP is one of our only tools to reduce the colonization pressure that contributes to the risk of patients becoming colonized and of colonized patients becoming infected with the offending pathogen [191]. Our recommendation is to implement CIP for CRPA carriers.

Patient Cohorting and Dedicated Staff

There are no solid evidence-based studies that measured the impact of cohorting and instituting dedicated staff on the rate of CRPA infections. In one ICU outbreak, cohorting ended the outbreak [192]. However, united cohorting (i.e., cohorting patients with CRPA with carriers of other carbapenem-resistant GNBs), as discussed above, was associated with co-colonization of CRE, *A. baumannii*, and *P. aeruginosa* and increased antimicrobial resistance to carbapenems and to colistin [75]. Therefore, we strongly recommend against united cohort units as an infection control measure, in order to avoid emergence of pan-resistant GNBs [75].

Environmental Cleaning and Disinfection

P. aeruginosa is capable of colonizing a wide range of healthcare environments, mainly moistened sites, but it was isolated after prolonged periods from dry surfaces as well [147]. Several properties of *P. aeruginosa* favor its persistence in the hospital environment, as discussed above. In addition, *P. aeruginosa* is frequently resistant to some disinfectants such as biguanides and quaternary ammonium compounds, through the action of efflux pumps [193]. The significance of tap water and other moistened sites (e.g., connection pieces and basins) as a reservoir for patients' colonization was demonstrated in both outbreak and endemic settings [194, 195].

The role of water contaminated by *P. aeruginosa* has been largely described in the literature, causing both colonization and infection, especially in hematology and intensive care units [196, 197].

In several outbreaks, only manipulation of the tap water and water-associated sites, such as pasteurizing the water or replacement of the water source, was effective in abating the outbreaks [198–200]. Following one outbreak in an ICU, a combination of measures were applied: increasing the water temperature, using copper silver ionization, replacement of drinking water with *P. aeruginosa*-free bottled water, reinforcement of standard precaution, and hand disinfection with alcohol solutions instead of soap. These measures significantly reduced the rate of exogenous acquisition of *P. aeruginosa* (i.e., patient-to-patient transmission or faucet-to-patient transmission), whereas the endogenous acquisition remained without change [201]. In a different ICU, the presence of *P. aeruginosa* in tap water was associated with patients' colonization of the same strain [202]. In another study that evaluated colonization in intubated patients, tap water in the patients' rooms was colonized in 63% of samples [203]. While clinical data evaluating the impact of cleaning methods on CRPA-associated HAI are lacking, maintaining a clean environment provides the fundamental basis for all hygienic measures in preventing CRPA infection [191]. Healthcare water environment, including potable water, faucets, sink surfaces, and wastewater drainage systems, should be considered a potential source for CRPA outbreaks. These reservoirs should be looked for and mitigated as part of outbreak investigation. Efforts to reduce the load of CRPA and other MDR-GNBs in water environments should be implemented as part of the maintenance of environmental cleaning.

Decolonization for CRPA

Most CRPA decolonization regimens that were studied were part of HAP and VAP prevention bundle and were not aimed specifically as a measure to reduce CRPA acquisitions. However, *P. aeruginosa* are the most common GNBs causing VAP [166]. Since emergence of resistance to anti-pseudomonal agents was demonstrated with these regimens [99], and the clinical efficacy was not evaluated, this practice (i.e., decolonization of *P. aeruginosa* in order to reduce

HAP/VAP and/or CRPA acquisitions) is discouraged, particularly in areas with higher burden of resistance.

Antimicrobial Stewardship

Various methodologies were used in different studies to evaluate the impact of carbapenem exposure and the emergence of CRPA [204]. Though studies conducted at the ecological level (i.e., correlating hospital antimicrobial usage and incidence of diagnosing resistant strains) showed no impact [205], studies conducted at the individual patient's level (case-control analyses) demonstrated an association between previous exposure to imipenem and CRPA infection [161, 206]. Antibiotic stewardship interventions that were implemented to curb the emergence of new CRPA demonstrated a favorable impact of restricting carbapenems on CRPA rates. In a 22 university hospitals study, eight hospitals restricted the use of carbapenems between 2002 and 2006 and showed a significant reduction in CRPA acquisition rates [205]. In a quasi-experimental study conducted at a rehabilitation center, the impact of an antibiotic stewardship program on patterns of resistance before (between 2011 and 2012) and after (between 2012 and 2014) the intervention was evaluated. Reduced consumption of carbapenems and fluoroquinolones was associated with a decrease in emergence of XDR *P. aeruginosa* strains (from 55% in 2011 to 12% in 2014, $p < 0.001$). Of note, reduction of resistance rate was demonstrated among other pathogens as well [207].

Numerous studies in past years were conducted to assess the impact of ertapenem use instead of group 2 carbapenems (i.e., imipenem, meropenem, and doripenem), on CRPA acquisition rates. Most of these studies were sponsored by the pharmaceutical industry and showed that the substitution of ertapenem (a group 1 carbapenem) with other broad-spectrum non-carbapenem agents was not associated with an increase in CRPA rates [208–210]. In summary, all this data, although not always measuring this directly, indicated that antibiotic stewardship has a major role in curbing antimicrobial resistance among *P. aeruginosa* offending strains.

ESBL and/or AmpC-Producing *Enterobacterales*

Epidemiology and Microbiology

The first plasmid-mediated beta-lactamase in Gram-negative bacteria was discovered in Greece in the 1960s and had a narrow spectrum of activity against penicillin [211]. With greater use of broad-spectrum cephalosporins, beta-lactamases with broader spectrum of activity were discovered, and in 1983, the first extended-spectrum beta-lactamase (ESBL) bacterial strain was reported from Germany and later on spread exponentially throughout the globe [211]. Data from the Study for Monitoring Antimicrobial Resistance Trends (SMART), which evaluate trends of antimicrobial susceptibilities in different geographic regions among patients with urinary tract infections (UTI) between 2002 and 2010, revealed an increase in ESBL-producing *Enterobacterales* strains (e.g., *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *Proteus Mirabilis*) from less than 20% in 2002 to more than 40% in 2010 in Asia [212]. A similar increase was demonstrated in the Middle East [213]. In the National Healthcare Safety Network (NHSN) of the years 2015–2017, the prevalence of ESBLs among pathogens associated with HAIs in the USA was over 20% [26, 119].

ESBLs are classified as Ambler-A beta-lactamases and consist of various families of enzymes (TEM, SHV, and CTX-M). These enzymes can hydrolyze broad-spectrum penicillins and cephalosporins as well as monobactams and are typically inhibited by beta-lactamase inhibitors (e.g., clavulanate, tazobactam) [214]. There are other prevalent resistance mechanisms to broad-spectrum cephalosporins, most notably AmpC (bla_{AmpC}), which are Ambler-C beta-lactamases. AmpC are not inhibited by beta-lactamase inhibitors and are usually chromosomally encoded among typical *Enterobacterales* (e.g., *Enterobacter*, *Citrobacter*, *Morganella*, *Serratia*, and *Providencia*), though it could reside on mobile genetic elements as well (e.g., $bla_{\text{CMY-2}}$-producing *E. coli*) [215]. Despite the different type of enzymes in both ESBL and AmpC outbreaks, the two modes of resistance acquisitions (i.e., patient-to-patient transmission and the emergence of resistance) play a role [56]. Therefore, infection control measures addressing both modes should be rigorously implemented in order to effectively control an outbreak [17].

In the past, ESBLs were as associated with nosocomial infections, particularly in the intensive care unit (ICU) setting. Over the last two decades, the boundaries between inpatient and certain outpatient services were nearly abolished, with ESBL dissemination to LTCFs and back to acute-care hospitals [216]. This resulted in conflicting recommendations pertaining to infection control prevention measures [17]. Later on, ESBL strains were isolated also among young and previously healthy individuals with no established exposures to healthcare settings [217, 218]. The misuse of antimicrobials among patients in the community (e.g., fluoroquinolones and broad-spectrum beta-lactams [219, 220]), coupled with the dissemination through contaminated food and agriculture products (probably resulting from the large quantities of antimicrobials that are administered to food-producing animals for growth promotion), might have also play a pivotal role in the spread of ESBL strains in the community [221, 222]. In many regions, ESBLs are now considered common offending strains among

patients with community-onset infections [56]. An outbreak of an ESBL (bla_{CTX-M})-producing *E. coli* strain associated with dozens of deaths in 2011 among previously young and healthy individuals, mainly from Western Europe, was traced to a contaminated food product [223]. A meta-analysis also demonstrated strong association between traveling to endemic areas and ESBL carriage upon return (a risk ratio of 2.4, 95% CI 1.26, 4.58) [224]. A recent prospective study of international travelers to various destinations demonstrated that up to 68% of previously naïve patients had been colonized with ESBL *Enterobacterales* upon their return [32].

Since ESBLs became endemic in so many regions worldwide, the exact role of patient-to-patient transmission versus emergence of resistance is not well defined. Various studies reported a patient-to-patient transmission rate ranging from 1.5% to 52% [15, 225, 226]. There is also variability among ESBL species: patient-to-patient transmission and patient-to-environment contamination rates were shown to be higher for *K. pneumoniae* compared to *E. coli* [16, 227, 228].

Measures to Decrease Patient-to-Patient Transmission of ESBLs and AmpCs

Hand Hygiene

Even though the rate of patient-to-patient transmission in ESBL is variable, hand hygiene as part of standard precautions is a pivotal measure of prevention. Several studies have demonstrated that HCW hands are contaminated with GNB, including resistant GNB (e.g., ESBL and AmpC) [229, 230]. There is significant reduction in hand GNB inoculums by performing hand hygiene [48, 49, 231]. A recent study in the ICU setting demonstrated HH as the most efficient infection control measure to control ESBL. Their model showed that improving hand hygiene compliance from 55% to 80% before patient contact, and from 60% to 80% after patient contact, would reduce the proportion of patients who acquired ESBL within 90 days by 91% [232].

Active Surveillance

Asymptomatic colonization with ESBL is associated with future ESBL infection [233, 234]. In a meta-analysis of cancer patients, the pooled prevalence of rectal ESBL carriage was 19%, and colonized patients were more likely (by 13-fold) to develop bloodstream infection with ESBL compared to non-colonized patients [235].

Therefore, screening for asymptomatic colonization is considered one of the measures to reduce ESBL infections. However, of 287 patients who were screened in one endemic hospital, 69 (24%) were colonized during the study period (very high proportion), while only 5 developed ESBL infection. Moreover, only in three infected patients the same genotype as the colonizing organism was isolated [236]. Therefore, quantifying the exact benefit of ASC in such endemic settings, as the situation nowadays in many centers, is questionable. Moreover, the sensitivity and negative predictive value of screening the perirectal area and groin vary from 42% to 95% [12]. Due to the somewhat futile nature of investing in ASC implementation, this is not practiced today in many centers. In the setting of neonatal ICU (NICU), once-weekly ASC was associated with lower ESBL transmission when compared to screening upon demand (44% vs. 9%) [237]. However, discontinuing ASC program in another NICU was not associated with increased incidence of ESBL colonization, while compliance with infection control measures were maintained [238]. The resources associated with a comprehensive ESBL ASC program could be overwhelming in endemic settings, and as with CIP, we recommend, based on the current data, to implement ASC for ESBLs only during outbreaks or for specified prone populations as mentioned above.

Contact Isolation Precautions (CIP)

Studies that evaluated CIP impact on the spread of ESBLs were conducted mainly in a setting of an outbreak and as part of an entire bundle. In certain regions, where ESBL became so common in community settings, implementing CIP for all ESBL carriers upon admission to an acute-care hospital may not be worthwhile. When too many patients in a given department are subjected to CIP (not in an ICU), the compliance with CIP measures is known to decrease considerably, specifically HH [239]. This recommendation should not apply of course to regions with low endemic ESBL rates or to special circumstances or events (i.e., an outbreak in certain units, for example, neonatal ICUs) [17, 56]. One retrospective study that included two hospitals in France with similar rates of ESBL *E. coli* carriage, but with CIP applied in only one of the hospitals, demonstrated similar rates of ESBL *E. coli* transmission in both institutions [240]. A cluster-randomized trial with a crossover design showed no added value of CIP over standard precaution on the incidence of ESBL colonization or infection in 20 non-critical care wards with an established ASC program [241].

The European guidelines for MDR-GNB infection prevention do recommend implementing CIP in both epidemic and endemic settings [12]. In Switzerland, national guidelines recommend CIP for all patients colonized or infected with ESBL in acute-care facilities [225, 242]. Considering the lack of evidence to support CIP as a common practice for every ESBL carrier, we propose that CIP should be implemented during outbreaks or in specified units with prone populations, where the benefit may outweigh the disadvantages associated with CIP (as discussed above).

Patient Cohorting and Dedicated Staff

Evidence pertaining to the benefit of cohorting patients with ESBLs is lacking. An analysis from France modeled an ESBL outbreak in an ICU and evaluated the contribution of several strategies, concerning ESBL acquisition. Cohorting was the second most effective intervention in reducing ESBL acquisitions, following HH [232]. As discussed in section "Contact Isolation Precautions (CIP)", in current global era, cohorting patients colonized with ESBL in endemic settings might be perceived as a futile intervention that might not always be effective [17, 56].

Environmental Cleaning and Disinfection

The role of environmental contamination for curbing ESBL transmission is similar to that discussed above, in detail, in section "Carbapenem-Resistant *Enterobacterales*." In brief, there are controlled data suggesting that a colonized patient's immediate environment becomes colonized with the same MDR-*Enterobacterales* genotype relatively fast and for prolonged periods of time [77–79]. Evidence from controlled ESBL outbreak investigations demonstrated that cleaning the patient environment, specifically high-touch surfaces, can assist in reducing potential transmission [23, 77, 83, 84]. Even though evidence evaluating the sole impact of cleaning on ESBL acquisitions is lacking, maintaining a clean environment must be perceived as fundamental for all hygienic measures in preventing ESBL transmission and infections [76].

Decolonization for ESBLs and AmpCs

Data from a large meta-analysis that included 28,909 healthy individuals revealed fecal colonization rate of 2% in North America and 22% in Southeast Asia and Africa. Carriage of ESBL and AmpC could be prolonged (i.e., up to 25.4% of returned travelers remained colonized even after 12 months) [224, 243, 244]. In a meta-analysis of 26 studies performed in healthcare setting, the pooled CRE/ESBL colonization rate was 35.2% after 12 months.

Data pertaining to the impact of selective digestive decontamination (SDD) regimens on clinical outcomes of ESBL or AmpC carriers are scarce. A randomized controlled trial from Switzerland showed no significant decrease in the ESBL carriage, and in patients who did respond, the effect lasted only 4 weeks [245]. Other non-randomized studies that evaluated SDD for eradication of ESBL have shown inconsistent results pertaining to the success rate of decolonization, as well as to the impact on clinical outcomes [246]. Considering the risk of resistance emergence and spread, and the lack of data to support SDD for ESBL (or AmpC) carriers, we recommend not implementing such a routine practice.

Antimicrobial Stewardship

Emergence of resistance has an important role in the spread of ESBL and AmpC. Misuse and overuse of broad-spectrum antibiotics across healthcare systems (i.e., hospitals and LTCFs) and in the community are correlated with the prevalence of resistance [5, 47]. A study conducted in Greece demonstrated the importance of an antimicrobial stewardship team and policy: total antibiotic consumption decreased by 3.3%, restricted antibiotics decreased by 42% (primarily cefepime), and the resistance rate of *K. pneumoniae* resistant to third- and fourth-generation cephalosporins (representing both ESBL- and AmpC-producing strains) decreased from 29–37% to 12–15% [247]. In a prospective study conducted in Vanderbilt, TN, between 2002 and 2005, implementing stewardship program was associated with significant reduction in the use of anti-GNB antibiotics, coupled with a decrease in HAIs due to MDR-*Enterobacterales* [161]. In Denmark, the restricted use of cephalosporins, fluoroquinolones, and carbapenems, as part of an infection control bundle, resulted in a sustained reduction in the incidence of both colonization and infections caused by ESBLs [248].

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Active Surveillance Cultures for MRSA, VRE, and Multidrug-Resistant Gram Negatives

15

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Introduction and Definition

Infections due to multidrug-resistant (MDR) bacteria including gram-positive and gram-negative bacteria are responsible for a significant proportion of healthcare-associated infections [1]. Infections caused by MDR pathogens are associated with worse patient outcomes including increased morbidity, mortality, healthcare costs, and increased hospital lengths of stay when compared to infections by drug-sensitive pathogens [2, 3]. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and multidrug-resistant gram-negative bacteria (MDR-GN) including extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL), carbapenem-resistant *Enterobacteriaceae* (CRE), MDR *Pseudomonas*, and MDR *Acinetobacter* are responsible for most drug-resistant infections occurring in healthcare settings [1]. Patients can be also colonized with these pathogens without developing infection, and studies show that most often colonization by these bacteria precedes development of infection [4–6]. Patients colonized or infected by MRSA, VRE, and MDR-GN can be a source of spread to other patients in a healthcare facility usually through hands of healthcare workers, contaminated environment, or contaminated fomites [7]. There is also frequent movement of patients colonized or infected with these pathogens between healthcare facilities including acute-care hospitals, nursing homes, and long-term acute-care facilities leading to organism spread [8–10].

Various infection control measures are used to prevent the spread of these pathogens among patients and between healthcare facilities. Active surveillance (AS) is one such infection control measure which involves detection of patients colonized with the targeted MDR pathogen by culture or molecular methods. This approach is based on the observation that patients colonized with MDR pathogens might go undetected if a healthcare facility relies on the detection of these pathogens based on clinical cultures only (passive surveillance).

Once colonization with MDR pathogens is detected by AS, further spread to other patients can be prevented with the use of infection control measures such as contact precautions, patient isolation, and environmental cleaning. Active surveillance is also used to estimate the incidence and prevalence of MDR pathogens in a healthcare facility or to investigate an outbreak due to a MDR pathogen [11–13]. Active surveillance could also help identify patients who would benefit from decolonization treatments [14].

Evidence to Support or Refute Active Surveillance

Despite the use of AS as part of routine infection control, studies have been conflicting on the effectiveness of surveillance to control or decrease MDR organism spread. This is especially true in studies where the MDR pathogen is known to be endemic or sporadically detected in a facility [14–18]. Since AS by itself will not lead to control of MDR pathogen spread, studies evaluating the effectiveness of AS are usually coupled with other infection control measures such as contact precautions and cohorting in private rooms or separate units of patients known or suspected to be colonized by the MDR pathogen. Studies have also used various decolonization treatments as part of control measures [14]. Most of these studies have targeted a single MDR pathogen, pathogens having similar resistance mechanisms or pathogens resistant to the same class of antibiotics, and generally targeted patients admitted in wards or intensive care units (ICUs) where the likelihood of patients colonized with the MDR pathogen is high [18–20].

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_15

There are several factors which can influence the outcome of studies determining the efficacy of AS, and these factors must be closely considered. Since studies use multiple infection control interventions concomitantly or sequentially, each of these interventions (such as decolonization, hand hygiene) can influence the outcome unless controlled during the study analysis. In studies with before-after study design which fail to control for secular trends, it will be unclear if changes in outcomes are due to the intervention or due to persistence of secular trends itself [21]. Outcomes will also depend on compliance with AS, contact precautions, patient isolation, and decolonization treatments which are frequently not measured in studies. It is also important to consider the sensitivity and specificity of microbiologic methods used to identify the pathogen and the turnaround time of the test since this will accurately identify the population targeted for the infection control interventions and help implement them in a timely manner to derive the maximum benefit. Lastly, AS is unlikely to be effective if the nosocomial transmission rate of a pathogen is at low levels. In such a scenario, the majority of patients are already colonized at the time of admission with no or minimal cross-transmission occurring after admission [22–25].

Studies Evaluating the Effectiveness of AS for MRSA

With regard to MRSA, there are a handful of studies that either support or refute the effectiveness of AS. The Veterans Affairs (VA) study which was implemented in VA hospitals nationwide showed a decrease in MRSA transmission and healthcare-associated MRSA infections in both ICUs and non-ICU hospital units when compared to baseline with the use of universal AS and contact precautions in patients who tested positive for MRSA [26]. Hand hygiene and a change in the institutional culture whereby infection control became the responsibility of everyone who had contact with patients were also promoted during the intervention period. Routine decolonization was not recommended, and the use of mupirocin for nasal decolonization of MRSA did not increase during the intervention period.

In another retrospective study with an interrupted time series design in eight ICUs, a series of infection control interventions were implemented one at a time. Among the infection control interventions only AS for nasal MRSA carriage coupled with contact precautions for patients who tested positive showed a decrease in MRSA bacteremia in ICUs and hospital wide [20]. Other interventions such as the use of sterile barrier precautions during central venous catheter placement, alcohol-based hand rub use, or hand hygiene promotion were not associated with a decrease in MRSA bacteremia. This is despite compliance with hand hygiene increasing to 80% in the campaign year. Although AS and isolation were implemented in only ICUs, the authors hypothesized that reduction in opportunities for MRSA transmission in non-ICUs was because of fewer MRSA carriers being discharged from ICUs leading to hospital-wide decrease in MRSA bacteremia. In addition, there are multiple ecological studies where AS and contact isolation proved successful in controlling MRSA outbreaks in different types of healthcare settings [7].

However, results from randomized trials on AS are less encouraging. The STAR ICU study was a cluster randomized trial in 18 ICUs where patients in intervention ICUs were assigned to contact precautions if clinical or surveillance cultures were positive for MRSA or VRE; all other patients in the intervention group were assigned to care with universal gloving until discharge or until surveillance cultures obtained at admission came back negative [27]. Patients in control group were maintained on standard precautions, and contact precautions were only assigned if MRSA or VRE was identified on clinical cultures. Despite surveillance cultures identifying a large proportion of colonized patients, this study did not find a difference in ICU-level incidence of MRSA or VRE infection or colonization in intervention and control groups. Prolonged turnaround time of 5 days for reporting culture results which increased the proportion of time MRSA- or VRE-positive patients were assigned to universal gloving instead of contact precautions, less compliance with contact precautions than required especially during contact with environment only and the short duration of the intervention period were some of the reasons that were noted for lack of effectiveness of AS.

Similarly, in the REDUCE MRSA cluster randomized trial in 74 ICUs, there was a decrease in MRSA-positive clinical cultures and a decrease in ICU-attributable bloodstream infection due to any pathogen in the universal decolonization group when compared to targeted decolonization or screening and isolation groups [28]. However, screening and isolation for MRSA were already the standard of care in all ICUs with 90% of admitted patients undergoing screening; therefore the effectiveness or otherwise of AS cannot be evaluated, but this study provides evidence that universal decolonization might confer added benefit to control MRSA.

In another three-phase ICU study, the baseline period was followed by interrupted time series study of universal chlorhexidine bathing combined with hand hygiene improvement for 5 months (Phase 2) [29]. This was then followed by a cluster randomized trial when conventional AS for MRSA and VRE was compared with rapid-based screening for MRSA, VRE, and highly resistant *Enterobacteriaceae* (Phase 3). The study reported decrease in MDR acquisition in Phase 2 mainly due to decreased acquisition of MRSA, and no further decrease in acquisition noted in Phase 3

regardless of whether screening was done with conventional or rapid testing [29].

Another study that has been extensively quoted to recommend against the use of AS is a prospective interventional cohort study with crossover design conducted in Switzerland involving surgical patients [14]. This study found that AS surveillance with contact isolation, decolonization with chlorhexidine plus nasal mupirocin, and adjustment of preoperative antibiotics in nasal MRSA carriers did not decrease nosocomial MRSA infections when compared to control group. No difference in nosocomial surgical site infections due to MRSA was noted between study groups. However, only 31% of MRSA carriers were identified prior to surgery, only 66% of MRSA-positive patients in the intervention group received appropriate preoperative antibiotics, and only 41% of MRSA carriers received decolonization prior to surgery. In addition, none of the 26 patients who were identified as MRSA positive as outpatients and received appropriate decolonization and preoperative antibiotics developed MRSA infection.

In addition, a systematic review in 2008 concluded that although the existing evidence may favor active surveillance for MRSA in ICUs, evidence is of poor quality, and definitive recommendations cannot be made [15]. In another systematic review and meta-analysis in 2009, there was no reduction in MRSA acquisition with rapid screening when compared to conventional screening [30]. There was however reduction in MRSA bloodstream infection with rapid screening when compared to no screening. Both these reviews noted that other interventions such as decolonization with nasal mupirocin, chlorhexidine baths, and hand hygiene promotion were used concomitantly with AS; therefore the efficacy of individual interventions was difficult to assess [15, 30].

Lastly, a comparative effectiveness review conducted by the Agency of Healthcare Research and Quality in 2013 on MRSA screening concluded that there is low strength of evidence that universal screening of hospitalized patients decreases MRSA infections [21]. There was also insufficient evidence on other outcomes of universal MRSA screening to support or refute MRSA screening on any outcomes in other settings [21]. Following this review there has been one major randomized trial which did not show benefit of screening and isolation for MRSA and VRE when added to a policy of universal chlorhexidine and hand hygiene improvement [29].

Studies Evaluating the Effectiveness of AS for VRE

In outbreak settings, VRE has been successfully controlled with AS, contact precautions, and isolation/cohorting [31–33]. VRE outbreaks have also been successfully controlled in an entire region involving many different healthcare facilities with AS of high-risk patients, contact precautions, and communication between healthcare facilities about VRE status of patients at time of transfer [13]. Most of these studies concurrently used other interventions such as hand hygiene promotion, decolonization, staff cohorting, ward closure, environmental cleaning, and antibiotic restriction to contain an outbreak making the efficacy of individual interventions difficult to assess [13, 31–33]. Studies also indicate that infection control measures can only be targeted against certain strains more likely to cause nosocomial transmission [34]. A study conducted in the Netherlands differentiated outbreak from non-outbreak VRE strains by pulsed-field gel electrophoresis (PFGE) and used contact precautions and cohorting on patients infected or colonized with outbreak strain only, and this led to successful control [34].

As noted above, in an endemic setting, randomized trials on VRE failed to show decrease in VRE infection or colonization with AS and contact isolation [27, 29]. Similarly, VRE bacteremia rates in a hematology-oncology unit remained stable after discontinuation of AS and contact precautions [19]. On the contrary, a study comparing two hospitals noted twofold more cases of VRE bacteremia and more clonally related VRE isolates in the hospital not screening patients for VRE colonization compared to the hospital conducting AS of high-risk patients and using contact isolation for colonized patients [17]. This suggests that horizontal or common source spread as the primary means of VRE dissemination in the hospital and screening and isolating VRE carriers may be of limited value.

Studies Evaluating the Effectiveness of AS for MDR-GN

Studies demonstrating successful control of MDR-GN outbreaks note that only one or few closely related strains were responsible for the outbreaks indicating that infection control measures prevented patient-to-patient cross-transmission [35–38]. Outbreaks of CRE, ESBL *Enterobacteriaceae*, other MDR *Enterobacteriaceae*, MDR *Pseudomonas*, and MDR *Acinetobacter* were successfully controlled with infection control measures either implemented concomitantly or sequentially [35–39]. A review which evaluated efficacy of stepwise implementation of infection control bundles in CRE control concluded that the combination of AS and patient/staff cohorting was the most effective strategy [40]. With regard to some gram negatives such as *Acinetobacter* and *Pseudomonas*, the hospital environment can play an important role in organism persistence, and environmental surveillance cultures are useful to identify possible sources [36, 41].

In an endemic setting, many observational studies have noted low rates of nosocomial transmission among non-CRE *Enterobacteriaceae* especially ESBL *E. coli* questioning the utility of isolation measures [16, 25, 42–44]. In one observational study which tested 133 contacts of patients infected or colonized with ESBL *Enterobacteriaceae* while on standard precautions, there were only two instances of cross-transmission [16]. Controlled trials have come to similar conclusions. A cluster randomized trial conducted in non-critical adult wards with extensive surveillance screening did not find reduction in incidence density of colonization or infection with ESBL *Enterobacteriaceae* with the use of contact precautions compared to standard care [45]. Similarly, a study in 13 European ICUs did not find a decrease in acquisition of highly resistant *Enterobacteriaceae* with screening and isolation when added to a program of hand hygiene improvement and chlorhexidine body-washing [29].

CRE acquisition in endemic settings likely depends on colonization pressure in a hospital or unit, indicating that patient-to-patient transmission plays an important role in CRE spread [46]. Therefore, infection control measures have proved effective in decreasing CRE rates in an endemic setting including when such measures have been implemented nationwide [47]. However, this might only apply to CRE where carbapenem resistance is due to production of beta-lactamases capable of hydrolyzing carbapenems rather than resistance to carbapenems due to other mechanisms [47]. In the latter case, organism acquisition is likely from patients' own flora from antibiotic pressure. Although various infection control measures have been implemented to control CRE making efficacy of each intervention difficult to assess, one study indicated that AS was likely responsible for the decrease in carbapenem-resistant *Klebsiella pneumoniae* in their ICU [11]. A systematic review also indicated that there was strong evidence on the role of active surveillance for CRE control in both outbreak and endemic settings [48]. With regard to other gram-negative pathogens including MDR *Acinetobacter* and *Pseudomonas*, few studies on the efficacy of active surveillance have been done in an endemic setting [11, 49–52].

Infection control bundles in endemic MDR control – is AS a necessary component:

England achieved >50% reduction in MRSA bloodstream infection in 2008 compared to 2003–2004 without resorting to universal screening [53]. Control measures were focused on hand hygiene improvement, prudent use of antimicrobials, and the deployment of expert improvement teams in organizations that failed to meet their improvement targets [53]. On the contrary, MRSA has been successfully controlled in Finland and the Netherlands with a very low prevalence by using a search-and-destroy strategy which involves active surveillance and strict application of contact precautions and isolation in colonized and infected patients [54–56]. The patient population to target and the frequency of screening are also unclear. Guidelines from the Society of Healthcare Epidemiology of America and Healthcare Infection Control Practices Advisory Committee (HIPAC) therefore recommend the use of active surveillance cultures only as part of an intensified approach when MRSA is not effectively controlled with basic practices [57, 58]. Furthermore, the level of compliance with standard precautions might be sufficient to prevent nosocomial transmission of certain MDR pathogens, the addition of AS, and isolation measures unlikely to provide further benefit [16, 59–61].

Sites and Method of Surveillance

MRSA

Studies consistently show that specimens from nares have high negative predictive value for ruling out MRSA colonization [62, 63]. In addition, cultures from site of skin breakdown are also recommended [62]. Screening for MRSA has traditionally relied on conventional culture methods which usually have a turnaround time of few days leading to delay in implementation of contact precautions for MRSA-positive patients, or if preemptive isolation is used, it will lead to unnecessary isolation in patients who would eventually test negative [27]. To circumvent these drawbacks, various rapid screening methods are used for earlier detection. Rapid screening methods for MRSA can be broadly classified into two categories: those using chromogenic media and those relying on molecular methods. Real-time PCR has the shortest test time of less than 1 h, and results of chromogenic media can be obtained as early as 22 h [64, 65]. In addition, both categories of rapid screening have high sensitivity [64, 65]. Despite the short turnaround time and decrease in isolation days with rapid screening, they do not reduce MRSA transmission compared to conventional cultures as previously noted in the meta-analysis and the cluster randomized trial [29, 30].

VRE

Stool, rectal, and perirectal swabs are all sensitive methods to detect VRE colonization [66, 67]. Studies have also evaluated stool specimens sent for *Clostridium difficile* testing to screen for VRE [68]. However, using this method as the only surveillance strategy can miss a significant proportion of VRE-colonized patients [68]. Similar to MRSA, both rapid and conventional culture methods are used to detect VRE colonization [66, 69]. Among the rapid methods, chromogenic agars have high sensitivity and specificity when com-

pared to culture-based methods [66, 69]. They also reduce turnaround time of screening [66]. Sensitivity of culture and chromogenic agar is lowered by low vancomycin MIC of the tested VRE isolates, low fecal VRE density, and high vancomycin concentration in the culture media [70].

Real-time PCR methods which detect VanA and VanB genes directly from stool or rectal samples are also increasingly used for VRE screening [66]. PCR has high sensitivity and NPV but generally has low positive predictive value especially for VanB containing Enterococci [66, 69]. Therefore, a positive result would require culture confirmation since this could be from detection of VanB genes in non-enterococcal species including gram-positive anaerobic bacteria [66]. Poor PPV of PCR-based screening could also be due to low prevalence of VRE in the tested specimens or the gold standard culture method used for comparison with PCR [66, 69].

MDR-GN

Rectal or stool samples are usually used to screen for CRE, ESBL *Enterobacteriaceae*, and other multidrug-resistant *Enterobacteriaceae* [71–73]. Surface sampling of large areas of the skin with a premoistened sponge had the highest yield followed by buccal mucosa for *Acinetobacter* [74, 75]. As *Acinetobacter* is sparsely distributed on skin surfaces, sampling with swabs which cover only a small area of the skin is not recommended [74, 75]. With regard to surveillance samples for *Pseudomonas*, it is unclear which sites are associated with the highest sensitivity. Previous studies have used various sites for screening purposes including the rectum, stool, skin, pharynx, urine, and tracheal aspirate [39, 76–78].

The most commonly used culture methods to screen for ESBL *Enterobacteriaceae* are MacConkey agar and Drigalski agar with or without enrichment usually supplemented with third-generation cephalosporin to select growth of resistant bacteria [43, 79]. Chromogenic agars are also used for screening purposes due to their short turnaround time and increased sensitivity [80]. Confirmation of ESBL phenotype is by double-disk synergy test or one of the other phenotypic methods [43, 81].

Screening for CRE can be done with conventional culture-based methods or use of chromogenic agars [11, 71, 72]. If screening is positive, then confirmation of carbapenemase production is required. This can be done by phenotypic methods or with PCR [71]. Carba-NP test which is based on in vitro hydrolysis of imipenem resulting in the change of pH value of the indicator is a very sensitive and specific method to confirm carbapenemase production [72]. Currently PCR can be used directly on rectal surveillance samples to detect CRE with results available in <1 h [82]. However drawbacks of PCR-based screening are the increased costs and inability to detect previously unidentified resistance genes [72].

Patient Populations to Screen, Frequency of Screening, and Testing for Clearance

Studies on VRE and MDR-GN screening have mainly targeted patients admitted in high-risk units such as ICUs and units housing immunocompromised patients [17, 19, 43, 47]. Some studies have also targeted patients known to be at high risk of colonization such as patients with prolonged hospitalization, history of recent antibiotic use, nursing home patients, or known contacts of colonized patients [6, 47]. In addition to the above populations, studies on AS for MRSA have used universal screening as a surveillance strategy [26]. Studies have also been conducted to define populations at increased risk for colonization who need to be targeted for AS [5, 32, 83]. Decision on which populations to target should depend on the epidemiology of the MDR pathogen in that facility as well as in surrounding facilities which frequently transfer patients.

With regard to frequency of screening, studies have either screened patients at admission, admission and discharge, or admission weekly and at time of discharge [18, 27, 28]. Screening is continued in patients who test negative at time of admission to determine new acquisitions. Since frequent screening requires considerable resources and increases laboratory workload and workload of staff responsible for taking surveillance samples, healthcare facilities planning to implement AS should determine the frequency of AS after considering these factors. Another strategy which can be utilized in areas with low MDR prevalence is conducting point prevalence surveys in units or populations positive for the MDR pathogen [35].

Another issue that needs to be considered by facilities employing AS is to determine when to repeat surveillance to document clearance of the MDR pathogen to avoid unnecessary contact isolation in patients with history of previous colonization. Median time to clearance of MRSA colonization is 7–9 months although some studies show shorter duration of carriage [84–87]. Most hospitals wait at least 3 months prior to assessing an individual for discontinuation of isolation with most requiring three negative specimens to document clearance of MRSA [88, 89]. Similarly, duration of VRE colonization can vary, and immunocompromised patients and use of antibiotics are associated with prolonged VRE carriage [89–91]. Current guidelines suggest discontinuation of contact precautions for VRE if one to three stool or rectal swab cultures taken 1 week apart following treatment of VRE infection are negative [89]. With regard to MDR-GN, guidelines recommend consideration of discontinuation of isolation after at least 6 months has elapsed since

the last positive culture [89]. At least two consecutive negative surveillance tests obtained at least 1 week apart with no active infection and no ongoing antibiotic use are needed to consider an individual negative [89]. Indefinite contact precautions are recommended for extensively drug-resistant bacteria when there is no or limited treatment options [89].

Conclusions

AS has been used as an infection control strategy to control MDR pathogen spread in healthcare facilities during the past few decades. Outbreaks due to many MDR pathogens including MRSA, VRE, and MDR-GN have been successfully controlled with this strategy when combined with other infection control measures. More recent studies however have questioned the effectiveness of AS especially in settings where the MDR pathogen is known to be endemic.

Future studies should use design features and analytical strategies to control for important confounders to arrive at definite conclusions to support causal inference. Until then, a two-tiered approach to implementation of AS as recommended by the Centers for Disease Control and Prevention/HICPAC should be considered [58]. This approach should be tailored to each healthcare facility based on the local circumstances, feasibility, and the specific MDR pathogen being transmitted with frequent reassessment to determine the efficacy of the implemented measures [58].

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C. difficile Microbiome Manipulation

16

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Introduction

The burden of *Clostridioides difficile* infection (CDI) had been increasing in the past decade in terms of incidence, mortality, morbidity, recurrence, and healthcare cost [1–4]. Rates of CDI in US hospitals increased steadily from 1993 until 2011. In 2009, there were more than 336,000 CDI-related hospital stays, comprising 0.9% of all hospital stays. More recent estimates put national burden of CDI at 462,100 cases in 2017, an estimated incidence of 143.6 per 100,000 population [3]. Incidence of death related to community CDI infections are estimated to be 1.3 per 100,000 persons and is higher in hospital-acquired CDI, up to 5 deaths per 100,000 persons [3]. Recurrent CDI occurs after 20–30% of initial episodes and after as many as 40–60% of first recurrences [5]. CDI is also a common healthcare associated pathogen, and in a 2015 prevalence survey, *C. difficile* was the most commonly reported pathogen causing 15% of the healthcare-associated infections identified [5]. The average cost estimate for CDI case management in 2015 was over $42,000 in US dollars [6].

C. difficile transmission occurs not only via the contaminated hands of healthcare workers but also from the environment, where the spores can persist for a long period of time [7]. Skin contamination and environmental shedding of *C. difficile* often persist after resolution of diarrhea and for 1–4 weeks after therapy [8]. Moreover, *C. difficile* spores can remain viable on hard surfaces for up to 5 months, providing a reservoir for infection transmission. Current guidelines for control of CDI recommend contact precautions, meticulous hand hygiene, proper environmental decontamination, and antimicrobial stewardship [9]. Despite efforts by hospitals to adhere to these guidelines, however, CDI remains a significant contributor to healthcare-associated infections [10]. Since one of the risk factors for developing CDI is alteration of the ecological environment of the gut by antimicrobial use, manipulation of the human gut microbiome holds promise as a strategy to prevent and control CDI.

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Clostridioides difficile

CDI manifests as a range of symptoms from mild diarrhea to, in the severe complicated cases, pseudomembranous colitis, toxic megacolon, sepsis, or death [11]. The symptoms are a result of *C. difficile* enterotoxin TcdA and cytotoxin TcdB, which act together to deplete intestinal cytoskeleton integrity and tight junctions, reducing transepithelial resistance and causing fluid accumulation. Further degradation of intestinal epithelium occurs from inflammatory cytokines mediated by TcdA and TcdB, causing neutrophil chemotaxis and damage to the mucosa [11]. This drastic disturbance to the intestine is both a result and cause of profound destruction of resident gut bacteria.

Intestinal Microbiota

The human intestine contains an estimated 1000 microbial species with a genome 100-fold greater than the human host [12]. This gut microbiome contributes to vital functions for host homeostasis including nutrient metabolism, vitamin production, immunity, gastrointestinal motility, and preservation of the intestinal epithelial barrier [13]. In 2012, the Human Microbiome Project Consortium performed a study with 242 participants analyzing the healthy Western microbiome [14]. The study found considerable variation in microbial composition, particularly in abundance of the genus *Bacteroides* [14]. However, the metagenomic carriage of metabolic pathways was constant among the participants, suggesting that a healthy microbiome may be better defined by its ability to maintain normal metabolic functions rather than by its proportions of particular species [14]. The study

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_16

found that an average of 86% of genes in the gut were found to encode an unknown function [14]; thus, our microbial inhabitants remain largely elusive.

Microbiome and *C. difficile*

While significant interpersonal variation in gut microbes is the rule, there are also clear differences between cohorts that differ by age, environment, and diet [12]. Furthermore, alterations of the microbiota—dysbiosis—have been consistently correlated with disease, including CDI [15]. Antibiotic therapy leads to gut dysbiosis characterized by low diversity, enabling growth of opportunistic pathogens, which no longer need to compete for resources, and can utilize carbon produced from bacterial lysis [16].

These altered conditions enable *C. difficile* proliferation and infection, which in turn further drive dysbiosis [17]. Murine models have demonstrated that susceptibility to CDI after antibiotic therapy is associated with an overall decrease in bacterial diversity, with a relative increase in the abundance of the phylum Proteobacteria, and relative decreases in *Bacteroidetes* and *Firmicutes* [18]. Critical illness also has been shown to change microbiota composition in a similar manner [19]. Schubert et al. used a murine model to study the effect of seven antibiotics from six classes at different doses and subsequent challenge with *C. difficile* spores. Different antibiotics caused distinct alterations of bacterial compositions, which resulted in significant differences in *C. difficile* colonization susceptibility [20]. Skraban et al. studied the human gut microbiome associated with *C. difficile* by comparing fecal samples from patients who tested positive for *C. difficile* with those of healthy controls. Healthy participants had a larger number of bacterial groups and significantly greater diversity than participants positive for *C. difficile*. Within the participants positive for *C. difficile*, there were considerable differences in microbial composition among different *C. difficile* ribotypes. Stools positive for the particularly virulent ribotype 027 had the smallest number of bacterial groups and least diversity [21]. Thus, it appears that *C. difficile* colonization may be associated less with changes in abundance of specific groups of bacteria and more with the composition of microbes working in a consortium [20, 21].

Studies of Microbiome Manipulation and *C. difficile*

Existing prospective studies of microbiome manipulation and *C. difficile* are limited by small sample sizes. Yet combining or comparing studies is difficult because of their heterogeneity in methodology, patient populations, severity of disease, and microbial preparations.

Probiotics

In the United States, probiotics are marketed as dietary supplements and thus not all are reviewed for safety by the FDA [22]. The World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations define probiotics as "live microorganisms that confer a health benefit on the host when administered in adequate amounts" [23]. *Lactobacillus* and *Bifidobacterium* are common probiotic genera and largely considered safe by the FAO. They may even be safe for high-risk populations; systematic reviews of studies testing *Lactobacillus* and *Bifidobacterium* in medium-risk and critically ill patients observed no adverse events associated with the probiotics [24]. However, reports of infection in patients who were immunocompromised or had artificial heart valves do suggest a need for caution when recommending or administering probiotics to vulnerable patients until clinical trials have definitively determined their safety [24].

Probiotics for Primary Prevention of *C. difficile*

Studies of probiotics to prevent primary infection (the first episode of CDI) have found conflicting results. In 2007, Hickson et al. performed a randomized double-blind, placebo-controlled study with 135 hospitalized patients receiving antibiotics [25]. The probiotic studied was a mixture of *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* administered in a yogurt drink twice a day during antibiotic administration and for one additional week after completion of the antibiotic course. In the ensuing 4 weeks, 9 out of 53 in the placebo group developed diarrhea caused by *C. difficile*, whereas none of the 56 participants in the probiotic group had positive *C. difficile* tests, a statistically significant difference. Additionally, there were no reported adverse events attributable to the probiotic. Of note, over 80% of patients screened were excluded, which limits the applicability of the results to the general population [25].

In contrast to the significant results found by Hickson et al. and others [26, 27], the largest single published study of probiotics for *C. difficile* prevention did not find a significant effect. The study was carried out at five hospitals in England and Wales and included 2941 patients aged 65 and older who were exposed to at least one antibiotic [28]. Participants consumed a probiotic with a combination of *Lactobacillus* and *Bifidobacterium* for 21 days. Within 12 weeks, 0.8% of patients in the probiotic group and 1.2% of patients taking the placebo experienced diarrhea due to *C. difficile*. Measures of diarrhea severity, abdominal symptoms, length of hospital stay, and quality of life also showed no statistical difference [28]. This study adds to others

studying *Lactobacillus*, *Bifidobacterium*, and the yeast *Saccharomyces boulardii* that have failed to detect a difference between probiotics and placebo in prevention of CDI [29–31].

In 2017, Goldenberg et al. performed a systematic review including randomized controlled trials of adults and children co-administered probiotics with antibiotics for prevention of CDAD (*C. difficle* associated diarrhea) [32]. From the 39 studies included, it was suggested that probiotics reduce the risk of CDAD by 60%, although subgroup analysis did show that the baseline risk for developing CDAD did affect the outcomes significantly. Adverse events were assessed in 31 of the 39 studies and demonstrated more adverse events in control groups (those not receiving probiotics), with adverse events risk reduction of 17% in those receiving probiotics [32]. A systematic review and meta-analysis published in 2016 by Lau et al. included 26 randomized controlled trials with 7957 patients and found a 60.5% lower risk of CDAD in the probiotic group as well [33]. Subgroup analyses found the evidence for efficacy to be strongest for *Lactobacillus*, *Saccharomyces*, and mixed probiotic formulations [33].

Conflicting results from trials likely result from their heterogeneity and may depend on different patient populations. Probiotics may also have greater utility in higher-risk groups, such as patients taking proton pump inhibitors, and studies could be targeted to these populations [34].

Guidelines for Use of Probiotics for Primary *C. difficile* Prevention

Currently, national guidelines do not recommend probiotics to prevent initial episodes of *C. difficile.* The 2017 SHEA/IDSA guidelines state that there is insufficient data to recommend probiotics for primary prevention [35], which is in line with the 2013 American College of Gastroenterology guidelines [36].

Probiotics for Secondary Prevention of *C. difficile*

Probiotics may be more effective for secondary prevention of recurrent CDI, once *C. difficile*-associated dysbiosis has occurred, than for primary prevention. Approximately one third of patients who develop CDI will later suffer from recurrent CDI [35], and these infections are not only more challenging to treat but can be drastically more expensive. The estimated cost per case for primary CDI is $5243, in comparison to $13,655 per case for recurrent CDI [37].

In 1994, McFarland et al. studied the effect of *S. boulardii* for prevention of recurrent CDI in a randomized double-blind, placebo-controlled multicenter trial and found a significant reduction in later recurrent episodes when given in combination with standard antibiotics to treat *C. difficile*. However, antibiotic therapy, dosage, and duration were not controlled [38]. In 2000, Surawicz et al. expanded upon this research by performing a randomized double-blind, placebo-controlled trial with *S. boulardii* for prevention of recurrent CDI while controlling antibiotic therapy. Participants, who were randomized to high- or low-dose vancomycin or metronidazole, received *S. boulardii* or placebo starting on day 7 of antibiotic therapy and continuing for 28 days. *S. boulardii* effectively decreased both the frequency and number of CDI recurrences at 8 weeks in the patients who received high-dose vancomycin, but not in those who received low-dose vancomycin or metronidazole [39]. A smaller study by Wullt et al. in 2003 studied the effect of lactobacillus on recurrent CDI through a double-blinded, placebo-controlled randomized trial which found a trend towards fewer recurrences in those receiving lactobacillus, although given the small sample size results were not statistically significant [40].

Guidelines for Use of Probiotics for Secondary *C. difficile* Prevention

There are slightly more confident recommendations for the use of probiotics as secondary prevention for *C. difficile* as compared with the recommendations for primary prevention. The 2017 Society for Hospital Epidemiology of America/Infectious Diseases Society of America guidelines state *S. boulardii* may decrease the number of *C. difficile* recurrences but should be avoided in critically ill and immunosuppressed patients. They do note that significant and reproducible efficacy has not been demonstrated in controlled clinical trials [35]. The 2013 American College of Gastroenterology guidelines state that "although there is moderate evidence that two probiotics (*L. rhamnosus GG* and *S. boulardii*) decrease the incidence of antibiotic associated diarrhea, there is insufficient evidence that probiotics prevent *Clostridium difficile* infection" [36].

Probiotics as Adjunctive Therapy for *C. difficile*

In 2006, McFarland conducted a meta-analysis including randomized controlled trials of probiotics for the treatment of *C. difficile* [41]. Six studies including 354 subjects were analyzed. Of these, five were for treatment of *C. difficile* and one was for prevention. Two (33%) reported significant reduction of *C. difficile* by probiotics. All of the studies enrolled adults only, and half included only patients with recurrent disease. Antibiotics for *C. difficile* were administered concurrently, and the type and dose of antibiotic were

not randomized or standardized. Doses, strains, and duration of probiotics varied among the studies. When combined for meta-analysis, data revealed a relative risk of 0.59 (95% CI 0.41–0.85) indicating a significant benefit associated with the use of probiotics for *C. difficile*. Dendukuri et al. [42] criticized the McFarland meta-analysis [41] for combining results from studies that could not have been drawn from the same population, resulting in, in their estimation, an artificial narrowing of the overall confidence interval for the efficacy of probiotics. They cited other reasons why they deemed the use of meta-analysis in this case inappropriate, such as the different types and doses of probiotic, different lengths of follow-up, and different definitions of diarrhea and response to therapy. These authors contended that the point estimate of the pooled odds ratio for effectiveness in *C. difficile* was almost entirely determined by the one study that showed a statistically significant benefit, while the confidence interval became narrower due to the increased sample size achieved by combining the studies. They pointed out that a systematic review would have been more appropriate. Indeed, these authors had published just such a review on the use of probiotics for prevention and treatment of CDAD in adults in 2005 [42]. Four randomized controlled studies (all included in the McFarland meta-analysis) were identified with CDAD as the primary outcome. Four additional randomized controlled studies identified CDAD as a secondary outcome. Only two studies showed a benefit for probiotics in treatment of *C. difficile*, particularly in patients with more severe disease; however, the variability in the use of concomitant antibiotics against *C. difficile* makes interpretation of the results difficult.

In 2008, Pillai and Nelson performed a systematic review on the use of probiotics for the treatment of *C. difficile* infections in adults [43]. The review, which included some of the same studies that had been included in the McFarland meta-analysis [41] and the Dendukuri systematic review [42], included four randomized controlled studies. They concluded that probiotics did not show a significant consistent beneficial effect when used in the treatment of *C. difficile*. Only one study found a benefit in the treatment of recurrent CDI, but not in the initial episode. Data were not pooled for analysis because of the variations in recruitment criteria, the type of probiotics used, and the type of concomitant antibiotic therapy and high dropout rates.

More recently, given the promising results of FMT trials for treatment of *C. difficile*, attention has turned to the use of multi-strain probiotic combinations, which perhaps more closely approximate stool (or perhaps not), for treatment of CDI. The probiotics for *Clostridioides difficile* infection in adults (PICO) study was a randomized, double-blind, placebo-controlled trial by Barker et al. studying the efficacy of a combination of four strains of probiotics in adult patients with CDI [44]. This study found a significant improvement in diarrhea outcomes including duration of symptoms and total symptom days, although there was no significant difference in rate of CDI recurrence or functional improvement over time in the treatment versus control groups.

Probiotic Mechanisms

The potential mechanism by which probiotics might treat or prevent CDI has been debated, but likely involves multiple components. A better understanding of the mechanisms of action of probiotics could in the future allow for intervention at several different stages of the disease process. Probiotics are thought to provide enhanced colonization resistance, improve integrity of the intestinal barrier, secrete antimicrobial peptides, and cause downregulation of gene expression through quorum sensing [23]. *Lactobacillus* has a direct inhibitory effect against many pathogens, believed to be due to secretion of organic acids, hydrogen peroxide, and bacteriocins [45]. The probiotic formulation Bio-K+ (*Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Lactobacillus rhamnosus* CLR2) has been found to effectively neutralize *C. difficile* toxins in addition to having cytotoxic effects [45]. All *Lactobacillus* species do not appear to have equal activity against *C. difficile*. *Lactobacillus* mixed cultures have strong inhibitory effects against *C. difficile*, while *L. casei* and *L. rhamnosus* pure cultures have demonstrated less pronounced inhibition compared to the mixed cultures, and *L. acidophilus* has no effect [45]. Due to the limited information and variable results of studies on the efficacy of probiotics for the treatment of *C. difficile*, Schoster et al. performed in vitro analysis of 17 probiotic strains [44]. Five of the 17 tested probiotic strains inhibited the growth of *C. difficile*. Those five strains included *L. plantarum* (BG112), *L. rhamnosus* (LRH19), *L. plantarum* (LPAL), *L. rhamnosus* (SP1), and *B. animalis* ssp. *lactis* (BLC1), further demonstrating the varying efficacy of *Lactobacillus* species [46]. *S. boulardii*, not a normal inhabitant of the intestine, has been shown to increase host concentrations of immunoglobulin A and antitoxin A and to produce a protease that hydrolyzes *C. difficile* toxins A and B [26].

An emerging concept is the use of prebiotics for infection prevention. A prebiotic is defined as "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health" [47]. Prebiotics can also be combined with probiotics as synbiotics [48]. Prebiotics are thought to alleviate diarrheal disease by increasing short-chain fatty acids, or reducing the pH of the intestine [49], but little research has yet to ascertain whether prebiotics would be effective for *C. difficile*. In 2005, Lewis et al. conducted a randomized trial to study the

effects of the prebiotic oligofructose on recurrent CDI [50]. The study found that patients taking oligofructose were less likely to develop recurrence of symptoms than those in the control group. These initial findings support the theorized benefit of prebiotics.

Oral Full-Spectrum Microbiota Therapy

One of the newest therapies being investigated are oral full-spectrum microbiota (FSM) products. These contain various functional microorganisms which can engraft in the host microbiome to help restore gut flora [51]. CP101 is an oral FSM being studied as part of the PRISM3 randomized, double-blinded, placebo-controlled study for treatment of recurrent *C. difficile* infections. The study randomly assigned patients to CP101 or placebo after an appropriate course of CDI antibiotics, and initial results showed a 74.5% sustained clinical response in the CP101 group compared to 61.5% in the placebo group [52]. This looks to be a promising new area in treatment of recurrent CDI.

Fecal Microbiota Transplantation for *C. difficile*

Evidence Behind the Efficacy of FMT

Permanent alteration of the gut microbiota is challenging because of immune tolerance to the resident microbes, which inhibits colonization of new organisms [53], requiring a drastic event to significantly change the composition. FMT may be a more effective method of *C. difficile* treatment and/or prevention because the procedure provides three times the order of magnitude of bacteria compared to that from probiotics [54]. FMT has been shown to considerably alter the recipients' microbiota for at least 24 weeks, whereas probiotics are associated with short-term microbiota modifications of 10–14 days [55, 56].

Although the research on FMT is still limited, the early results are promising. In 2013, Van Nood et al. conducted a single center open-label trial for recurrent CDI with three arms: vancomycin alone, vancomycin with bowel lavage, and vancomycin with bowel lavage and donor feces infusion via nasoduodenal tube [57]. The study terminated early after an interim analysis because of its striking success. Out of the 16 patients receiving the infusion of donor feces, 13 had no further evidence of infection after one infusion and two others experienced resolution of their relapsing CDI after a second infusion. Resolution occurred in only 3 out of 13 patients in the bowel lavage group and 4 of 13 in the vancomycin alone group. Analysis of stool samples from participants in the infusion group demonstrated increased fecal microbiota diversity following the procedure, with a greater proportion of *Bacteroidetes* and *Clostridium* clusters IV and XIVa and a reduction in Proteobacteria. Except for mild diarrhea and abdominal cramping on the day of infusion, there were no significant differences in adverse events among patients in the three arms [57].

The high rate of resolution of recurrent CDI following FMT remains when all studies are combined in systematic reviews. A meta-analysis by Kassam et al. in 2013 included 11 observational studies comprised of 273 patients, and the weighted pooled rate of clinical resolution was 89% [58]. FMT was associated with minor adverse effects of cramping, belching, and abdominal discomfort, but no serious adverse events [58]. A systematic review in 2014 of case series, case reports, and a randomized controlled study testing FMT for recurrent CDI found a resolution rate of 87% [59]. A more recent meta-analysis by Baunwell et al. in 2020 had similar findings [60]. From the studies included in this analysis, clinical effect at week 8 overall was 91% for repeat FMT and 85% for single FMT. And clinical effects were seen as early as week 1 at 94%, which persisted until final assessment at week 8 [60]. Comparing repeat FMT to antibiotic treatment such as tapered vancomycin, the number needed to treat (NNT) was found to be 1.5, and 2.9 for single FMT [60], further demonstrating the efficacy of FMT as a treatment for CDI.

Controversies in Use of FMT for CDI

While there is increasing evidence supporting the efficacy of FMT, there still remains areas of controversy where more data is needed including route of administration, single versus multiple administration, donor characteristics, and the use of FMT for pediatric populations.

Stool transplants can be delivered through many different routes: nasogastric or nasojejunal tube, oral capsules, upper endoscopy, retention enema, as well as colonoscopy [61]. Ongoing studies are evaluating whether route of administration affects efficacy. Youngster et al. studied 20 patients with refractory or recurrent CDI who received frozen stool suspension from an unrelated donor via colonoscopic or nasogastric administration. At 8 weeks, 14 patients (70%) experienced resolution of diarrhea and no recurrences. Five patients received a second infusion and four were cured bringing overall resolution rate to 90%. The study did not find a significant difference between the colonoscopic or nasogastric routes [62]; however, systematic reviews and meta-analysis have found some differences between the lower and upper GI routes of donor stool administration. Kassam et al. detected a trend toward an improved response for delivery via a lower GI route [58], and Cammarota et al. observed lower GI administration resulted in a slightly

higher rate of resolution than upper GI routes, 81–86% compared to 84–93%, respectively [55]. Similar findings were found in the systemic review by Quraishi et al. favoring lower GI administration, with 95% resolution compared to 88% with upper GI administration [59]. Costs of each method may be an important factor in the decision, as well as patient characteristics. The optimal route of administration may even depend on the most desired species to be delivered. Some spore-forming *Firmicutes* species need to pass through the upper GI tract for efficacy [63], whereas *Bacteroidetes* may need administration via a lower route to prevent destruction by gastric acids [64].

There is contrasting data regarding the use of single FMT compared to multiple administrations for CDI as well. In one of the largest RCT evaluating FMT for RCDI, a single fresh or frozen FMT was successful in 53% and 51% of patients, respectively, compared to 75% and 70% after 2 FMTs and 91% and 86% after more than 2 administrations [65]. Other RCTs have shown efficacy after a single administration though, with one trial showing success in curing infection in 81% of subjects after a single FMT by nasoduodenal administration [57].

Another debated question is whether there is an increase in efficacy when the recipient is related to the donor. A systematic review in 2011 of 27 case series and reports, comprising 317 patients, observed a slight increase in resolution with stool from a related donor (93% vs. 84%) [66]. However, the meta-analysis by Kassam et al. found no significant differences in resolution whether or not the donor was related [59]. A randomized controlled study by Kelly et al. in 2016 evaluated the efficacy of heterologous (donor stool) versus autologous (patient's own stool) FMT administered by colonoscopy [67]. Heterologous FMT was safe and more efficacious than autologous FMT. Heterologous FMT also restored normal microbiome diversity with reductions in Proteobacteria and Verrucomicrobia and increases in Bacteroidetes and Firmicutes, which was not seen in autologous FMT [67].

Relatively little is known about FMT for *C. difficile* in children. *C. difficile* colonizes the intestine of 60–70% of infants in their first month, but by 1 year of age carriage decreases to 10%, and at adulthood drops to 0–3% [68]. CDI is more commonly viewed as a disease of older adults, but there has been a concerning rise of CDI incidence in children, with a tenfold increase between 1991 and 2009 [69]. In 2014, both Pierog et al. and Walia et al. reported case series of FMT performed on children with recurrent CDI. Pierog et al. described cases of stool donation from parents to six children, with the youngest age 21 months, who all recovered post FMT [70]. Walia et al. reported two children under 3 years old with recurrent CDI who received the donation from a mother and grandmother [71]. Both children experienced resolution of CDI and remained without symptoms over 6 months after the procedure. A larger multicenter retrospective cohort study performed by Nicholson et al. in 2020 followed 335 pediatric patients aged 11 months to 23 years [72]. The overall success rate in this cohort was 87% [72], similar to success rates reported in the adult population [55, 58]. Predictors of success included the use of fresh stool versus previously frozen, lower GI administration, and fewer CDI episodes prior to FMT [72]. This adds to the limited literature on pediatric FMT for CDI and suggests the procedure is safe and effective for infants and children, but more robust trials are needed.

FMT for Immunocompromised Patients

Like probiotic research, in which nearly all studies for probiotics exclude immunocompromised patients [29], FMT trials also exclude these patients due to safety concerns, yet immunocompromised individuals are at a particularly high risk of developing CDI and of having complications such as recurrences.

A systemic review [73] found 43 published case reports and case series of FMT in immunosuppressed patients and 1 retrospective cohort study, with 303 total recipients. Combined analysis shows efficacy is comparable to non-immunocompromised patients: over 87% resolution after first FMT procedure and over 90% after the second [73]. However, one study found a higher relapse rate in cancer patients [74], and there have been severe adverse events in patients with IBD, although infectious complications are uncommon [75]. The evidence of FMT for immunocompromised patients is extremely limited and heterogeneous, but encouraging, and indicates trials with safety precautions are warranted.

FMT Mechanisms

Antibiotic therapy has been shown to cause many metabolic alterations. These enhance the capacity of *C. difficile* to proliferate; thus, some of the proposed mechanisms of FMT involve restoration of traditional metabolic, rather than microbial, composition.

Antibiotics deplete normally occurring gut bacteria that convert primary bile acids to secondary bile acids [18]. Weingarden et al. analyzed the fecal microbiota of 12 recurrent CDI patients prior to and post FMT and found substantial differences in bile acids. Prior to FMT, primary bile acids were elevated compared to their concentration post procedure, and three types of secondary bile acids were present post FMT that were absent prior [76]. Taurocholate (the conjugated bile acid of cholic acid with the amino acid taurine) and glycine have been shown to bind to *C. difficile* spores

and activate germination [77]. CamSA is a meta-benzene sulfonic acid derivative of taurocholate and competitively inhibits taurocholate-mediated germination of *C. difficile* spores. In mice inoculated with a high concentration of *C. difficile* spores, those treated with a high dose of CamSA did not develop CDI, and the mice given a lower dose experienced delayed onset and decreased severity of disease [77]. The results of these studies indicate that FMT restores primary and secondary bile acid proportions that may prevent the conditions for *C. difficile* proliferation. In an analysis of the metabolome of the *C. difficile* susceptibility state, researchers compared the cecal content of healthy and CDI mice. In the CDI susceptible state, there was a marked increase in primary bile acids, taurocholate, and other tauro-conjugated bile acids and a decrease in the secondary bile acid deoxycholate [78].

In the same study, there were also considerable differences in metabolites other than bile acids. The researchers found an increase in carbohydrates and decrease in short-chain fatty acids, indicating a decrease in carbohydrate fermentation [78]. In a murine model, it was found that antibiotic treatment transiently increases succinate and *C. difficile* upregulates a metabolic pathway to convert succinate to butyrate [79]. In a study with 75 CDI participants and 40 healthy controls, the CDI microbiome displayed a significant reduction in butyrate-producing C2–C4 anaerobic fermenters [80]. Additional metabolites, including butyrate and succinate, appear to be associated with CDI, and FMT may reestablish normal proportions for resolution. In vitro experiments with primary bile acids and specific carbohydrates directly indicated that *C. difficile* utilizes metabolites of the antibiotic-altered microbiome for germination and proliferation [78].

Guidelines for Use of FMT in CDI

The only US FMT guidelines available are from the Fecal Microbiota Transplantation Workgroup [81]. Without stating the basis for their recommendations, the authors suggest consideration of FMT for patients with refractory or recurrent CDI, moderate CDI that did not respond to treatment after 1 week, and severe CDI that did not respond to treatment after 48 h. The workgroup cautions performing FMT in immunocompromised patients and does not recommend specific criteria for stool donors other than exclusions (see Table 16.1), citing a lack of data [81]. European guidelines strongly recommend FMT only as a treatment option for mild to moderate recurrent CDI [82].

The lack of standard protocol for screening of FMT donors raises the concern of uncontrolled transmission of known infections and unknown ramifications from an altered microbiota. For example, transmission of resistant gram-negative organisms such as extended-spectrum beta lactamase producing *E. coli*, related to FMT administration [83]. The Fecal Microbiota Transplantation Workgroup has put forth proposed donor qualifications shown in Table 16.1. The workgroup recommends a questionnaire and then serum and stool testing. Serum tests should screen for HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus, and syphilis, and stool should be screened for typical enteric pathogens, *C. difficile* toxin, Giardia antigens, *Cryptosporidium* antigens, *Helicobacter pylori* antigens, helminths, ova, and parasites [82].

Table 16.1 Fecal microbiota transplantation workgroup proposed FMT donor for CDI characteristics

Absolute contraindications	Human immunodeficiency virus (HIV); hepatitis B or C infections; exposure to HIV or viral hepatitis within the previous 12 months; high-risk sexual behaviors; use of illicit drugs; tattoos or body piercing performed within 6 months; incarceration or history of incarceration; current communicable disease (e.g., upper respiratory tract infection); risk factors for variant Creutzfeldt–Jakob disease; travel within the last 6 months to areas high risk of traveler's diarrhea; history of inflammatory bowel disease, irritable bowel syndrome, and other functional diseases; history of gastrointestinal malignancy or known polyposis; use of antibiotics within the preceding 3 months, immunosuppressant, chemotherapeutic drugs; and recent consumption of a potential allergen for the recipient
Relative contraindications	History of major gastrointestinal surgery; metabolic syndrome, autoimmune diseases, atopic diseases, and chronic pain syndromes

Microbiome and Resistance to CDI

Although it has been established that a healthy intestinal microbiome provides resistance to CDI that is disrupted by antibiotic use, the specific elements of the microbiome responsible for this protection remain unknown. Buffie et al. sought to determine the specific bacterial changes within the intestine that provide resistance to CDI [83]. Mice were administered different antibiotics, which created varied disturbances in the microbial communities and in turn varied vulnerability to CDI. The researchers then correlated the microbial changes to the acquisition of CDI. They found that individual species were responsible for CDI prevention rather than a community structure and identified 11 bacterial operation taxonomic units (OTUs) associated with CDI prevention, the greatest association being with *Clostridium scindens*. The study continued with a human population of 24 allo-HSCT patients, 12 of whom were diagnosed with CDI, and the remaining 12 were *C. difficile* carriers without

infection. The bacteria that exhibited protection against CDI in the human cohort were then compared to those in the murine cohort, and two OTU associated with resistance to CDI were shared in both groups, with the strongest again being *C. scindens.* To determine whether this correlation was causal, the researchers adoptively transferred a four-bacteria consortium associated with *C. difficile* inhibition, *C. scindens* alone, or vehicle (PBS). Adoptive transfer of the consortium or of *C. scindens* alone ameliorated CDI, associated weight loss and mortality, while adoptive transfer of the other three bacterial isolates individually did not have a substantial impact on resistance to CDI. Using a bile-acid sequestrant, the researchers determined that the bile-acid production was the mechanism of *C. scindens* CDI protection [83].

Reeves et al. had determined that after a cocktail of five antibiotics and *C. difficile* challenge, mice with mild CDI were primarily colonized with bacteria from the family *Lachnospitacea*, whereas moribund mice had a predominance of *E. coli* [84]. Reeves et al. then analyzed the effect of *Lachnospitacea* and CDI in germ-free mice [84] by precolonizing a cohort with *Lachnospitacea* before *C. difficile* challenge. These precolonized mice had significantly decreased *C. difficile* colonization, toxin levels, and disease, compared to mice that were not precolonized or that were precolonized with *E. coli*, and only 20% mortality compared to 100% in the *E. coli* precolonized mice. Further study of the *Lachnospitacea* family may result in greater knowledge of the mechanisms of CDI resistance as well as mechanisms for prevention and treatment [84].

The Future of FMT: Manufactured and Synthetic Microbial Therapeutics

The next direction in FMT research is to determine the specific beneficial groups of organisms and isolate these protective strains for transplantation. One study found both human and mouse fecal matter transplanted into mice with recurrent CDI increased *Bacteroidetes* groups, which include *Bacteroides* and *Porphyromonadaceae*, and *Firmicutes* groups, which include *Clostridiales* and *Lachnospiraceae* [85]. Another study also found key *Bacteroidetes* species conferred CDI protection through FMT when stool from CDI-resistant mice was transplanted to CDI susceptible mice. Further analysis showed that these species induce the antimicrobial peptide Reg3γ which prevented *C. difficile* from accessing colonic crypts and the resulting intestinal inflammation and stem cell injury [86]. A compound in development by Seres Therapeutics, SER-262, is a second-generation composition of purified bacterial spores which has been shown to be highly effective for prevention of CDI in mice [87]. The company's first product, SER-109, failed to show a difference in subsequent CDI recurrence when given to patients with recurrent CDI in a phase 2 study [88]. Unlike SER-109, SER-262 is completely synthetic. SER-262 is currently in phase I clinical trials [89].

FMT may also shift into administration of purified intestinal stool cultures, also known as "human probiotic" or "synthetic stool" which could prevent the "ick factor" of traditional stool infusions and reduce concerns of disease transmission from FMT donors. In 1989, Tvede and Rask-Madsen reported that a cocktail of ten facultative aerobes and anaerobes was effective against recurrent CDI in five patients [90]. Petrof et al. tested the effect of purified intestinal bacterial cultures, which they called "RePOOPulate," containing 33 strains from a healthy stool donor for recurrent CDI. Two patients with CDI who failed at least three antibiotic courses received the stool substitute via colonoscopy. Both patients experienced resolution of diarrhea in 2–3 days and remained without symptoms for 6 months. Additionally, the patients' microbiota compositions following the procedure resembled the stool substitute, as is seen in traditional FMT [91].

Conclusion

Research on treatment and prevention of *C. difficile* infection through the manipulation of the microbiome has a promising future that could take many different paths.

Further study is required, with larger trials to elucidate the many contradictions and questions that remain. Studies testing specific probiotic strains under controlled conditions should resolve conflicting results regarding which probiotic strains are protective against primary and secondary CDI in which patients and which strains might be useful as adjunctive therapy for treatment of disease. Data are needed to determine if different modes of delivery of probiotics, FMT, or purified culture have greater efficacy, in all or certain patient types. Research on safety should be ongoing in probiotic, FMT, and purified culture studies to determine if benefits outweigh the risks in vulnerable patients. Finally, clear protocols will be needed to ensure standardized, safe treatment for patients undergoing microbiome manipulation for *C. difficile*.

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Air Contamination in the Hospital Environment

17

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Introduction

Air is postulated to be a mode of transmission for multiple infectious organisms. The importance of air in the transmission of infectious processes has always interested the medical community; this is well-exemplified by the use of the terms "miasma" or "malaria" in which "bad air" was thought to be responsible for the origin of many diseases [1]. This phenomenon has been extensively studied in diseases caused by organisms such as *Mycobacterium tuberculosis* and *Aspergillus species*, among others [2].

In the era of multidrug-resistant organisms, there is a clear relationship between environmental contamination and nosocomial infections; nonetheless, there is still an unanswered question of whether or not air plays a role in the horizontal transmission of such infections, contributing to the development of outbreaks in this setting [3, 4]. Air has also been implicated as a possible vector in the spread of different mechanisms of resistance between organisms [1, 4].

Over the past decades, there has been an increased interest to better understand the close relationship between the different components of hospital environment, including indoor air [4]. This phenomenon is due to a dramatic increase in infections caused by multidrug-resistant organisms that are acquired during hospital admissions and also due to the increasing number of potentially susceptible population such as transplant or oncological patients, resulting in increased morbidity and mortality [5].

In recent years, the appearance of novel coronaviruses (CoV), such as the Severe Adult Respiratory Syndrome CoV (SARS-CoV) 1 and 2 and the Middle East Respiratory Syndrome CoV (MERS-CoV), has created an increased interest in the mechanisms involved in transmission of such viruses and the possible role of air contamination leading to hospital-acquired infections [6, 7].

Furthermore, there is no standardization regarding the indications for air sampling in the hospital setting, what method should be used, and how to interpret the results in order to put them into practice from an infection control perspective [5]. This review aims to summarize the existing data on air contamination within the healthcare system. We also aim to explore air contamination in the hospital setting due to viruses such as SARS-CoV-2.

General Principles

Biological aerosol is defined as a collection, either naturally or artificially created, of biological particles that are diffused in the air or in another gaseous phase [2, 8–10]. Based on this principle, microorganisms can be found in the air in two forms depending on its size. The first one is a small conglomeration that includes microorganisms, small dust particles, and water or body fluid secretions [2, 8, 9, 11]. This corresponds to the mode of transmission of airborne pathogens such as *M. tuberculosis* and they are most commonly referred to as aerosols [12, 13]. The second form is an aggregate of microorganisms associated with dry particles, either from body sources (e.g., skin) or fomites, which are usually referred as droplets [2, 11]. This is the suspected mechanism

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_17

implicated in the spread of most respiratory viruses and of healthcare-associated pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant gram-negative bacteria [2, 11, 13].

As mentioned before, the size of airborne microbial particles contained within biological aerosols varies greatly from 2 μm up to >100 μm [2, 14]. The larger particles or droplets will settle very fast, being deposited over the floor or other horizontal surfaces and will not travel more than couple of meters from their site of origin [14]. In contrast, smaller particles or aerosols will settle very slowly [2]. It has been described that a 2 μm droplet nucleus could take up to 4 hours to fall a distance of 2 meters [14]. Given this long suspension time, these particles can be carried long distances by air currents and thus be distributed widely throughout a hospital [2]. For this reason, the behavior of some forms of biological aerosol is influenced greatly by the ventilation conditions within each room [14].

Another important factor contributing to the ability of biological aerosols to cause environmental contamination and later on development of nosocomial infections is the intrinsic characteristics of the organisms themselves. Some bacteria are not designed to be aerosolized, finding the air to be a hostile environment where they are subject to desiccation, nutrient deprivation, and damaged by radiation, oxygen, and free radicals [8, 15, 16]. Other bacteria will form spores when aerosolized, allowing them to survive for extended period of times; such is the case for the *Clostridioides* and *Bacillus species* [8, 15, 16]. Some gram-positive bacteria have also been described to survive desiccation for prolonged period of times, and such is the case of *S. aureus* [17]. On the other hand, gram-negative bacteria are thought to survive for shorter periods when aerosolized [18]. There are few exceptions to this, as in the case of *Acinetobacter spp.* and *Pseudomonas species* [19, 20].

Thus, the effect of biological aerosols will depend greatly on the characteristic of the environment where they were formed and released and its biological composition including the ability of the organisms to survive free in the environment.

Indications for Sampling Air in the Hospital Setting

There are several situations when air sampling in the hospital setting is indicated [2, 5, 9]. Epidemiological investigation of nosocomial infections and outbreaks is one of such indications. While the acquisition of most nosocomial infections is associated with direct person-to-person contact leading to cross-contamination of the hospital surfaces, and hence, the use of contact precautions with gowns and gloves implemented around patients colonized or infected with multidrug-resistant organism such as MRSA, the possible role of airborne transmission of nosocomial infections is also under consideration [21]. This observation arises in cases in which the degree of contamination of the hospital environment is much heavier and more extensive than expected, implying the presence of a different mechanism of dissemination [22]. Airborne transmission is thought to be responsible for as much as 10% of nosocomial infections including MRSA, *Acinetobacter,* and *Aspergillus spp*. [14]. In fact, orthopedic prosthetic joint infection rates correlate with the number of airborne bacteria within 30 cm of the surgical wounds [23]. Furthermore, air filtration through high efficiency particulate air (HEPA) filters has been shown to reduce the rate of invasive pulmonary aspergillosis in immunocompromised patients [24]. When evaluating air contamination in the setting of clinical infections, it is imperative that the aerosolized isolate is concordant to the patient's isolate and that the degree of air contamination is clinically significant [5].

Even in the absence of outbreaks, air sampling can be used for research purposes. When patients are colonized with MRSA, it is a standard practice to implement contact precaution with gowns and gloves [25]. However, recent studies demonstrated aerial dispersal of MRSA from patients infected or colonized with this organism, proposing the use of masks around such patients [26]. Further research is necessary to determine the clinical significance of these findings. In addition to further elucidating the transmission risk of known microorganisms, microbiological sampling of the environment is crucial for emerging infectious diseases. During the SARS-CoV-2 pandemic, researchers evaluated multiple air samples to determine the presence of viable virus in air samples collected at a certain distance from patients [27]. At the time of this writing, the exact transmission dynamics of SARS-CoV-2 is still a controversial topic. Studying the aerial dissemination patterns of microorganisms can help elucidate the appropriate level of infection precautions (contact, droplet, airborne) that should be exercised, which in turn will lead to containment of such infections.

Culturing air samples can be used to identify hazardous procedures and confirm resolution of the problem after necessary changes are implemented. Many healthcare equipment like vaporizers, humidifiers, respirators, vacuum cleaners, and ultrasonic surgical instrument cleaning devices are associated with aerosol generation [28, 29]. Air sampling can be used to assess the quantity of released microbes and determine the efficacy of repair [11]. Similarly, in the setting of bioterrorism, air sampling can be used to detect presence of hazardous agents and confirm successful removal after appropriate cleansing [30].

Finally, air sampling can act as quality measure in infection control to assess new housekeeping practices. One hospital determined that minimizing number of door opening led to reduced operating room air microbial contamination

[31]. Besides evaluating new interventions, air sampling can be used to ensure proper function of already existing systems. Maintaining properly installed heating, ventilation, and air conditioning (HVAC) filters by preventing air leakages and dust overloads is fundamental to controlling infections [29, 32]. One can inspect air samples around the filters during periodic filter inspections and also after filter manipulation (i.e., repair, cleaning) to confirm operation. Finally, hospital renovations and construction projects are very common in the world of ever-expanding healthcare. Surveillance of airborne environmental disease during these times is imperative for patient safety [29].

Blindly obtaining air samples without an objective is discouraged due to the ambiguous clinical significance of the result [13]. For instance, in order to investigate the continued *Aspergillus* contamination of tissue culture in a research laboratory, air samples were used to determine that a contaminated filter of the incubator was the culprit [11]. Such as this, there should always be a purpose and an intention to act on the results obtained.

Air Sampling Methods

The method chosen to sample air will depend on various factors, including the purpose for which air sampling is being performed, the type of organism being studied, the expertise or preferences of the investigator, and the resources available for such task. Ideally, all of the points mentioned above should be fulfilled when selecting a method.

Methods used for sampling air can be classified into two categories: passive and active methods [33]. The passive methods are based on sedimentation, whereas the active ones use more complex devices such as air impactors, centrifugal air machines, or filtration systems [11].

Passive Methods for Sampling Air

Passive air sampling is performed using settle plates, relying on gravity to deposit biological particles containing bacteria into a culture plate [11, 33]. The average particle size encountered in the hospital setting is of approximately 13 μm [11]. It has been described that an agar plate of 100 mm in diameter could potentially collect particles from $1ft^3$ of air in approximately 15 min at a sedimentation speed of 0.46 cm/s [11, 33, 34].

The main advantages of settle plates include being an easy method to use, affordable (especially important in poor-resources settings), and readily available [33]. Also, the results obtained with this method are considered reproducible and reliable, in contrast to active sampling methods, mainly because settle plates directly measure bacterial sedimentation on horizontal surfaces rather than suspended biological particles in the air, where it would be difficult to predict where and when they would sediment [35, 36].

The main limitation of the passive method is that it provides a qualitative result of air contamination, which might weakly correlate with the real degree of contamination of the environment being tested [1, 33]. Also, this method is easily influenced by airflow present in the vicinity of the plate, making the results vary depending on the location of the plate [11]. It can be insensitive in cases in which the bacterial load is low [33, 37, 38]. Passive methods also require longer periods of sampling, compared to the active methods, of at least 1 hour [33]. There have been reports in which settle plates have been left open for periods equal or longer than 24 hours, making the plates dry upon collection [38]. In this instance, it has been described that swabbing the plates with a premoistened Q-tip and later transferring into liquid media could increase chances of recovering organisms [37–39].

Active Methods for Sampling Air

These devices force air flow directly onto the surface of culture media [8]. The standard measurement of air contamination with these methods is based on the number of CFU per cubic meter of air suctioned (CFU/m^3) [33]. This is based on the principle that each particle that impacts the culture media will form a colony [8, 9]. There are several different types of devices that belong to this category (Table 17.1).

Several studies have compared different devices for active air sampling. The majority of these studies showed that there is a great variability of the results when using them, even at the same place and same time, making it difficult to determine a superior device among the others [9, 33, 40–44].

The main benefit of active air sampling is the proposed higher sensitivity to detect air contamination [9, 33, 44]. As mentioned earlier, this method provides more detailed and specific results including the volume of air suctioned during their use and the number of colonies in each plate [9, 33, 40–43]. Some specific air impactors could also provide an exact time in which air contamination occurred, allowing the investigator to correlate those findings with activities happening inside the patients' rooms [22, 45].

There are many drawbacks with the use of these devices. They are expensive and time-consuming. Machines are noisy, thus making them difficult to be used for prolonged periods of time in occupied rooms [44]. They are also difficult to sterilize, fact that could give false-positive results due to prior contamination of the device [33]. There is one major limitation with these methods, which is the limited sample size of air being tested, probably requiring multiple cycles of sampling to obtain a representative indoor air sample [33].

Table 17.1 Different types of the most common commercially available air samplers

Impactors: These are the most commonly used active sampling methods. Air is drawn into a sampling head by a pump or fan into a solid media, via narrow slit (slit samplers) or perforated plate (sieve samplers). The velocity of the air is determined by the width of the slit in slit samplers and the diameter of the holes in sieve samplers. When air hits the surface of the media plate, it makes a tangential change of direction and any suspended particles are thrown out by inertia, impacting onto the agar plate. After incubating the plate, counting the number of visible colonies gives a direct quantitative estimate of the number of colony-forming units in the sampled air.	*Slit type* Casella single slit and four slit sampler Mattson-Garvin air sampler New Brunswick STA air sampler Bourdillon sampler BIAP Slit sampler Reyniers slit sampler *Sieve type* Andersen 2, 6, and 8-stage sampler Ross-Microban sieve air sampler Personal particulate aerosol collector Surface Air System (SAS) system Joubert 3-stage biocollector
Impingers: Impingers use a liquid media for particle collection. Sampled air is drawn by a suction pump through a narrow inlet tube into a small flask containing the collection media. When the air hits the surface of the liquid, it changes direction abruptly and any suspended particles are impinged into the collection liquid. Once the sampling is complete, the collection liquid can be cultured to enumerate viable microorganisms. Since the sample volume can be calculated using the flow rate and sampling time, the result is quantitative.	All-glass impinger 30 and pre-impinger Midget impinger with personal air sampler May 3-stage Glass impinger Folin Bubbler Cyclone Sampler
Filtration samplers: In this method, air is drawn by a pump or vacuum through a membrane filter. The filter medium may be polycarbonate or cellulose acetate, which can be incubated directly by transferring onto the surface of an agar medium, or gelatine, which can be dissolved and analyzed by regular culture methods.	Millipore membrane-filtered monitor Gelman membrane filter air sampler MSF 37 monitor Sartorius MD8 Air Sampler
Centrifugal samplers: In this method, air is forced by an impeller drum concentrically into the surface of a culture media. After collecting the sample, the agar media is incubated and the colonies counted. Because this method draws a precise amount of air per minute, the detected number of colonies can be calculated per unit volume of air.	Rotary centrifugal air sampler (RCS) Well sampler

Also, it is believed that the growth of some of the organisms could be inhibited by the impact into the culture media [8, 39, 44, 46]. It has also been reported that the sampling time also affects greatly the successful recovery of bacteria from air, finding that prolonged periods of sampling could potentially inhibit growth of susceptible bacteria or could cause bacteria to bounce out of the culture media into the environment [8, 47].

Active or passive air sampling?

Comparisons between active and passive methods for air sampling have shown mixed results. There are some reports that conclude that there is correlation between both methods for detecting air contamination [9, 34]. One study concluded that in instances in which the level of air contamination was low, there was discrepancy between both methods, probably due to the relative low sensitivity of settle plates when compared with air impactors [9].

Given the differences between active sampling methods, the mixed results obtained when comparing active versus passive methods, and the lack of standardization, it is difficult to determine which type of method is superior among the others. Factors that can affect the results when comparing methods for sampling air include the levels of contamination in the environment, the type of airflow in the room being tested, and the different activities happening inside the room [9].

The ideal method for sampling air should be easy to use, should not be expensive in order to be widely available, should be able to detect all aerosolized biological particles present, should provide a quantitative result that strongly correlates with the real degree of contamination of the environment, should minimize the amount of nonviable organisms in the culture media, and should provide a specific time in which air contamination occurred [11].

Respiratory Viruses

Four main methods of transmission have been described for respiratory pathogens, which include direct person-to-person contact, indirect contact via fomites/ surfaces, droplets, and aerosols [48]. Traditionally, respiratory viruses have been thought to be transmitted via large droplets. Nonetheless, that concept has been challenged by the outbreaks of novel coronaviruses, making the scientific community start focusing on possible airborne transmission of such pathogens. Based on this, Roy et al. proposed a new classification of airborne transmission of infectious agents, including obligate, preferential, and opportunistic based on the infectious agent capacity to be transmitted and cause disease through aerosols [49]. Based on this new proposed classification, *Mycobacterium tuberculosis* would fall in the category of

obligate airborne transmission. Agents that fit the category of preferential airborne transmission would include viral diseases such as measles and smallpox. Opportunistic agents of airborne transmission would include pathogens that traditionally spread via droplets or contact, but can also initiate infections via fine particles of aerosols when certain conditions are met [49]. We will focus on coronaviruses in this chapter, given the controversial role of air contamination as a method of transmission in the hospital setting.

Coronaviruses

Coronaviruses are responsible for respiratory and gastrointestinal infections in humans and animals [50]. Historically, coronaviruses have not been associated with severe disease in humans until the development of outbreaks caused by the SARS-CoV-1 and MERS-CoV [7, 51].

During the SARS-CoV-1 outbreak, Yu et al. described a cluster of 187 cases at an apartment complex in Hong Kong [6]. The researchers studied the association between the location of index and secondary cases and a computational fluid analysis model of aerosols generated by the index patient [6]. A concentrated aerosol plume originated from sewage contaminated by the index patient was thought to be responsible for the majority of secondary cases in the apartment complex, thus raising the possibility of airborne transmission of SARS-CoV-1 [6].

In December 2019, a novel coronavirus disease (COVID-19) was identified in Wuhan City, Hubei Province in China, in a cluster of patients with severe pneumonia [52]. Given the rapid spread of the SARS-CoV-2 outbreak, the WHO categorized it as a pandemic on March 2020 [53]. As of January 2021, COVID-19 has caused more than 24 million cases with at least 405,000 deaths solely in the USA [54]. Animal models have suggested airborne transmission of SARS-CoV-2. Kim et al. established an infection and transmission model in Ferrets [55]. In this study, SARS-CoV-2 was transmitted between the study animals with both direct and indirect contact, suggesting potential airborne transmission [55]. In another study from the University of Hong Kong, Sia et al. also described an animal model of transmission for SARS-CoV-2 using golden hamsters [56]. To prove this virus was transmitted via aerosols, the researchers paired inoculated hamsters to naïve ones, placed in different wire cages in close proximity one to the other [56]. On this study, aerosols' transmission was efficient proven by the fact that viral RNA was isolated from nasal washes from all naïve hamsters [56].

There is controversy about the potential role played by air contamination with SARS-CoV-2 in the development of hospital-acquired infections. Using a quantitative PCR method, Liu et al. analyzed aerosols in two different hospitals in Wuhan, China [57]. RNA of SARS-CoV-2 was found in aerosols collected from patients' rooms, public areas, and health care workers' (HCW) areas [57]. The concentration of SARS-CoV-2 was higher in non-ICU patients' rooms and HCW areas. Minimal concentrations were noted in ICU rooms with negative pressure and in well-ventilated public areas [57]. Even though viability of the virus isolated on aerosols was not tested in this study, the investigators provide a possible transmission pathway via aerosols in the hospital setting. Binder et al. performed environmental and aerosol sampling among 20 patients admitted with COVID-19 [58]. For each patient, eight aerosol samplers were placed around the bed of the patient and at 1 m of height. The samplers were ran for 4 hours in each patient and allowed the investigators to separate particles by size (>4 μm, 1–4 μm and <1 μm) [58]. Out of the 20 patients who participated in the study, only three patients had one positive aerosol sample. In two of those patients, the aerosol samples were <4 μm in size, whereas in the remaining one, the aerosol was bigger than 4 μm [58]. Even though the authors concluded that aerosolization is a rare event in patients with COVID-19, this study provides data about the sizes of those aerosols particles.

On the contrary, Lucar et al. described a case of 11 HCWs that were exposed to a single patient while undergoing surgery, including aerosol generating procedures (e.g., intubation) [59]. That patient later on tested positive for SARS-CoV-2 [59]. After 32 days of the event, none of the exposed HCW developed symptomatic SARS-CoV-2 infection [59]. In another study from the University of California Davis, investigators looked at the pattern of transmission from two nosocomial outbreaks originated from two different COVID-19 patients [60]. The two index cases were admitted to the hospital without initial suspicion for COVID-19 and were not placed on contact/ droplet precautions. A total of 421 HCW were exposed to the two index patients [60]. During their hospital stay, the index patients underwent aerosol-generating procedures such as noninvasive ventilation, bronchoscopy, and intubation. Investigators found a total of eight secondary infections among HCW [60]. All of those HCW had close contacts with the index cases and airborne transmission was not thought to be responsible for the secondary cases [60].

Furthermore, a group of investigators from an academic hospital in Wisconsin compared the degree of air contamination with SARS-CoV-2 between inpatient rooms and households occupied by COVID-19-positive individuals. The inpatient rooms selected had negative pressure relative to the hallways and were set to at least six air changes per hour, as per CDC recommendations [61, 62]. For this study, the investigators used an air sampler device close to the head of the patient and obtained samples between 1000 L and 4000 L of air [61]. This study found eight times higher positive

samples in households when compared to inpatient rooms. Another important finding is that inpatient rooms required higher volume of air sampling and close proximity of the sampler device to patients' bed to detect SARS-CoV-2. One of the main conclusions from the investigators is that the main determinant of air contamination by SARS-CoV-2 in the hospital is the degree of ventilation in each room (e.g., air changes per hour) [61, 62].

Even though the aforementioned studies do not show strong evidence of widespread airborne transmission, it raises the possibility that SARS-CoV2 could be considered at least an opportunistic airborne pathogen in the hospital setting when certain conditions are met.

Gram-Positive Organisms

Classically, gram-positive bacteria such as *Staphylococcus aureus* have been thought to be the dominant type of bacteria contaminating the indoor air of hospitals as described in several reports [63, 64].

Methicillin-Resistant *Staphylococcus aureus*

MRSA was first reported in 1962 in the British Medical Journal, which at that time was named "Celbenin"-resistant staphylococci [17, 65]. Currently, it is recognized as a major hospital-acquired pathogen in community hospitals, long-term care facilities, and tertiary care hospitals [66]. This pathogen has become endemic in hospitals worldwide, presenting a major concern in hospital hygiene [67], especially since studies have shown that *S. aureus* has the potential to survive for long periods and is resistant to desiccation [68]. It has been documented that the primary route of transmission is via the hands of healthcare workers and that colonized or infected patients are the primary reservoirs [68]. That being said, hand washing is widely recognized as the single most important factor for preventing subsequent colonization and infection [69]. Conversely, MRSA has been recovered from many sites, including floors, linen, medical equipment, and furniture; therefore, whether transmission via inanimate environments may also play an important role, however, remains uncertain [66].

The role of environmental contamination and transmission of MRSA has been studied for many years now. As early as in 1960, Colbeck described one human experiment, which was made with a woolen thread, dried for 10 days [70]. In this experiment, a superficial scratch was made on the skin and the woolen thread was rubbed on the linear scratch. After 3 days, there was definite abscess formation, as well as edema and axillary adenitis [70]. Although there is no evidence demonstrating the direct transmission through MRSA from the environment to patients, there is evidence that contamination of the environment with MRSA is sufficient to contaminate the gloves of HCWs, and thus, leading to transmission to patients [71].

More recently, Hardy et al. from the University of Birmingham in the United Kingdom conducted a study aimed to examine the presence of MRSA in the environment and its relationship to the patients' acquisition of MRSA [68]. This prospective study was conducted in a 9-bed ICU for 14 months, and at every environmental screening, samples were obtained from the four sites in each bed space, these being: underneath the bed, workstation, control buttons on the monitors, and a ledge positioned behind bed. Results demonstrated that MRSA was isolated from the environment at every environmental screening, when both small and large numbers of patients were colonized [68]. On only 20 (37.5%) of 56 occasions were the strains isolated from the patient and those isolated from their immediate environment indistinguishable [68]. However, there was a strong evidence to suggest that 3 of 26 patients who acquired MRSA while in the intensive care unit acquired MRSA from the environment [68]. These observations show the magnitude of the spread of the organism within hospital environment and provide evidence that there is another mechanism, such as air, involved in the spread of MRSA besides direct person-to-person contact.

Another study performed by Huang et al. examined the duration of survival of two strains of MRSA on three types of hospital fomites. Results demonstrated that MRSA survived for 11 days on plastic patient chart, more than 12 days on a laminated tabletop, and 9 days on a cloth curtain [72]. The fact that MRSA can survive in dry conditions at room temperatures for the periods demonstrated by this study suggests air and environmental contamination may be an important and overlooked reservoir of the MRSA through which non-colonized patients can acquire the organism.

Airborne transmission of MRSA is generally considered to occur at lower frequency than transmission via direct contact, but MRSA in the form of biological aerosols can contaminate air and cause airborne infection. In a study conducted in Japan by Shiomori et al., the number of airborne MRSA before, during, and after bed making was investigated with an Andersen air samples in the rooms of 13 inpatients with either MRSA infection or colonization [66]. MRSA-containing particles isolated were 2–3 μm in diameter before bed making and >5 μm during bed making. The number was significantly higher 15 minutes after bed making, suggesting that MRSA was recirculated in the air, especially after movement [66]. Another study conducted by Wilson et al. at the Nepean Hospital ICU in New South Wales studied air sampling at six locations three times weekly over a period of 32 weeks in a new, initially MRSA-free ICU to examine if this organism was found in air

samples, and whether its presence was affected by the number of MRSA-colonized patients present [73]. A significant correlation was found between the daily numbers of MRSA colonized or infected patients in the unit and the daily number of MRSA-positive air sample cultures obtained [73]. However, airborne transmission from patients colonized with MRSA warrants further investigation, not only in terms of improving infection control recommendations for patients, but also for the indication and use of personal protective devices by healthcare workers [17].

Vancomycin-Resistant *Enterococci*

The two most common human pathogens within the *Enterococcus* family are *E. faecalis* and *E. faecium*. They are well known to cause different infections including wound infections, urinary tract infections, and bacteremias, most commonly in the health-care setting [74, 75]. It is estimated that 30% of the enterococci infections caused by these organisms are due to vancomycin-resistant strains [74].

The role of environmental contamination with VRE has been studied and described in the literature as an important contributor to the spread of these organisms within hospitals [76]. The importance of air contamination and its implications from the infection control point of view has not been established and the evidence is scant or almost not existing. A study performed in a hospital in London looked into the spread of enterococci into the environment from patients who were either colonized or infected with these organisms [75]. They incorporated air sampling as part of the investigation, using a MAS Eco air sampler for 10-minute periods [75]. Air and environmental samples were taken twice per week for a total length of 17 weeks and were obtained from a combined medical and surgical ward that consisted of single occupancy rooms and also common bays with four beds each. Air samples were positive during this surveillance, and more than 80% of the positive air samples belonged to a single unrecognized carrier that was taking laxatives during the surveillance period when increased rates of air contamination were observed. Molecular typing was performed by PFGE and confirmed clonality between the patient and air isolates [75].

It is thought that aerosolization of enterococci poses little direct risk for patients, but contributes greatly to environmental contamination, which has been shown to increase the risk of inpatients to acquire these pathogens.

Clostridiodes difficile

Clostridiodes difficile is a spore-forming gram-positive bacterium. In recent years, the emergence of an epidemic strain of *C. difficile* known as North American pulsed-field gel electrophoresis type NAP1 – polymerase-chain-reaction type 027 – has been associated with large outbreaks mainly in the USA, Canada, and Europe [77, 78]. As mentioned before, given its ability to form spores, *C. difficile* can survive for several months or even years in hospital surfaces when shedded in the stools, not only from infected patients but also asymptomatic carriers [79–81]. It has been reported that up 15% of patients who are asymptomatic could be carriers of toxigenic strains of *C. difficile*, fact that poses an enormous challenge from the infection control point of view in order to control outbreaks due to this organism [81].

The role of environmental contamination in the spread of spores contributing to outbreaks has been studied [79]. The possibility of aerosolization of *C. difficile* spores has been studied in the past decades with no apparent success. In 1981, a study conducted by Fekety and colleagues looked into possible air contamination with spores of this organism [80]. Air samples were obtained with a slit impactor, but the sampling time was not reported. In this study, all of the air samples were negative for *C difficile* [80]. One strong reason to believe why air could contribute to the spread of this organism is the extensive contamination of surfaces seen not only inside the rooms of infected patients, but also in other common areas in the hospital [77, 78].

It has not been until recent years that the possible implication of the aerial route in the spread of *C. difficile* was demonstrated [79]. The first report of aerosolization of *C. difficile* into the environment is from 2008 when Roberts and colleagues used a portable cyclone air sampler in a geriatric ward housing patients with confirmed *C. difficile* infection (CDI) [82]. The air sampler was used for 15-minutes periods at 30 minutes intervals for two consecutive days. Air was blown into an enriched liquid media specially designed by the investigators to isolate the organism of interest [82]. In this surveillance, 23 out of 32 air samples were positive with the bacterium and molecular typing showed isolates were indistinguishable from each other [82].

Best et al. looked into concomitant contamination of air and environmental surfaces with *C. difficile* [22]. Here, air samples were obtained using an AirTrace Environmental sampler that rotates the plate constantly over 360 degrees allowing to determine the exact time in which air contamination happened during the surveillance period [22]. The air sampling was separated into three different periods [22]. The first one was performed for 1-hour sampling time, which yielded only 12% of positive air samples. The second one was performed in patients with suspected CDI but not yet confirmed diagnosis, for 10-hour period each time. One air sample was positive in a patient prior to confirming the diagnosis of *C. difficile*, which could suggest that the shedding of the spores happens in patients before being placed on contact precautions [22]. The final air sampling period was performed

also for 10-hours, but this phase was done in patients with confirmed *C. difficile* colitis. Among the latter, air samples were positive in seven out of the ten patients studied. Molecular typing was performed showing that the air, environmental, and clinical isolates were related to each other [22]. Increased rates of air contamination were associated with activities happening inside the rooms such as bed changing or medical rounds [22].

Subsequently, the same investigators evaluated the influence of toilets after flushing in the degree of air contamination with *C. difficile* [83]. For this experiment, both settle plates and an AirTrace Environmental sampler were used. Experiments were performed using preparation with fecal suspension from patients with confirmed CDI [83]. Spores were found in the air after flushing the toilets and remained in the air for up to 90 minutes. Positive settle plates were obtained when toilets were flushed only with the lid open, but no air contamination was found on settle plates when the lids were closed [83].

Gram-Negative Organisms

Acinetobacter baumannii

Carbapenem-resistant *A. baumannii* has become an important nosocomial pathogen in recent years, given the limited therapeutic options available to treat this organism [74, 84]. In 2013, the Center for Disease Control and Prevention estimated that multidrug-resistant *A. baumannii* causes more than 7000 infections and leads to more than 500 deaths per year solely in the USA [74]. These numbers have increased in the following years. Certainly, this pathogen has become endemic in several hospitals around the globe [85–88]. An important characteristic of *A. baumannii* is its ability to survive desiccation for prolonged periods of time, making the hospital environment a major reservoir for this organism [74, 87, 89, 90]. For this reason, air has been postulated to be a possible vector contributing to environmental contamination.

There have been several reports in the literature describing outbreak investigations due to *Acinetobacter* species in which air samples were obtained. The first one is from 1987, when Gerner-Smidt and colleagues found positive air samples with *A. calcoaceticus* serovar *anitratus* during a 2-year outbreak in a Danish ICU [89]. Here, air samples were obtained using a slit sampler and settle plates that were left open for 3–6 hours periods [89]. In the same year, an outbreak investigation caused by *A. anitratus* in two hospitals in the UK reported positive *Acinetobacter* samples from air [90]. Air sampling was performed using settle plates placed 3 m from the patients, obtaining 16 positive samples with *Acinetobacter spp.* from a total of 82 settle plates used [90]. The time for which plates were left open was not reported [90]. A study from 1989 conducted in the Netherlands found *Acinetobacter* in the air using slit samplers in 12 out of 104 (11%) samples, but these isolates did not match with the epidemic strain when molecular testing was performed [91]. A report from a hospital in Turkey from 2006 described an epidemiological investigation of all *A. baumannii* isolates found at that institution [88]. Molecular testing was performed and it was found that there were various genotypes that were endemic during the surveillance period. Some of the isolates analyzed were obtained from the air using an air impactor [88]. One study from Argentina published in 2008 aimed to evaluate the prevalence of multidrug-resistant *A. baumannii* [92]. Air samples were obtained as part of their surveillance project using three different methods that included settle plates, air impactor, and a liquid impinge [92]. In this study, *A. baumannii* was found only in 4 samples out of 54 total air samples, all of them were obtained by the air impactor [92].

More recently, a group from the University of Miami looked into aerosolization of carbapenem-resistant *A. baumannii* in a single ICU in a teaching hospital in Florida where this organism is endemic and where patient-to-patient transmission was observed [93]. Air samples were obtained in three different days in rooms occupied by *A. baumannii*-positive patients. Air was sampled using open blood agar plates left open for 24 hours. It was found that 23% of air samples were positive with *A. baumannii* [93]. PFGE was performed to the clinical and air isolates, proving clonality [93]. Later on, the same group evaluated presence of *A. baumannii* in consecutive days among inpatients colonized with this organism in either rectum or respiratory tract [37]. Samples were collected daily for up to 10 days using settle plates. Air samples were positive for *A. baumannii* in 21% of the instances [37]. Interestingly on this study, patients with rectal colonization contaminated more their ambient air compared to patients colonized in the respiratory tract (26% versus 11% respectively; $p = 0.01$). Rep-PCR demonstrated clonality of the isolates [37]. In another study from the same institution, air and environmental samples were obtained concomitantly among inpatients admitted in adult ICUs [38]. This study confirmed the prior results, showing higher degree of air contamination in patients with rectal colonization with *A. baumannii* compared to patients with respiratory colonization (38% versus 13% respectively; $p = 0.0001$). In this study, it was also evaluated if the type of ICU (single occupancy rooms versus open layout ICU) where patients were admitted to played a role in the results. There was no difference between the two types of ICU with regard to degree of air contamination, but there was a higher degree of clonality by PFGE between air and patient's isolates in the single occupancy ICUs [38].

Contradictory data exist with regard to the presence of *A. baumannii* in the air. In a study published by a group from

the University of Maryland, only 1 out of 12 air samples belonging to rooms occupied by *A. baumannii*-positive patients were positive for this organism [94]. This study used an air impactor as the sampling method, for a testing period of 1 hour [94]. Another study from Thailand also evaluated the presence of air contamination in ICUs housing close-circuit mechanical-ventilated *A. baumannii*-positive patients. Their air sampling technique consisted of placing two settle plates next to each patient twice per week. None of the air samples were positive for *A. baumannii* [95]. Mousa et al. performed air sampling around ten ventilated patients with positive carbapenem-resistant *A. baumannii* respiratory cultures, using a sieve impactor [96]. The investigators sampled 252,000 L of air, from which 39,600 L (16%) were positive for *A. baumannii* [96]. The positive air samples occurred intermittently, especially after periods of patient care such as endotracheal tube suctioning, changing bedsheets, or diapers [96]. These new findings would suggest that aerosol spread may depend on local variables such as air changes per hour, humidity, temperature, and patient layout.

Pseudomonas aeruginosa

P. aeruginosa is a common pathogen associated with hospital-acquired infections including pneumonias, bloodstream infections, urinary tract infections, and surgical site infections, among others [74]. Nearly 8% of all healthcare-associated infections are caused by *P. aeruginosa*, and 13% of these infections are caused by multidrug-resistant strains leading to increased morbidity and mortality among inpatients [74].

Patients with cystic fibrosis (CF) comprise a special population since they tend to have chronic and recurrent respiratory infections with multiple organisms, most commonly due to *P. aeruginosa* [97–99]. These patients are exposed frequently to multiple classes of antibiotics, being more prone to acquired resistant strains [97–99]. Once patients with CF acquired this organism, it is almost impossible to eradicate it from their airways, making them of special interest from the infection control point of view [98, 99]. Given this phenomenon, they can contribute to aerosolization of such organisms into the environment [97]. It has been described that *Pseudomonas* can survive desiccation for up to 5 days when released in sputum, making this an important characteristic that could contribute to contamination of the environment and potentially leading to horizontal transmission among inpatients [97].

The presence of *P. aeruginosa* in the air has been described in the literature. The main body of evidence is based on studies among patients with CF. In 1983, a study performed in Denmark in a CF clinic aimed to determine the prevalence of environmental contamination with this organism [97]. Here, environmental and air samples were taken as part of the investigation from both the CF clinic and from other areas of the hospital that served as the control group. Air was cultured using both settle plates and a centrifugal air sampler. Settle plates were left open for 2-hour period. The air samples obtained from the clinic were all positive for *P. aeruginosa*, compared to none in the control group [97]. Another study from 2005 in a CF center in the UK also evaluated the presence of an endemic strain of *P. aeruginosa* in the air as part of a surveillance study [100]. Air samples were collected using a slit sampler for 15 minutes sampling time. The endemic strain was detected in 80% of the air samples taken from inside the patient's rooms and in 60% from samples taken in the corridors of the ward [100]. Interestingly, the presence of the organism was not detected after terminal cleaning, highlighting the importance of cleaning in the prevention of environmental contamination [100].

The use of air humidifiers for respiratory therapy among inpatients has also been shown to produce high degree of air contamination with *P. aeruginosa* [101]. In a study from 1970 performed by Grieble et al., it has been shown that the presence of this organism in the air correlated with the use of these instruments [101]. Air sampling was performed by using settle plates that were placed randomly inside the rooms. The degree of air contamination decreased after thorough disinfection with phenolic acid, but it did not halted the presence of *Pseudomonas* in the air in the following days [101].

Klebsiella-Producing Carbapenemases (KPC)-Producing Gram-Negative Rods

KPCs are plasmid-mediated enzymes belonging to the Ambler class A of beta-lactamases [102, 103]. They were first described in a *Klebsiella pneumoniae* isolate in 1996 [104]. In recent years, it has spread to many other gram-negative bacteria, thus making them of special concern from the infection control point of view due to high morbidity and mortality associated with these pathogens when infection develops given the limited therapeutic options available [102, 105–108].

Certainly, KPC-producing organisms have become endemic in multiple hospitals around the world [102]. The implementation of bundles to decrease the incidence of infections due to these organisms has served as a proof that hospital environment serves as a reservoir for them [109]. It has also been proposed that air contamination leading to later environmental contamination is involved in the horizontal transmission of these organisms.

There is scant data regarding air contamination with KPC organisms. Munoz-Price at al. evaluated concomitant air and surfaces' contamination in patients who were either

colonized or infected with KPC-producing organisms [110]. Most of the isolates studied in this project were *K. pneumoniae* as the organism harboring this enzyme, but also *E. coli*, *Enterobacter aerogenes,* and *Citrobacter freundii* were present [110]. Patients were either colonized in the rectum or respiratory tract or had positive clinical cultures. Air was sampled using settle plates located close to the head of the bed of the patients [110]. KPC organisms were detected in the air, but there was no difference in the degree of air contamination between the three groups [110].

Conclusions

The role of air in the spread of healthcare-associated organisms has been reviewed here with different degrees of evidence. There are several indications for air sampling in the hospital setting such as epidemiological investigations of nosocomial infections and outbreaks. Air sampling should also be considered as a quality control measure to ensure proper functioning of medical equipment, monitor hazardous procedures or during remodeling/ construction of healthcare facilities, or just for research purposes to better understand transmission dynamics of clinically relevant pathogens.

Air sampling is not routinely done in the hospital setting, and the results obtained will depend mainly on the indication for performing such task, the resources available in each hospital, the circumstances in which it will be performed, and the intrinsic characteristics of the pathogen being studied. Less importance should be given to the method used, whether it is a passive or an active method, since there is no clear evidence demonstrating which method is superior among others, and results obtained can be similar with either of them, especially if the points mentioned above are taken into consideration.

With recent development of outbreaks of novel coronaviruses, including the COVID-19 pandemic, the concept of large droplets as the main mode of transmission of respiratory viruses has been challenged. A new classification has been proposed based on the infectious agent's capacity to be transmitted and cause disease via aerosols, including obligate, preferential, and opportunistic. Based on the current evidence, SARS-CoV-2 could be classified as an opportunistic pathogen for airborne transmission in the hospital setting.

There is no doubt that contamination of the hospital environment with nosocomial pathogens is a crucial step for the development of horizontal transmission with such organisms among inpatients. In instances where the degree of contamination is much greater than expected, it might be logical to think of air as a possible vehicle of transmission as demonstrated by the evidence displayed in this chapter.

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Vertical Versus Horizontal Infection Control Interventions

18

Salma Muhammad Abbas and Michael P. Stevens

Vertical Versus Horizontal Infection Control Interventions

Healthcare-associated infections (HAIs) are often preventable diseases that are not only a major concern for patient safety but also represent a major economic burden on a nation's healthcare system [1, 2]. These include, but are not limited to, surgical site infections (SSIs), central line-associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and infections (BSIs) caused by multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Candida auris* [3, 4]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently emerged as a pathogen of epidemiologic importance, causing a pandemic and overwhelming healthcare facilities worldwide [5]. Reducing the spread of infection is the key goal of infection prevention programs and numerous strategies such as hand hygiene, contact precautions, and chlorhexidine bathing have been implemented to achieve this. Some of these targeting specific microorganisms are called "vertical" strategies, while others aim to reduce infections caused by multiple pathogens simultaneously and are known as "horizontal" strategies (Fig. 18.1) [6].

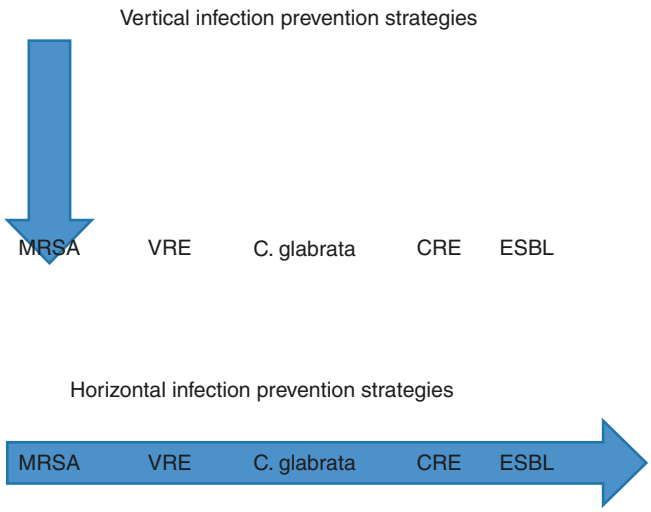

Fig. 18.1 Vertical vs. horizontal infection prevention strategies. Edmond and Wenzel [6]

Compare and Contrast Vertical and Horizontal Strategies

Patients are at risk for exposure to organisms such as MRSA, VRE, and CRE during hospital admissions and can become colonized with them. They may go on to develop infections with these organisms or transmit them to other patients. A vertical strategy targets patients colonized or infected with a specific microorganism and aims to decrease the number of infections caused by this single pathogen. On the contrary, the horizontal approach is a more holistic strategy adopted to reduce infections caused by all microorganisms sharing a common means of transmission. As a result, the horizontal approach is generally a utilitarian strategy, while the vertical strategy supports exceptionalism by prioritizing the eradication of specific pathogens [6]. Resource utilization for vertical strategies typically surpasses horizontal strategies. Horizontal strategies are more patient-centric strategies, in so much that patients benefit from prevention of all infections simultaneously, not just those caused by specific micro-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_18

Table 18.1 Vertical vs. horizontal infection control strategies [5]

	Horizontal	Vertical
Focus	Population-based	Pathogen-based
Population	Universal	Selective or universal
Resource costs	Relatively low	Usually high
Philosophy	Utilitarian	Exceptionalism
Values favored	Patient	Hospital, infection prevention experts
Temporal focus	Present, future	Present

organisms. In addition, vertical strategies are short term as efforts are made to prevent the spread of infections caused by a specific pathogen at a given point in time, while horizontal strategies, by virtue of their larger scale, are not only relevant to a hospital's current situation but may play a greater role in the long-term prevention of infections as well. Finally, both types differ in the types of infection–prevention approaches used: examples of vertical programs include active surveillance for MRSA and vaccination against specific pathogens, whereas horizontal strategies encompass implementation of measures such as hand hygiene, bathing patients with antiseptics such a chlorhexidine gluconate (CHG), antimicrobial stewardship, and environmental disinfection to name a few [6]. Both strategies have been used to prevent infections and many studies have been conducted to determine their effectiveness (Table 18.1).

Evidence for Vertical Infection Control Strategies

Vertical strategies are mostly based on the results of active surveillance and testing (AST), a strategy aimed at reducing colonization of various anatomic sites by pathogens and thereby reducing infection and transmission of these by identifying carriers. This approach has been most widely implemented for the eradication of MRSA, VRE, and CRE and numerous studies have been conducted to elucidate the effects of AST with or without additional decolonization measures [7, 8].

Methicillin-Resistant *Staphylococcus aureus*

The overall incidence of MRSA infections has increased significantly since its emergence in the 1960s. Additionally, due to the virulence of community-acquired MRSA strains and their growing contribution to HAIs, MRSA identification and eradication has been identified as an important infection control strategy [9]. Intensive care units (ICUs) are considered high-risk settings for the transmission of MDROs such as MRSA and multiple studies have been conducted to determine the impact of infection prevention strategies on the incidence of HAIs in these units. Huskins and colleagues conducted a cluster-randomized trial in adult ICUs to evaluate the effect of active surveillance and isolation for MRSA and VRE compared with standard practice. During a 6-month study period, 5434 admissions to 10 ICUs were assigned to the intervention arm and 3705 admissions to 8 ICUs were assigned to the control arm. The results of this study did not demonstrate any benefit of AST and isolation for infection prevention as the difference in the mean incidence of MRSA and VRE colonization and infection-related events per 1000 patient days between the two groups was not statistically significant (40.4 ± 3.3 and 35.6 ± 3.7 in the intervention and control groups, respectively; $p = 0.35$) [10]. Similarly, a comparative effectiveness review performed by Glick and colleagues found insufficient evidence for the use of targeted MRSA screening as a sole infection prevention strategy [11]. Zafar and colleagues conducted a prospective observational study to assess the prevalence of nasal colonization among patients with community-associated MRSA infection admitted to a 600-bed urban academic center between 2004 and 2006. A total of 51 patients underwent nasal swab cultures and only 41% were found to have nasal colonization with MRSA. The results of this study demonstrated that MRSA infections may occur in a high percentage of patients without nasal MRSA carriage which argues against the utility of vertical infection prevention strategies given their narrow focus [12]. Moreover, MRSA screening does not have an impact on other organisms such as VRE and CRE (as opposed to many horizontal infection control strategies that impact multiple organisms simultaneously) [9].

Given the widespread use of mupirocin for MRSA decolonization, emerging resistance is an area of major concern. Mupirocin is a protein synthesis inhibitor which acts by inhibiting bacterial isoleucyl-tRNA synthetase. *S. aureus* strains may harbor alterations in the isoleucyl-tRNA synthetase *ileS* gene which confers low-level resistance (MIC = 8–256 μg/ml) or *mupA* gene which is associated with high-level resistance (MIC ≥ 512 μg/ml) [13]. Fritz and colleagues conducted a study to determine the prevalence of high-level mupirocin resistance among 1089 pediatric patients admitted with skin and soft tissue infections. Cultures were obtained from axillae, anterior nares, and inguinal folds and 483 patients were found to be colonized with *S. aureus.* Of these, 23 isolates (2.1%) carried the *mupA* gene. A total of 408 patients, including four patients colonized with *S. aureus* harboring a *mupA* gene, underwent nasal decolonization with twice daily application of mupirocin for 5 days (with or without antimicrobial baths) and 258 underwent daily CHG bathing for 5 days. Patients were followed with colonization cultures for up to 12 months. Among the patients carrying mupirocin-resistant *S. aureus*, 100%

remained colonized at 1 month compared to 44% of the patients who were carriers of mupirocin-sensitive *S. aureus* ($p = 0.041$) [13].

Carbapenem-Resistant *Enterobacteriaceae and Acinetobacter baumannii*

Carbapenems are an important antimicrobial class given their activity against gram-negative organisms with Amp-C-mediated β(beta) –lactamases or extended-spectrum β(beta)–lactamases (ESBLs) [14]. Selection of carbapenem-tolerant *Enterobacteriaceae* was uncommon in the United States in the 1990s, prior to the recognition of novel β(beta)–lactamases with carbapenem-hydrolyzing activity. *Klebsiella pneumoniae* carbapenemase (KPC) is the most commonly identified carbapenemase in the United States. Others such as the Metallo-β(beta)-lactamases are more common in other parts of the world. The Centers for Disease Control and Prevention (CDC) currently recommend point-prevalence surveys to identify CRE carriers in units where infections caused by these organisms have been identified over the past 6–12 months. The recommendations to prevent their transmission include implementation of hand hygiene, contact precautions, and testing contacts of CRE patients. Infection prevention personnel should be promptly notified regarding the detection of CRE and additional measures such as skin decolonization may be employed if felt necessary [15].

CRE are a major challenge given the frequency of infections caused by these organisms as well as the associated mortality which may be as high as 50% among ICU patients [16]. Patel and colleagues conducted two matched case-control studies to determine the epidemiology of CRE infections and determine risk factors and clinical outcomes associated with infections secondary to carbapenem-resistant isolates among 99 patients when compared with a similar number of patients with infections caused by carbapenem-susceptible organisms. It was concluded that infections caused by KPC producers were associated with a longer duration of mechanical ventilation ($p = 0.04$), exposure to antimicrobials (cephalosporins, $p = 0.02$; carbapenems, $p < 0.001$), and higher mortality due to infection (38% vs 12%, $p < 0.001$) [16]. Measures such as chlorhexidine gluconate (CHG) bathing for skin antisepsis have also been studied in addition to standard precautions to prevent the spread of resistant gram-negative organisms. Chung and colleagues carried out an interrupted time series study to determine the effect of daily CHG bathing on carbapenem-resistant *Acinetobacter baumannii* acquisition in a medical ICU. A 12-month CHG bathing period was compared with a 14-month control period. A reduction of 51.8% was observed in CRAB acquisition rates following the introduction of CHG bathing (44.0 vs 21.2 cases/1000 at risk patient days, $p < 0.001$) [17].

In addition to the inpatient setting, CRE infections are an emerging threat in long-term acute-care hospitals (LTACHs) where patients are at high risk for acquisition and transmission of these organisms. Moreover, the residents of these facilities can also introduce CRE into hospitals during admissions. In a study conducted in four LTACHs, a stepped-wedge design was used to assess the effect of a bundled intervention (screening patients for KPC rectal colonization, contact isolation, daily CHG bathing for all patients and healthcare worker education, and compliance monitoring). A total of 3894 patients from the preintervention period were compared to 2951 patients admitted after the introduction of the intervention bundle. With this strategy, the incidence rate of KPC colonization demonstrated a significant decline in the intervention arm (4 vs 2 acquisitions per 100 patient-weeks; $p = 0.004$) [18].

Vancomycin-Resistant *Enterococcus*

VRE have been recognized as a cause of HAIs since the 1980s and are implicated in about 20,000 infections in the United States annually [19]. Guidelines for VRE prevention have been in place for over two decades. Recommendations include surveillance testing, contact precautions, hand hygiene, and limiting the use of vancomycin, without a consensus on the best approach [15]. A recent meta-analysis identified hand hygiene as a more effective strategy to prevent VRE infections when compared to contact precautions [20]. Of note, the small number of studies focusing primarily on VRE precluded meta-analysis for surveillance screening and environment decontamination.

Candida auris

C. auris is an emerging fungal pathogen. It is often resistant to multiple antifungal agents and is difficult to identify using standard laboratory methods. It can cause outbreaks in healthcare facilities. *C. auris* has been isolated from various body sites such as ear canals, wounds, the biliary tract, the respiratory tract, and urine. Bloodstream infections have constituted about 50% of the infections reported in the United States [21]. Asymptomatic patients may harbor *C. auris* on skin, nares, oropharynx, rectum, or other body sites. Healthcare facilities may consider AST to screen contacts of patients with *C. auris* infection or colonization and those with an overnight stay in a healthcare facility outside the United States over the past year if cases of *C. auris* had been reported in that country. Healthcare facilities with evidence or suspicion of ongoing transmission may perform point-

prevalence surveys to estimate the burden of colonization and institute necessary measures including isolation and institution of contact precautions [22]. Guidelines for the optimal control and prevention of *C. auris* infections and asymptomatic carriage are currently evolving.

Severe Acute Respiratory Syndrome Coronavirus 2

Severe acute respiratory syndrome virus coronavirus 2 is a beta coronavirus, first identified in December 2019. The infection has been named coronavirus disease 2019 (COVID-19). The disease spectrum ranges from asymptomatic infection to severe pneumonia and acute respiratory distress syndrome (ARDS). The case fatality associated with COVID-19 is determined by factors such as age, sex, comorbid health conditions, race, and ethnicity, and values ranging from 0.1% to 25% have been reported in the literature [23]. This highly communicable disease evolved into a pandemic and overwhelmed the global healthcare infrastructure.

The recommendations to prevent transmission include implementation of hand hygiene, environmental cleaning, contact precautions using impermeable gowns and gloves, eye protection and droplet precautions for patients with mild infection and low supplemental oxygen requirements, and those not undergoing aerosol-generating procedures (AGPs such as intubation, noninvasive ventilation, bag ventilation, bronchoscopy, nasopharyngeal sampling, etc.). Airborne precautions are recommended for patients undergoing AGPs. Additional transmission mitigation strategies include tracing and testing contacts of patients with COVID-19, quarantining individuals with high-risk exposures to patients with COVID-19, universal masking, optimization of engineering controls, maintaining physical distancing of six feet between individuals, limiting visitors, and minimizing physical interaction with patients by introducing telemedicine. Healthcare facilities may consider pre-procedure and/or pre-admission COVID-19 testing to identify individuals with COVID-19 and take necessary steps to minimize the transmission of infection [24]. Infection prevention personnel should be promptly notified regarding the detection of SARS-CoV-2 PCR-positive patients and employees to ensure that necessary additional measures such as isolation and contact tracing may be deployed expeditiously.

Early in 2020, COVID-19 overwhelmed healthcare supply infrastructure globally and resulted in constrained resources and shortages of personal protective equipment (PPE), specifically N-95 masks. N-95 masks are designed for single use. However, many healthcare facilities adopted N-95 reuse or extended use guidelines and/or prioritized the use of N-95s for AGPs during periods of shortage. Limited reuse refers to using the same N-95 masks for multiple patient encounters, but removing the mask following each encounter to be stored or decontaminated. Ultraviolet germicidal irradiation, vaporous hydrogen peroxide, and moist heat are strategies that have been deployed for N-95 mask decontamination. Extended use means wearing an N-95 mask for multiple patient encounters without doffing the mask between patients. N-95 masks must be checked for a tight seal around the face and mouth upon each use. Masks with poor fit, damage, and visible soiling or contamination must be discarded [25].

Evidence for Horizontal Infection Control Strategies

This approach encompasses the implementation of measures such as hand hygiene, universal decolonization, universal masking, selective digestive tract decolonization (SDD), antimicrobial stewardship, and environmental decontamination to prevent infections and emergence of MDROs regardless of the colonization status of patients [7].

Hand Hygiene

Hand hygiene has been the cornerstone of infection prevention for over a century and is often considered the most important infection prevention strategy [26]. Transmission of healthcare-associated organisms through contamination of healthcare workers' (HCWs) hands has been well-studied and established as an area of major focus. To be transmissible, the organisms must be present on a patient's skin or have contaminated the environment, come in contact with and be transferred to hands of HCWs, and survive on their skin for several minutes, with failure to be eradicated due to inadequate hand hygiene and be spread to another patient as a result of direct skin contact. The adherence of HCWs to hand hygiene varies across centers and ranges from 5% to 89% [27]. Hand hygiene is effective at preventing spread of organisms such as MRSA, VRE, and resistant gram-negative organisms. The CDC currently recommends the following five moments for hand hygiene: before patient contact, before performing aseptic procedures, following exposure to body fluids, after contact with patients, and following contact with their surroundings [28]. Strict compliance with hand hygiene may reduce the rates of HAIs by up to 40% [29].

Universal Decolonization

While conventional methods, such as hand hygiene, have been in place for a long time, there has been a recent surge in the use of CHG for universal decolonization with its use

being more widespread in ICUs. Multiple studies have been conducted to examine the effect of CHG bathing on the acquisition of MDROs and the incidence of HAIs. Several studies evaluating CHG bathing were published in 2013. Climo and colleagues carried out a multicenter cluster-randomized, nonblinded crossover trial to evaluate the effect of daily CHG bathing for 6 months compared to bathing with nonantimicrobial washcloths in nine intensive care units and bone marrow transplant units. A total of 7727 patients were included in the study. The results showed a significant reduction in overall bloodstream infections (4.78 cases per 1000 patient-days with CHG bathing vs 6.60 cases per 1000 patient-days with nonantimicrobial cloth; $p = 0.007$) as well as the acquisition of MDROs (5.10 cases per 1000 patient-days with CHG bathing vs 6.60 cases per 1000 patient-days with nonantimicrobial washcloths; $p = 0.03$) [30]. Huang and colleagues conducted a pragmatic cluster-randomized trial among 74,256 ICU patients randomized to three different strategies: screening and isolation for MRSA; targeted MRSA decolonization; and universal decolonization. The hazard ratios for bloodstream infection with any pathogen were 0.99, 0.78, and 0.56 among the three groups, respectively ($p < 0.001$), demonstrating a significant reduction in the universal decolonization group [31]. Similarly, a cluster-randomized crossover trial including 4947 pediatric ICU admissions investigated the impact of daily bathing either with CHG or standard practice on infection acquisition during two 6-month study periods. Per-protocol analysis demonstrated a lower incidence of bacteremia among the CHG bathing group when compared with standard practice (3.28 per 1000 days vs 4.93 per 1000 days; $p = 0.044$) [32]. While the results of these studies were promising, a recent pragmatic cluster-randomized crossover trial did not support daily CHG bathing. A total of 9340 patients admitted to five adult ICUs were included in the study and bathed daily with either CHG or nonantimicrobial cloths for 10 weeks, with a 2-week washout period prior to switching to the alternate bathing treatment for 10 weeks. Intervention with CHG bathing did not lead to a significant reduction in the incidence of HAIs [33]. It is important to note that the overall low rates of HAIs and single-center design of this study may have impacted its results.

With the heightened interest in the use of CHG as a disinfectant in the healthcare setting, emerging resistance has been a concern. CHG resistance is attributed to *qacA/B* genes among MRSA and *qacE* genes among *Klebsiella* species which encode multidrug efflux systems [34, 35]. CHG susceptibility testing is not routinely performed and no breakpoints have been established by the Clinical and Laboratory Standards Institute (CLSI) [35]. In the pediatric study conducted by Fritz and colleagues mentioned above, 10/10891 (0.9%) patients harbored CHG-resistant *S. aureus* at baseline and two of these underwent daily CHG bathing for 5 days. At 1 month, there was no difference in colonization status among these patients when compared to patients carrying no CHG-resistant microorganisms ($p = 1.0$) [13]. The lack of an appreciable association may, however, be attributed to the low overall prevalence of CHG resistance in the study. Continued vigilance for emerging CHG resistance seems warranted.

Universal Masking

Universal masking refers to implementation of mask-wearing for all individuals. The rationale for doing so is that masks contain respiratory secretions and prevent transmission of infectious respiratory particles to others and act as a physical barrier to secretions from those who may not be wearing masks. This strategy was widely implemented in healthcare facilities to curb the spread of COVID-19. In a study by Tong et al., universal masking resulted in a decline in the incidence of respiratory viral infections in a neonatal step-down unit for very low birth weight infants from 1.1 to 0.3 per 1000 patient-days ($p = 0.008$) [36]. However, universal masking is not a panacea and must be combined with other strategies such as hand hygiene, environmental cleaning, and be used with other PPE including gowns, gloves, and eye protection where indicated.

Selective Digestive Tract Decolonization

SDD is a prophylactic measure to reduce infections caused by *Candida*, *Staphylococcus aureus,* and gram-negative organisms among patients with gastrointestinal carriage of these organisms. Protocols vary across centers, and can include the following: a short course of parenteral antibiotics such as a third- or fourth-generation cephalosporin, nonabsorbable enteral agents (e.g., polymixin E, amphotericin B, and vancomycin), and oral and rectal surveillance cultures on admission and at 2 week intervals thereafter to monitor the effectiveness of SDD. Although multiple trials have demonstrated its effectiveness in reducing pneumonias and bloodstream infections among critically ill patients, its use remains controversial due to concerns such as the selection of resistant organisms [37]. Reig and colleagues conducted a retrospective observational study to evaluate the efficacy of intestinal decolonization among 45 patients with a history of at least two ESBL *E. coli* infections and persistent intestinal carriage (determined by positive rectal and/or stool cultures). Patients were treated with either low- or high-dose oral colistin or oral rifaximin for 4 weeks. ESBL *E. coli* eradication occurred in 19/45 (42%) patients. The use of single-drug oral regimens for intestinal decolonization is not well-established and additional studies are required to further explore this [38].

Antimicrobial Stewardship

Antimicrobial Stewardship Programs (ASPs) are considered crucial for combatting the emergence of antimicrobial resistance and can be linked with infection prevention programs. According to the CDC, 20–50% of all antibiotics used in the United States are unnecessary. Antibiotic use is associated with drug reactions, *Clostridioides difficile* infections as well as antibiotic resistance [39]. A bundle approach consisting of staff education, early identification, expanded infection control measures including hand hygiene, and judicious use of antibiotics was introduced at a tertiary care center in the United States to manage high *C. difficile* infection rates (7.2 per 1000 hospital discharges). The rate of *C. difficile* infections fell to 3.0 per 1000 hospital discharges within 6 years (71% reduction, $p < 0.001$) [40].

Environmental Cleaning

Contaminated surfaces such as bedrails, bed surfaces, nurse call buttons, television remotes, and medical equipment have been identified as reservoirs for organisms such as MRSA, VRE, *C difficile*, *Acinetobacter* species, *Pseudomonas aeruginosa*, SARS-CoV-2, and norovirus. Persistence of these organisms in the environment and ineffective environmental cleaning strategies result in transmission of these organisms to other patients [41]. The current CDC recommendations for effective environmental decontamination include assignment of dedicated staff members to clean different units, thorough decontamination of surfaces such as bedrails, charts, and doorknobs along with frequent monitoring of units to assess for adherence to outlined protocols [15].

Financial Considerations

According to a decision tree analysis to compare costs of various MRSA surveillance strategies, universal MRSA screening was deemed more cost-intensive compared to targeted surveillance, but interestingly, the latter was more cost-effective than no screening [42]. However, when MRSA surveillance strategies with and without decolonization were compared to other approaches such as universal contact precautions and universal decolonization in a recent cost-effectiveness model using a hypothetical cohort of 10,000 adult ICU patients, universal decolonization was deemed the most cost-effective infection prevention strategy for MRSA colonization prevalence of up to 12%; as this drops from 12% to 5%, AST with selective decolonization may be the more optimal approach, emphasizing the consideration of local factors prior to making decisions regarding the best infection prevention strategy [43]. According to an estimate focusing mainly on infection prevention in the ICU setting and surgical units, interventions such as hand hygiene, contact isolation in the setting of known MDRO infections or colonization, and environmental cleaning led to a net global saving of US $13,179 per month between 2009 to 2014 by reducing HAIs such as central line-associated bloodstream infections, ventilator-associated pneumonias, and surgical site infections [44].

Conclusion

MDROs are a major healthcare concern and along with HAIs have become a major infection prevention focus. Vertical and horizontal infection control strategies have been used to combat HAIs. These strategies include measures such as active surveillance testing, hand hygiene programs, universal masking, universal skin decolonization with antiseptics such as CHG, and antimicrobial stewardship. Many studies have shown beneficial results with lower rates of HAIs resulting from both vertical and horizontal strategies. However, there is still controversy over which strategies are most optimal in different settings. In terms of HAI prevention, generally horizontal strategies are more likely to have a broader impact and are more cost-effective. While a horizontal approach seems optimal for many situations, adverse effects of horizontal strategies must also be considered. For instance, a theoretical concern is the development of CHG resistance with the wide deployment of CHG bathing. Although vertical strategies have a role in the management of outbreaks of specific pathogens, in general horizontal strategies have a greater impact at a lower cost.

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The Role of the Hospital Epidemiologist

19

Kristina A. Bryant

Background

Ignaz Semmelweis has been described as the original hospital epidemiologist, and his work is not dissimilar to that of modern practitioners [1]. In the mid-nineteenth century, he identified an outbreak of puerperal fever and conducted a stepwise investigation that implicated a lack of hand washing between autopsy and the operating room as the likely cause. He designed and implemented a hand hygiene intervention, and measured the effect on infection rates. Despite objective evidence, his colleagues dismissed the importance of his work [2]. Semmelweis left the practice of medicine, and it would take another century for the value of the epidemiologist in preventing healthcare-acquired infections to be realized.

New York physician Joseph Felsen is credited with being the first to use the term "hospital epidemiologist" to describe an expert in the "investigation of infectious disease outbreaks arising or spreading within an institution" [3]. In a 1939 presentation before the epidemiology section of the American Public Health Association, Felsen called for the appointment of an epidemiologist to the staff of every hospital as part of a comprehensive program to prevent infectious diarrhea [4].

Unfortunately, his ideas were slow to catch on despite a growing recognition of the problem of healthcare-acquired infections. More than a decade later, Felsen made the same argument in a letter to JAMA [5]. "…we are stressing the importance of the hospital epidemiologist," he wrote. "As you know, intramural outbreaks of various types occur frequently in our hospitals but are poorly managed or inadequately studied." Fellow physician Leopold Brahdy likewise noted the occurrence of preventable diseases among doctors, nurses, other hospital personnel and patients in medical institutions [6]. "A hospital epidemiologist is a major step toward ending unnecessary illness and unnecessary death from disease acquired right in our own territory," he wrote.

In 1962, public health authorities in New York City ordered the creation of a local hospital epidemiology program, in part to foster collaboration between the health department and medical facilities and "enhance preventive medical activities" [7]. As part of a pilot project, 16 hospitals in the borough of Brooklyn each designated a medical staff member to serve in the position of epidemiologist. These physicians participated in a standardized training program (ten weekly lecture-seminars organized by the Columbia University School of Public Health) and were paid as part-time employees of the health department in recognition of the incremental increase in their work responsibilities. Their duties mirrored those of many healthcare epidemiologists today: They identified and investigated outbreaks, developed a system for reporting select diseases to the health department, including HAIs, and provided education to their peers as well as nonprofessional staff. They chaired infection control committees, worked with employee health services, and coordinated immunization programs. Citing improvements in the timely investigation of syphilis cases as well as more efficient use of public health and hospital laboratories for the diagnosis of viral and rickettsial diseases, organizers declared the program a success and proposed expansion to every hospital in the city.

The Study on the Efficacy of Nosocomial Infection Control (SENIC), conducted by the Centers for Disease Control and Prevention (CDC) in 1976–1977, provided additional objective evidence about the value of the healthcare epidemiologist. SCENIC demonstrated that hospital infection prevention programs led by a physician with expertise in healthcare epidemiology had lower rates of HAIs [8, 9]. More than half of study hospitals had a physician or microbiologist serving in a leadership role, with higher rates among larger hospitals and those affiliated with academic medical centers [10]. Most physician leaders were pathologists (40%), surgeons (11.7%), internists (9.2%), or infection disease specialists (8.7%). Just over a quarter had completed

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_19

formal training in healthcare epidemiology, and most (62%) devoted only between 1 and 4 h weekly to infection surveillance and control activities.

When hospitals were resurveyed in 1983, the overall percentage with a physician hospital epidemiologist was slightly better (57% vs. 51%), but few individuals appeared to be pursuing hospital epidemiology as a career. Only 15% had received specific training in the field, and there was a high rate of turnover in the position.

In 1997, the CDC partnered with the Association for Professionals in Infection Control and Epidemiology (APIC) to reassess the state of infection prevention programs in the United States [11]. In the prior year, 47.6% of 187 participating healthcare facilities had at least one part-time or full-time epidemiologist, but only 66% provided financial compensation for epidemiology services. Most epidemiologists were individuals with an MD or PhD with training in infectious diseases, and they spent a small fraction of their work assignment (median 15% or less) on infection control activities. In 2011, in a similar sample of acute care facilities, half still lacked an epidemiologist [12]. While more recent data are not available, it seems likely that the vision articulated in the 1960s—a trained, adequately compensated epidemiologist in every hospital—has not yet been realized.

Training

In the twenty-first century, healthcare epidemiologists are most often physicians with subspecialty training in infectious diseases and a background in internal medicine or pediatrics. Although the ranks of epidemiologists occasionally include professionals from fields other than medicine (e.g., nursing or clinical microbiology specialists with graduate degrees in public health), guidance from the Society for Healthcare Epidemiology of America (SHEA) suggests that the clinical insight of a physician is invaluable in this role [13]. In particular, the physician epidemiologist brings an understanding of the nuances of clinical care that affect the development and implementation of infection prevention practices.

While the Accreditation Council for Graduate Medical Education program requirements stipulate that trainees in infectious diseases (adult and pediatric) "demonstrate knowledge of infection control and hospital epidemiology," not every fellowship graduate will have the skills and training necessarily required of the healthcare epidemiologist [14, 15]. A 2012 survey of pediatric infectious diseases training programs in the United State found that little time was devoted to formal instruction or experiential learning in healthcare epidemiology [16]. Only a third of programs had a dedicated "infection control" rotation, and didactic sessions were limited, typically only 1–2 h.

SHEA has published a comprehensive review of the skills and competencies required of the healthcare epidemiologist, many of which are beyond the scope of most infectious diseases training programs [13]. Online resources include the SHEA/CDC Outbreak Response Training Program (ORTP), a comprehensive training program designed to prepare hospital epidemiologists to respond to both facility-level outbreaks as well as community outbreaks of emerging pathogens. The ORTP provides expert-authored and selected resources in incident management, with tools and trainings for development and implementation of policies and identification of resources. A training certificate course in healthcare epidemiology is offered by SHEA in partnership with the CDC.

At present, there is no national certification process for healthcare epidemiologists analogous to the certification for infection preventionists, nor is there a single, recommended training pathway. One state, California, has established mandatory minimum requirements for physicians who have authority over the infection prevention and control program [17].

Duties of the Healthcare Epidemiologist

In the twenty-first century, HAIs are increasingly occurring outside acute care hospitals [18]. The burden in long-term care facilities is well recognized, with an as many 2 million infections occurring in United States nursing homes annually [19]. Formal systematic surveillance in ambulatory settings is more limited, but outbreak reports document healthcare-associated infections in doctors' and dentists' offices, outpatient surgery centers, pain clinics, and imaging facilities [20]. Although ambulatory and community settings are even less likely than acute care settings to have adequate epidemiology support, the term "healthcare epidemiologist" has largely replaced the term "hospital epidemiologist" in recognition of the need for this specialized expertise across the healthcare continuum. Alternately, the title "medical director for infection prevention" is used in some organizations.

Healthcare epidemiologists provide oversight of a facility's infection prevention program, often in collaboration with an infection preventionist. They serve as subject matter experts on topics ranging from pathogen transmission to diagnosis and treatment of infectious diseases. While specific responsibilities may vary according to institutional needs and priorities, common duties are listed below.

Administration

In some facilities, the healthcare epidemiologist functions as a manager: He or she is involved in day-to-day operations, supervising other professionals, overseeing budgets, and directing projects. In the pay-for-performance era, healthcare epidemiology/infection prevention programs may be cost-saving, but they are not revenue-generating. Effectively advocating for resources and demonstrating return on investment are essential skills for the healthcare epidemiologist.

In every facility, the healthcare epidemiologist has the opportunity to serve as a leader, broadly defined as person of influence within an organization and one who has the opportunity to effect change in the behavior of others [21]. Outlining the functions of a leader, Richard Wenzel wrote that the healthcare epidemiologist leader must "articulate the mission, convince others to follow, create the high standards and the philosophy for success, and help design the culture of an organization" [22]. This may happen in both formal and informal settings. For example, the epidemiologist is often called upon to chair interdisciplinary committees, including the infection control committee. Leadership also happens in the doctors' lounge or the cafeteria. As a respected expert on infectious diseases and infection prevention, the epidemiologist is in a position to recruit support from peers and others for initiatives to reduce HAIs, even when these require changes in personal practice.

In some organizations, epidemiologists are involved in formal or informal review of physician practice. As such, their duties could include communication with surgeons about their surgical site infection rates, with hospitalists about hand hygiene compliance, or with intensivists about adherence to central venous catheter insertion bundles. The inherent tension associated with giving negative feedback to colleagues can create particular challenges for the epidemiologist who also maintains an infectious disease practice that is dependent on referrals [23].

Surveillance

Surveillance—the process of gathering, managing, analyzing, and reporting data—has been a core function of the healthcare epidemiologist since the days of Semmelweis. The modern epidemiologist participates in the development of a risk assessment, which is used in combination with regulatory mandates to drive the data that are collected. He or she must have a working knowledge of the National Healthcare Safety Network surveillance definitions for healthcare-associated infections, and be able to articulate the difference between these and clinical definitions of infection to both front-line providers and administrators. In mature programs, data collection and preliminary data analysis are done by another member of the infection prevention team, while the healthcare epidemiologist is focused on interpretation of data and using it to develop interventions and improve patient outcomes. As noted by Robert Haley in an address at Columbia University in 1986, it is the job of the epidemiologist to report surveillance data in a way that is clinically relevant to other physicians [23].

With advances in information technology, artificial intelligence and machine learning are transforming the way surveillance is performed and, in some cases, identifying at-risk patients before infections occur [24]. Healthcare epidemiologists need a working understanding of opportunities and limitations of these tools.

Outbreak Investigation

Outbreak investigation is no less important now than in the 1960s, when hospital outbreaks of dysentery fueled the demand for physician epidemiologists. In 2010 survey of a representative sample of U.S. hospitals, one-third had investigated an outbreak in the preceding 24 months [25]. The health epidemiologist participates in all phases of an outbreak investigation, including recognition, case finding, conduct of a case control, and implementation of control measures. He or she may be responsible for communication with internal stakeholders (facility administrators, healthcare providers, and risk management) and external stakeholders (public health authorities, regulatory agencies, and the media).

Public Health

Healthcare epidemiologist may be involved with public health at the international and national level, working with the World Health Organization, the Centers for Disease Control and Prevention, or a nonprofit organization focused on health outcomes. They also serve in leaderships positions in state and local health departments. Those employed in community healthcare facilities still have the opportunity to shape national policies and practices related to infection prevention by serving on the Healthcare Infection Control Practices Advisory Committee (HICPAC), a federal advisory committee assembled to provide advice and guidance to CDC and the Secretary of the Department of Health and Human Services (HHS), or as members of guidelines committee of professional organizations. At the local level, healthcare epidemiologists collaborate with public health authorities on a number of issues, including recognition and investigation of infectious disease outbreaks.

Emergency Preparedness

Healthcare epidemiologists are at the forefront of emergency preparedness activities ranging from response to pandemic influenza to bioterrorism to new and emerging infections such as SARS-CoV-2. They play a key role in the incident command structure in hospitals, frequently serving as subject matter experts [26]. The breadth of activities undertaken by healthcare epidemiologists in response to the SARS-CoV-2 pandemic is depicted in Table 19.1.

Education of personnel, patients, and families is a core activity of IP/HE programs. Healthcare epidemiologists must utilize adult learning principles to develop and implement educational activities for peers, other professional and nonprofessional staff, and the public. "Education" may take a number of forms, including formal lecture presentations, workshops, hands-on simulations, computer-based modules, small group discussions, and printed materials.

Employee Health

The healthcare epidemiologists may serve as the medical director for employee health services. Potential duties include policy development, evaluation and treatment of personnel after blood and body fluid exposure or other infectious disease exposure, oversight of immunization programs, and clearance of employees to return to work after an illness [27].

Quality Improvement and Patient Safety

The tools used by the healthcare epidemiologist to reduce HAI are also key to reducing noninfectious adverse outcomes. Many healthcare epidemiologists have developed expertise in the use of performance improvement methodologies, and can serve as resource for design and implementation of projects not specifically related to infection prevention. The healthcare epidemiologist works collaboratively with the patient safety officer to reduce patient harm.

Table 19.1 Representative activities of healthcare epidemiologists in response to SARS-CoV-2 pandemic

Created and implemented protocols for screening of patients for signs and symptoms of SARS-CoV-2
Devised algorithms for testing of patients and healthcare providers when testing resources limited
Developed guidelines for isolation of patients with suspected or confirmed infection
Produced protocols for furlough of infected and exposed healthcare workers
Revised guidance for personal protective equipment use in the setting of critical shortages
Investigated clusters of healthcare-associated infection and implemented control measures
Educated healthcare community
Performed media interviews
Assisted with implementation of vaccination programs for patients and healthcare workers
Collaborated with local, state, and national public health authorities
Leveraged professional networks to rapidly share new or evolving data

Antimicrobial Stewardship

The goals of antimicrobial stewardship include the optimization of drug selection, dosing, route of administration, and duration of therapy in order to improve patient outcomes and reduce adverse events. The Infectious Diseases Society of America and SHEA have recommended that antimicrobial stewardship programs (ASP) be led by infectious disease physicians with additional stewardship training [28]. Critical skills and competencies for required antimicrobial stewardship leaders have been defined and are distinct from those required of the healthcare epidemiologist. Because effective antimicrobial stewardship is considered essential to efforts to eliminate healthcare-associated infections, including those caused by multidrug-resistant organisms and *Clostridioides difficile*, collaboration between the HE and ASP program is essential, and in some facilities, the healthcare epidemiologist also leads the ASP.

Research

Most HEs are involved in work that advances the science of infection prevention. Research is a broad term that encompasses investigator-initiated, randomized-controlled trials involving interventions, products or devices, retrospective observational studies, and outbreak investigations. Those without significant protected time devoted to research can still contribute data to research networks and multicenter collaboratives. Using the "learning hospital" model, one infection prevention program at an academic medical center produced 121 peer-reviewed manuscripts in 16 years, largely in the absence of significant grant funding. These papers reflect a systematic assessment of infection prevention strategies and interventions, and 64% included learners as first or second authors [29].

Resources and Compensation

The SCENIC study suggested that optimal staffing for infection control programs in the United States included one infection control professional for every 250 occupied beds in acute care facilities [8]. As the scope and complexity of infection prevention have increased, the concept of staffing based on occupied beds has been challenged [30]. In 2015,

APIC conducted a workforce survey of its members that is expected to reshape recommendations for IP staffing in various healthcare settings.

Guidance for epidemiology staffing has also evolved. While noting the value of a part-time physician "with expertise in healthcare epidemiology," SCENIC investigators stopped short of making formal staffing recommendations. Guidance on epidemiology staffing remained limited for the next 30 years, although in 2007, members of the Dutch Society of Infection Prevention and Control in the healthcare setting (VHIG) and the Dutch Society of Medical Microbiology the Netherlands recommended 1 full-time equivalent epidemiologist or medical microbiologist per 25,000 admissions [31]. In 2016, SHEA published recommendations describing minimum staffing requirements for healthcare epidemiology based on the size of a facility and anticipated complexity of the patient population served (Table 19.2) [32].

Models for remuneration of hospital epidemiology services include hourly rate payments, a global fee for defined services, and a salaried position within an organization [33]. Among SCENIC participants, only 5% of physicians received compensation specifically for their infection surveillance and control work, although a minority received at least a part-time salary for other services. A 2006 survey of SHEA members indicated gains, but on the whole, hospital epidemiologists remained undercompensated based on the time dedicated [34]. Only 65% of the 526 survey respondents reported any compensation for their HE/IC services provided; the median percentage of total income provided by HE/IC services was 25%. Hourly compensation was reported by 102 individuals, at a median range of $101–150/h. SHEA members were resurveyed in 2015, and based on a limited sample of 146 respondents who self-identified as healthcare epidemiologists, 68% were specifically compensated for healthcare epidemiology or infection prevention activities (personal communication, Kristy Weinshel, Executive Director of SHEA). The mean salary in 2015 was $197,989. Twenty-eight percent reported compensation at an hourly rate. Of these, 50% indicated being paid $101–150/h, and 21% indicated being paid $151–200/h. Nearly a third felt they were poorly compensated for their work.

Table 19.2 Compensation for healthcare epidemiologists

	Recommended compensation	
	>300 beds and/or over 50 ICU beds	<300 beds and/or <50 ICU beds
Academic institutions	≥1.5 FTE of full professor salary[a]	≥1 FTE of full professor salary[a]
Community-based hospitals	≥1.0 FTE salary of regional market value	≥0.5 FTE regional market value

Adapted from Ref. [32]
[a]Based on Association of American Medical Colleges norms

Centers for Medicare and Medicaid Services pay-for performance initiatives that impose financial penalties on hospitals for HAIs have created an unintended benefit for the healthcare epidemiologist: It has never been easier to demonstrate the financial value of the epidemiologist to an organization. Frameworks for negotiating appropriate compensation for managing infection prevention and control activities have been published [27, 33]. In addition to salary or consulting fees, contracts should clearly delineate scope of duties, the anticipated time commitment, available administrative support, physical resources necessary to perform the requested duties (including but not limited to computer hardware, software, access to administrative databases, availability of molecular typing, etc.), as well as protected time and reimbursement for professional development/continuing medical education. Professional liability coverage should also be specified.

Ongoing Challenges

There is a growing shortage of infectious diseases physicians in the United States, as well as increasing and unmet needs for healthcare epidemiologists [35]. Over the last decade, roughly 40% of ID fellowship training positions have gone unfilled. Rising medical school debt and relatively low compensation of ID physicians compared to primary care providers and other subspecialists are two disincentives that must be eliminated.

Burn out is a pervasive and increasingly urgent problem in medicine. While data specific to healthcare epidemiologists have not been published, a 2017 Medscape survey revealed that burnout rates among infectious diseases physicians were among the highest of clinicians surveyed (55%) [36]. Factors driving burnout in healthcare epidemiologists may overlap with those that affect healthcare providers more globally, but some manifestations are specific to the field.

Too much work for too little reward is commonly cited as a cause of burnout. Serial surveys of healthcare epidemiologists in the SHEA Research Network in 2006 and 2013 described increased programmatic responsibilities for healthcare epidemiologists without increased financial support for these activities [34, 37]. This paradox was exacerbated during the COVID-19 pandemic.

Lack of control, another often-cited factor associated with burnout, is inherent to the field. Healthcare epidemiologists develop policies and guide evidence-based practice, but they neither have administrative oversight of those charged with implementation of policies and practice nor do they direct resource allocation in hospitals and healthcare systems. Misalignment between the actions advised by the healthcare epidemiologist and the priorities of healthcare administrators creates frustration and may contribute to burnout.

Conflict with colleagues and loss of community is another potential occupational hazard for healthcare epidemiologists. Implementation of quality improvement and infection prevention initiatives may necessitate evolution in clinician behavior. Anxiety or reluctance to change may lead to discord with healthcare epidemiologists who may be viewed as "enforcers" of new policies and procedures. Further research is needed to address the prevalence and sources of burnout and potential solutions.

Conclusion

Healthcare epidemiology is a rewarding yet demanding field. Healthcare epidemiologists improve the quality of care for patients and are instrumental in reducing HAIs across the healthcare spectrum. Effective epidemiologists have mastered a unique set of skills and competencies through specialized training. They should be compensated adequately and appropriately for their work by the healthcare facility or entity utilizing their services. Strategies to bolster the pipeline of qualified candidates and address burnout and attrition among practicing healthcare epidemiologists are urgently needed.

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Whole Genome Sequencing for Outbreak Investigation

20

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Introduction

Whole genome sequencing provides information at a level of detail previously unattainable with the molecular biology techniques that long served as tools for public health and epidemiology. Instead of making educated guesses based on epidemiologic data and helpful but imprecise estimates of microbial relatedness, epidemiologists can use the unambiguous results of sequencing to understand an outbreak.

Whole genome sequencing enables tracking of antimicrobial-resistant bacterial strains at a resolution unattainable with older methods, such as pulsed-field gel electrophoresis, repetitive element (REP) PCR, and multilocus sequence typing, which compare isolates using only a fraction of the organism's nucleic acids.

Overview of Whole Genome Sequencing and Older Typing Methods

Genome sequencing has advanced over the past 15 years from the Sanger method to next-generation sequencing. The original, Sanger method enabled sequencing of a single DNA fragment at a time up to 1000 bp in length, using radiolabeled or fluorescently labeled nucleotides. Whether sequencing was performed manually, using a glass plate, or by automated capillary devices, Sanger sequencing is an extremely laborious and time-consuming method of sequencing the entire genome of a microbe, much less a multicellular organism. Use of Sanger sequencing on whole genomes carries additional challenges, such as a requirement to know *a priori* a target sequence for amplification, as well as a limited ability to resolve mixed populations of similar sequences. Despite its limitations, Sanger sequencing was used to complete the Human Genome Project [1]. While this technology is still very prevalent in multiple applications in molecular biology, massively parallel methods have largely replaced it for sequencing of whole genomes. These will be described in the sections below.

Next-Generation Sequencing

Next-generation sequencing (NGS) refers to high-throughput sequencing in which thousands to billions of DNA fragments are amplified and sequenced in parallel ("massively parallel"). We will use "NGS" to refer to the second-generation methods that typically generate readouts of 35–300 base pairs (bp), also termed short read NGS, while the third-generation or long-read NGS will be described in the next section.

In the most common NGS technologies, fluorescently labeled nucleotides are detected as they are incorporated to the newly synthesized complementary strand, generating an individual sequence or "read" for each DNA molecule. Millions to up to several billion reads might be generated, depending on the device. The highest-throughput devices typically are large and reserved for shared use in core facilities. In the past 10 years, tabletop sequencers have become available and popular. These sequencers are medium-throughput, thus capable of sequencing a microbial genome but not an entire human genome. They are, however, far more accessible than high-throughput sequencers since they can be dedicated for use by individual labs. A number of high-throughput and tabletop sequencing devices are available on the market; their various sequencing platforms use similar workflow but different chemistry and methods of imaging to capture sequences as they are built [2–4].

Before sequencing begins, a library of DNA fragments is prepared from the genome of interest. The fragments are

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_20

amplified and attached to complementary adapters, or sequences that are recognized by the device. Sequencing proceeds with parallel sequencing and detection of the thousands to millions of fragments. After sequencing is completed (usually hours to days, depending on the quantity of genomic data and the "depth," or duplication, of sequencing), the multiple copies of short, overlapping sequencing reads (approximately 50–300 bp) are usually assembled de novo or aligned to an existing reference, by computer programs [5, 6]. Depth of sequencing is explained in a sentence prior to this one [7]. Assembled sequences are calibrated and corrected for misalignments and gaps [5, 6]. The finished sequences can then be compared to other sequences. Genome sequences are usually deposited in public databases that enable researchers to access reference genomes and compare strains.

"Third-Generation" Sequencing

More recently developed technologies directly target unfragmented DNA molecules, generating reads that span from 1000 to tens of thousands of base pairs while maintaining the massively parallel characteristic of NGS. These long-read technologies, often categorized under "third-generation" sequencing, include Oxford Nanopore and Pacific Biosciences single-molecule real-time (SMRT) technologies [3, 8, 9]. SMRT sequencing devices read the sequences of hundreds of thousands of individual long fragments of DNA ("single molecules"), generating reads spanning ~10,000 base pairs on average [9–11]. The hairpin adapters used in this technology allow for each long DNA molecule to be reread multiple times, reaching a consensus accuracy comparable to NGS. Currently, higher cost and lower throughput compared to NGS are the main factors limiting the more widespread use of SMRT. Nonetheless, the combination of high accuracy and long reads put SMRT sequencing data among the highest quality achievable with current technologies, especially given that its throughput is appropriate for the relatively smaller genomes of bacteria and viruses.

The second of these platforms, Oxford Nanopore technologies, uniquely functions by detecting nucleotide-specific ion current changes as DNA molecules pass through membrane-embedded nanopores in the device [3, 8]. A limitation of this method is lower accuracy than SMRT and NGS, with an error profile that is not easy to correct by additional sequencing depth. This technology emerged in 2014 and has been increasingly utilized for pathogen surveillance as well as clinical diagnostics due to both its ability to generate data in real time and its pocket-sized portability. The MinION device is only 3 inches long and can be powered by a USB port on a laptop, which allows for its rapid field deployment including in remote or resource-limited settings [12, 13].

Even though third-generation approaches still lack the high throughput and fine accuracy to fully replace short read technologies, the long reads generated are easier to assemble than short read sequences and therefore allow better assessment of variation in repeat regions of the genome. Additionally, short-read sequences from next-generation platforms can then be aligned to the long reads for error correction, known as "hybrid sequencing." [9, 14] Long reads are particularly useful for plasmid sequencing. Plasmids contain repeat regions and mobile genetic elements that make their contiguous assembly from short-read sequences challenging. Long-read sequencing can be used to recreate the framework of plasmids, where shorter sequences may not have sufficient overlap with unique sequences to differentiate a plasmid's structure [14]. Plasmid sequencing can be used to determine whether isolates of the same or different species may share the same plasmid, i.e., whether horizontal plasmid transmission between the isolates has occurred [14].

Older Bacterial Typing Methods

Many methods of typing have been used over the decades since public health and healthcare epidemiology experts began trying to determine relatedness of isolates. Pulsed-field gel electrophoresis (PFGE), repetitive extragenic palindromic (REP-) PCR, and multilocus sequence typing are just a few of the most common methods employed at various times since the 1970s. In PFGE, bacterial DNA undergoes cleavage by restriction enzymes, and the resulting large DNA fragments are separated by size due to multidirectional electrical pulses. The resulting bands for each isolate are compared, and established criteria are used to label the isolates as related or unrelated [15]. This technique is useful if isolates have sufficiently different band patterns that they are deemed unrelated, but similar or identical band patterns may give only a gross, qualitative estimate of relatedness. The technique is laborious, is time-consuming (at least 3 days), and is of low throughput.

Rep-PCR utilizes the arrangement of the numerous repetitive DNA sequences interspersed between coding regions of genomes to distinguish between strains of bacteria [16]. The process can be automated, with repetitive sequences amplified to produce amplicons of varying length and separated by electrophoresis, giving band patterns that can be read and compared by software among strains. As with PFGE, this technique is most helpful if it shows that isolates belong to different strains, whereas those deemed similar can still vary. An example is the community-acquired USA300 pulsotype of methicillin-resistant *Staphylococcus aureus*, whose isolates will all, by definition, have similar band patterns despite significant sequence variation [17].

Multilocus sequence typing (MLST) compares 400–500 bp sequences around seven loci that are selected in housekeeping

genes. The sequences are amplified using primers specific for those loci, followed by Sanger sequencing of the amplified fragment of DNA each locus. Each unique combination of sequences, or alleles, defines the sequence type of the organism, a classification that is standardized worldwide [18]. With the plummeting price of whole genome sequencing, [19] MLST performed by this traditional method costs more than whole genome sequencing [18].

With the availability of whole genome sequences, MLST can be implemented *in silico* using the same loci and alleles that are identified using the whole genome sequences of the relevant bacterial isolates. The combination of alleles detected in the whole genome sequence is then labeled with the predicted sequence type [20, 21]. In addition, with the availability of the organism's whole genome sequence, MLST schemes can be generated without being limited to the usual seven housekeeping genes. For instance, MLST using often thousands of loci in "core genes," i.e., the genome sequences that are common to all members of the set of bacteria being studied, has expanded the resolution of whole genome sequence-based MLST [22, 23]. Although this technique, named core genome MLST (cgMLST), can miss sequence variation at loci that are not used for the comparison, it has the advantages of requiring less computational labor and expertise than whole genome comparison and the ability to generate reproducible databases of classification schemes for application at other centers worldwide [24].

Similar to MLST, software tools to implement other older typing methods *in silico* on the organisms' WGS data are available. For instance, restriction enzyme-based [25] and PCR-based analyses [26] can be performed using software tools.

Comparison of Whole Genome Sequencing with Older Methods

Numerous published studies have compared whole genome sequencing with older techniques during the course of investigating microbial relatedness during outbreaks. For example, in a report of the use of whole genome sequencing to elucidate an outbreak of bla_{KPC}+ *Klebsiella pneumoniae,* Snitkin et al. noted that both REP-PCR and PFGE were performed on outbreak isolates, and that neither technique had the resolution to demonstrate differences. When microbial whole genome sequencing was performed, isolates sequences varied only within a range of 41 base pairs [27]. Even some more recent investigations have utilized pulsed-field gel electrophoresis or MLST as the first-line typing method, followed by whole genome sequencing to achieve higher resolution [28–30]. WGS-based methods seem to have robust correlation with traditional methods [31].

Sequence Analysis

When the goal of sequencing is to detect minor variations or relatedness among isolates, assembled sequences may be aligned and compared for the presence of single nucleotide variation (SNV), or differences at individual nucleotide base pairs. Such analysis is labor-intensive, but more importantly requires a high level of expertise to handle the variations that occur in repetitive sequences, gene rearrangements, and inserted mobile genetic elements. Another approach, which does not require de novo assembly of the sequenced genome, is to compare shared genomic sections with reference strains. Owing to inherent characteristics of short-read sequencing, this approach would not examine large-scale genomic variation, such as insertions and deletions of genes. When analysis at that level is not possible, investigators have used core genome SNV analysis or multilocus sequence typing as described above. There is no standard algorithm or threshold for determining what magnitude of allelic or single nucleotide differences is considered closely related or clonal.

In recent years, several graphical software tools for WGS processing have become available, significantly decreasing the amount of bioinformatics expertise required to obtain answers to genomic relatedness questions [24, 32]. These have made it possible, for example, to create core genome MLST (cgMLST) schemes and/or assign these to isolates of interest in the researcher's own collection, as well as to obtain information on presence/absence and typing of plasmids [33] and resistance genes/variants [34–36]. Large collaborative databases containing genomic features of epidemiologically important pathogens are increasingly available [37–39].

Once the sequence variants of a clonal outbreak strain are fully characterized by whole genome sequencing, researchers can develop a clone-specific set of PCR primers as a rapid diagnostic tool to identify isolates belonging to the outbreak strain [40–42]. Another technique, pan-PCR, is enabled by analyzing known sequences of a given bacterial species and generating a set of primers that can differentiate among strains of that species, providing species-specific strain typing [43].

Use of Whole Genome Sequencing for Outbreak Investigation

The power of whole genome sequencing for outbreak investigation may lie in uniting its output with the relevant epidemiologic data. Epidemiological and genomic data can be joined to develop putative models of transmission for healthcare or public health epidemiology. Genomic data lend precision to intrinsically inexact epidemiologic data, and epidemiologic observations provide essential real-world

context for the abstract results of genome sequencing. Examples from outbreaks on various scales demonstrate the remarkable insights that can be gleaned from this combination.

International Outbreak Investigation

Whole genome sequencing has been used to track the evolution and transmission of bacteria over great temporal and geographic distances. Two investigations in the past decade illustrate the power of WGS to pinpoint the geographic origins of outbreaks. A now-infamous example is the use of sequencing to trace the origin of the Haitian cholera epidemic that began in 2010, in the wake of a devastating earthquake, leaving thousands dead. Haiti had no previous cholera in the historical record, [44] and when infections first appeared in October 2010, officials speculated that the strain could have been introduced from the Americas or further afield.

Scientists were already conducting whole genome sequencing on historical and contemporaneous *Vibrio cholerae* isolates from around the world for an ongoing study to better understand the transmission dynamics of the seventh known cholera pandemic (in progress since the 1960s) [45]. The researchers included isolates from the Haitian outbreak, and through analysis of SNVs, determined that they were indeed part of the pandemic, and that they were closely related to recent South Asian strains [45]. Comparison of the SMRT sequences from the Haitian outbreak strain to sequences from around the world further confirmed clonality of the Haitian outbreak and supported recent importation from South Asia via "human activity." [46] The indisputable genomic evidence from multiple studies [44–47] concluded that the epidemic was introduced by a United Nations peacekeeper from Nepal. The epidemic was terminated in 2019.

Candida auris is an important, emerging pathogen that has recently materialized in healthcare settings on multiple continents. The organism, which has caused serious healthcare-associated outbreaks, provides another example of sequencing used to trace the relatedness of isolates from around the globe. *C. auris* was first appreciated as a distinct species when it appeared in a clinical culture in Japan in 2009 [48]. Database searches have identified very few isolates from before 2009 [49]. Nosocomial outbreaks of *C. auris* have occurred in numerous countries, with high rates of resistance to antifungal drugs and high associated mortality. Scientists from the US Centers for Disease Control and Prevention (CDC) conducted whole genome sequencing of isolates from each of the affected countries, as well as the type strain from Japan. Sequencing showed distinct clades in each region (South Asia, East Asia, South America, South Africa), suggesting that *C. auris* emerged simultaneously in each area rather than being transmitted by recent travelers or other vectors [49].

In a CDC report of the first seven patients identified with *C. auris* in the US, whole genome sequencing demonstrated that isolates from patients who had been inpatients in the same hospitals were closely related, and that each of the isolates could be traced to one of the international clades [50]. Investigators further showed that environmental isolates found in the investigation of two cases from the same hospital in Illinois closely matched the relevant patient isolates (<10 SNVs). In contrast, isolates from each of the international clades differed by tens of thousands of SNVs [50]. As *C. auris* spread across the US, the CDC used genome sequencing to further define its epidemiology. Isolates from the US remained genetically related to those arising from four global regions, suggesting multiple introductions into the US, with local spread and establishment of endemicity within facilities and regions [51, 52].

SARS-CoV-2

Many remarkable examples of the use of whole genome sequencing for tracking and controlling international outbreaks have been performed during the COVID-19 pandemic in 2019–2021, which is still ongoing at the time of this writing. The novel coronavirus SARS-CoV-2 was detected initially in December 2019 in Wuhan, China, [53] and rapidly extended worldwide. Remarkably, the complete genome of the virus was made publicly available within weeks, [53–55] which allowed worldwide collaborative efforts to be undertaken in the areas of diagnostics, treatments, vaccine development as well as epidemiological tracking. The complete SARS-CoV-2 genome sequence allowed for several approaches to be progressively adapted for COVID-19-specific use, evolving from the initial shotgun metagenomic/metatranscriptomic studies [54–56] to widely shared and uniformized protocols using specific PCR primers tiling the whole viral genome, followed by amplicon sequencing. These techniques have been adapted for both short-read [57, 58] and long-read [59, 60] technologies.

Whole genome viral sequencing has enabled the detailed study of COVID-19 outbreaks in healthcare personnel and their patients and families [61]. For instance, in one institution, WGS was used to elucidate transmission routes between healthcare personnel and patients with hospital-onset COVID-19, even in the absence of clear epidemiological links. With the aid of the high-resolution genomic data, several transmission clusters were uncovered as well as potential transmission to/from healthcare workers, which helped support infection control practices [57]. Larger, country-wide studies have also been carried out. In Iceland, a large genomic characterization study was performed, testing 6%

of the total country's population for SARS-CoV-2 [58]. By testing recent travelers in the early stages of the pandemic, viral sequencing and epidemiologic data allowed researchers to estimate the number of times different viral clades were imported into Iceland and from which regions, including the identification of clusters of infected persons who imported the virus from areas initially not considered high risk such as the United Kingdom. Similarly, viral genome sequencing data enabled researchers to dissect the process by which the virus was imported and spread within the USA, revealing multiple events of importation of different clades, even within the same region [62, 63], as well as domestic "coast-to-coast" transmission [64].

Genomic surveillance of SARS CoV-2 has also included cross-species investigations. For instance, extensive transmission to minks in Danish mink farms has been documented since June 2020, and subsequently, clusters of COVID-19 cases have been identified in mink farmers. In November 2020, genomic and epidemiologic investigations identified the transmission from minks of a viral strain possessing multiple spike protein mutations, possibly conferring antibody neutralization resistance [65]. This concerning finding resulted in the recommendation to cull large mink herds in Danish farms, in hopes to prevent a larger spread into the human population.

At the time of this writing, thousands of SARS-CoV-2 genomes have been made publicly available in collaborative databases, such as GISAID, [66] which allow visualization of the pathogen's evolution across time and geographical spread [37]. This global prospective surveillance has allowed the real-time tracking of viral evolution, as well as the identification of new genomic variants that may confer increased pathogenicity or transmissibility [67, 68]. For example, during late 2020, a distinct SARS CoV-2 variant quickly became dominant among cases in the UK and then spread worldwide, strongly suggesting a selective advantage. This lineage, later named B.1.1.7, possesses several spike protein variants that are thought to confer increased transmissibility [69] and an association with more severe outcomes [70]. Subsequently, heightened awareness of emerging variants resulted in enhanced international sequencing efforts, both prospectively and retrospectively, and the identification of additional variants of concern. In South Africa, a variant currently known as B.1.351 was found to have emerged independently of B.1.1.7, dating back to October 2020. This variant shares some spike mutations with B.1.1.7, as well as some unique mutations in the receptor binding motif which seem to diminish antibody binding affinity from convalescent sera as well as several therapeutic SARS CoV-2-specific monoclonal antibodies [71]. Most concerningly, this new variant was found to be associated with decreased efficacy in several vaccine trials [72–74] and reduced neutralization by sera from individuals immunized with other vaccines [75, 76]. Increased sequencing efforts are currently underway, and the number and impact of SARS CoV-2 variants in the course of the pandemic remain to be fully unveiled.

Hospital Outbreak Investigation

A first retrospective use of WGS to investigate a hospital outbreak was published in 2012 by Koser et al. [77] The investigators sequenced 14 isolates of MRSA, including those from neonates involved in a suspected 2009 nosocomial outbreak and, for comparison, contemporaneous MRSA-infected patients in other hospital wards. Analysis of SNVs in the isolates' core genome sequences confirmed that seven babies were indeed part of a clonal outbreak, but surprisingly revealed that two of the intended control MRSA patients had isolates that differed by only one SNV, likely representing unrecognized transmission. Of note, the authors reported that the isolates were sequenced within 1.5 days of extracting DNA from cultures. Although the sequencing and analysis were performed after the resolution of the outbreak, the researchers demonstrated the rapidity and feasibility of utilizing WGS as a nosocomial outbreak investigative tool, in combination with a classical epidemiological inquiry [77].

The first real-time use of WGS to investigate a hospital outbreak took place in 2011, when the US National Institutes of Health (NIH) Clinical Center, a clinical research hospital, experienced a nosocomial outbreak of bla_{KPC}-carrying *K. pneumoniae* that had reduced susceptibility to colistin [27]. The outbreak began with an index patient who was known to be colonized in multiple sites with bla_{KPC} + *K. pneumoniae* and was placed in contact isolation on admission. Five weeks elapsed between the index patient's presence in the ICU and detection of a second case of bla_{KPC} + *K. pneumoniae* colonization. Further surveillance cultures identified additional cases.

In the second month of the outbreak, isolates from the first five patients were sequenced. Snitkin and Segre used SNV analysis to confirm the clonality of the outbreak and the likely order of transmission among these first few cases. Their results prompted a shift in infection control efforts toward conducting increasingly broad, and ultimately hospital-wide microbial screening for the outbreak organism. These efforts ended the outbreak in December 2011, with one final nosocomial case 6 months later. Among 18 patients who had developed infection or colonization with the outbreak strain, seven had died of bacteremia by the time the outbreak ended. Snitkin and Segre sequenced the remaining outbreak isolates, and the rapid mutation rate of the organism made it possible to elucidate the chain of transmission throughout the entire outbreak. They constructed a putative model of transmission using an innovative algorithm to combine genomic relatedness with epidemiological data

such as the timing of patient locations in the various hospital wards [14, 27].

Numerous research teams throughout the world have since used whole genome sequencing as a tool to investigate suspected nosocomial outbreaks with a range of organisms, in combination with classical epidemiological techniques [78–82]. Whole genome sequencing has not only replaced older bacterial typing methods, but has also become a tool for understanding the sequence of events in an outbreak setting [83].

Plasmid Sequencing to Identify Horizontal Transmission of Resistance Genes

While infection control precautions for resistant bacteria are designed around their most likely modes of transmission – the hands of healthcare personnel, contaminated surfaces, or contaminated equipment – the dynamics of plasmid dissemination may be far more complex. In addition, mobile genetic elements such as plasmids and transposons may spread undetected, and there are no infection control measures to specifically address this problem.

Conlan retrospectively studied the NIH outbreak isolates and a number of other environmental and patient isolates, using SMRT sequencing to identify instances of horizontal transmission of carbapenemase genes and their plasmids. Environmental cultures done to investigate one patient's unexpected colonization with a non-outbreak strain of bla_{KPC}+ *K. pneumoniae* led to isolation of bla_{KPC}+ *Enterobacter cloacae* from a sink drain in the patient's room. Conlan demonstrated horizontal transfer of the patient's bla_{KPC} plasmid to the sink *E. cloacae* isolate. In addition, the *E. cloacae* isolate contained two other bla_{KPC} plasmids, including one containing a different bla_{KPC} subtype [14]. At the time, the origin of those plasmids was a mystery. However, plasmid sequencing in a later environmental sampling study found that the other two plasmids originated from the bla_{KPC}+ *E. cloacae* isolate of a patient who had occupied that room a year earlier [84]. Thus, SMRT long-read sequencing and plasmid assembly enabled determinations of plasmid transmission involving long-term persistence and transfer of plasmids in the hospital sink drain biofilm [14, 84].

In a large and remarkably tenacious outbreak of bla_{KPC}+ *E. coli* in a hospital in the United Kingdom, plasmid sequencing enabled investigators to ascertain that the wastewater environment served as a vast reservoir for isolates containing the outbreak bla_{KPC}-containing plasmids that eluded every outbreak control maneuver, including removal of plumbing [85].

Investigators at the University of Pittsburgh used long-read sequencing with analysis of chromosomal and plasmid sequences to delineate an outbreak of resistant *K. pneumoniae* associated with duodenoscopes and to differentiate scope-related cases from others [86]. They found not only that there had been transmission of bla_{KPC}+ *K. pneumoniae* ST258, but that person-to-person spread of bla_{KPC}+ plasmids may have occurred via contaminated scopes [86].

Other investigators have described the horizontal transfer of plasmids-carrying resistance genes in a variety of settings using short-read sequencing platforms. Skalova sequenced isolates from 20 patients who harbored *Enterobacteriaceae* with $bla_{OXA\text{-}48\text{-}like}$ carbapenemases (the first known cases in the Czech Republic). Several of the isolates came from nosocomial clusters, some associated with travel, and some seemingly community-acquired. The researchers identified a plasmid-mediated outbreak, with polyclonal $bla_{OXA\text{-}48}$+ isolates sharing a common plasmid, whereas $bla_{OXA\text{-}48\text{-}like}$ carbapenemases were carried on distinct plasmids [87].

Mathers and colleagues described a plasmid-mediated outbreak involving 16 isolates belonging to six species of *Enterobacteriaceae*; 12 isolates contained a distinct, promiscuous plasmid. The plasmid sequencing analysis was combined with epidemiologic data to develop hypothesized routes of spread within the hospital [41]. From plasmid sequence analysis, Mathers developed PCR primers specific for the outbreak plasmid and was able to deploy the PCR as a rapid diagnostic test to identify outbreak isolates [41]. In a later paper, the team demonstrated that plasmid sequencing combined with epidemiologic data could discriminate multiple independent importations of bla_{KPC}+ *K. pneumoniae* and transmission of the previously identified bla_{KPC}-carrying endemic plasmid [88].

In Oregon, plasmid sequencing identified a rare and important resistance mechanism in a regional healthcare-associated outbreak of *A. baumannii.* Three cases of extensively drug-resistant (XDR) *A. baumannii* isolates from patients in acute care hospitals prompted a public health investigation. Epidemiological detective work identified a long-term acute care hospital as the source of the outbreak, which ultimately involved 16 patients. Transfer of patients with repeated failure to communicate patients' colonization status with this XDR isolate had led to its spread across five healthcare institutions [89, 90]. Whole genome sequencing of the *A. baumannii* isolates from the 16 patients demonstrated clonality of the outbreak. Hujer et al. characterized the plasmid using SMRT plasmid sequencing, pinpointing the rare plasmid-carried $bla_{OXA\text{-}237}$ carbapenenase gene as the source of its carbapenem resistance [90].

The ability to sequence and track mobile genetic elements adds an important dimension to our understanding of the spread of antimicrobial resistance. Much research is needed to translate these observations into measures that can reign in the dispersion of mobile genetic elements within the healthcare setting.

Sequencing of Endemic-Resistant MDRO

In addition to its use for elucidating outbreaks, whole genome sequencing can be used to describe the epidemiology of endemic multidrug-resistant organisms in order to better understand the dynamics of spread along community and social networks. For example, Popovich and colleagues conducted SNV analysis of whole genome sequences of the USA300 pulsotype of MRSA from surveillance swabs collected from individuals seeking care within an urban community. They identified four pairs of individuals with closely related isolates, many of whom had in common illicit drug use and homelessness or residence in shelters. They also identified distinct transmission clusters among individuals who were African American and infected with HIV and a tendency for these clusters to be located in neighborhoods with high rates of past incarceration. The authors posited that transmission may have occurred in prisons, or through activity associated with imprisonment [91].

Hospitals that have the ability to conduct whole genome sequencing can develop their own institutional database of genome sequences from endemic multidrug-resistant bacteria (or other organisms of interest). Other groups have reported their experience building such a database, which included plasmid sequences, that informed their epidemiological observations and can serve as comparators for determining whether subsequent isolates represent nosocomial transmission [92, 93].

Regional Outbreak Investigation

Several studies have used whole genome sequencing to elucidate the transmission of highly resistant organisms between healthcare facilities, or even among healthcare facilities in a region.

Zhou reported the use of whole genome sequencing in combination with epidemiologic data to track spread of a high-risk clone of $bla_{\text{CTX-M}}$+ *K. pneumoniae* from a single source patient across several Dutch healthcare facilities in different cities, over 18 months [94]. Eleven patients ultimately acquired the outbreak strain from a hospitalized index patient, with several generations of transmission complicated by patient movement between facilities. Sequence analysis and recognition of clonality informed the epidemiological investigation, and later, use of a clone-specific PCR enabled rapid screening and management of additional suspected cases [94].

The rapid regional spread of bla_{KPC}+ *Enterobacteriacaeae* in the New York City metropolitan area in the mid-2000s led to endemicity of these organisms in many healthcare facilities in the region, followed closely by a national healthcare-associated epidemic in Israel [95, 96]. Kreiswirth and colleagues sequenced six bla_{KPC}+ plasmids from three species of *Enterobacteriacaeae* isolated from hospitals in the region between 2003 and 2010. The team found that the organisms harbored plasmids that were similar to the epidemic bla_{KPC}-carrying plasmid *pKpQIL*, and that all likely evolved from a common ancestor. The team developed a *pKpQIL*-specific PCR and implemented it to screen hundreds of healthcare-associated isolates from New York and New Jersey, learning that approximately a third of the isolates carried *pKpQIL*-like plasmids. Their analysis had implications beyond just the mid-Atlantic United States, as one sequenced bla_{KPC}-carrying plasmid from 2003 appeared to be a precursor of the plasmid from the predominant bla_{KPC}+ clone in Israeli. This suggests that an isolate containing this plasmid was carried by international travel from the New York region to Israel in the early 2000s, leading to a clonal healthcare-associated epidemic throughout Israel [40].

Retrospective sequencing of isolates in a given region has enhanced knowledge of the complexity of spread and selection of resistant clones, [97] and perhaps of suspected routes of transmission.

Whole Genome Sequencing to Elucidate Mycobacterial Transmission

The potential of WGS to aid with control of tuberculosis (TB) remains largely untapped due to resource limitations. WGS has the high resolution needed to discriminate isolates that are classified as a cluster by the conventional mycobacterial typing method Mycobacterial Interspersed Repetitive Unit–Variable Number of Tandem Repeat (MIRU-VNTR). Such discriminatory power allows WGS to serve as a better tool for contact tracing and public health investigations.

Gardy and colleagues studied a large Canadian TB outbreak in which isolates appeared clonal by MIRU-VNTR [98]. WGS and SNV analysis was combined with social network analysis to investigate with greater granularity the dynamics of the outbreak. Genomic analysis alone revealed a chaotic map with many possible connections among patients; addition of the epidemiological data elucidated the transmission dynamics. What had appeared to be a unitary outbreak was in fact two separate outbreaks with distinct lineages, and cases disseminated by a superspreader had outnumbered those due to secondary transmission [98].

WGS of *M. abscessus* isolates from persons with cystic fibrosis in the United Kingdom provided startling insights into the transmission of these multidrug-resistant organisms [99]. SNV analysis in combination with social network analysis demonstrated multiple episodes of transmission of a *M. abscessus* subspecies among a cohort of 31 cystic fibrosis patients, many likely occurring within the center in

which they received their care. Because of the granularity of WGS, investigators were able to discern person-to-person transmission of strains that had mutations conferring additional resistance to antibiotics. The researchers were also able to show that similar isolates of a different *M. abscessus* subspecies did not represent transmission, but rather colonization with a dominant circulating clone. The findings prompted enhancement of infection control precautions and initiation of routine microbial surveillance for cystic fibrosis patients at the authors' healthcare facility [99]. Other groups have used WGS to study *M. abscessus* clinical isolates from cystic fibrosis patient cohorts in similar fashion and found no evidence of transmission, apart from pairs of siblings [100, 101].

Whole genome sequencing has been used to pinpoint the origin of nosocomial outbreaks of serious postoperative *M. chimaera* infections that have occurred in multiple countries since 2013, with case-fatality rates as high as 50% [102, 103]. The infections were quickly traced to aerosols generated by contaminated heater-cooler units used during open-heart surgery, but one mystery was why the problem occurred simultaneously on distant continents and in devices from more than one manufacturer [102–108]. Investigators noted that a significant proportion of sampled units of different brands were contaminated with *M. chimaera*, even in countries where no infections had occurred [104]. Whole genome sequencing confirmed the clonality of isolates from patients and heater-cooler units [102] and in units from different countries that were made by the same manufacturer [104]. These findings pointed to production facilities as a source of contamination. An investigation discovered nearly identical strains contaminating newly built units at one manufacturing plant in Germany [109]. Specialists have already concluded that remediation of existing units is not possible [106, 110] and are focusing instead on ways to prevent patient exposure [110] and on improved design of future units or ways to divert aerosol generated by the units safely away from the operating room [111].

Whole Genome Sequencing for Foodborne Outbreaks

Whole genome analysis of foodborne bacterial outbreaks provided real-time, actionable output in addition to eye-opening microbiological findings [28, 112, 113]. In a particularly notable example, a Shiga-toxin-producing *E. coli* O104:H4 caused an enormous outbreak in Germany in 2011, with more than 3000 cases of infection complicated by an unusually high rate of hemolytic uremic syndrome at 22% [114, 115]. The strain could not be cultured using the methods typically used for the more common Shiga-toxic-producing *E. coli* 0157:H7.

WGS demonstrated that, rather than the expected enterohemorrhagic pathotype of *E. coli,* the German outbreak strain was actually a Shiga-toxin-producing enteroaggregative *E. coli,* a previously rarely encountered strain with characteristics of both *E. coli* pathotypes. During the outbreak, after investigators released the sequence of one patient's isolate into the public domain, open-source whole genome analysis resulted in assembly of the genome within 24 hours, and the release of strain-specific primers within 5 days [115]. The strain-specific primers could be used to identify rapidly the outbreak strain [115] and thus direct clinical and epidemiological resources in a highly targeted manner. Additional SMRT sequencing demonstrated that an ancestral strain of enteroaggregative *E. coli* had likely acquired a Shiga toxin-encoding phage and other virulence factors through horizontal gene transfer to form the outbreak strain – the first known example of such a strain causing a major outbreak [52].

In the USA, two national public health initiatives have converged to modernize surveillance and investigation of foodborne outbreaks. GenomeTrakr, a network using real-time whole genome sequencing, was deployed by the Food and Drug Administration in 2013 to monitor foodborne outbreaks and as an investigative tool. In the first year of use, GenomeTrakr identified and solved more outbreaks of listeriosis compared with previous years [116]. This network is a model for use of real-time sequencing to make urgent public health interventions [117].

PulseNet USA is a longstanding network of public health laboratories and federal agencies coordinated by the CDC that has traditionally used PFGE for molecular surveillance and typing of foodborne disease isolates. In recent years, PulseNet has combined its PFGE database with a WGS database and transitioned to use of WGS for subtyping isolates, [118] greatly enhancing the resolution of complex investigations, such as that involving the Blue Bell Creameries *Listeria* outbreak. That outbreak smoldered over 5 years in four states until WGS demonstrated relatedness of isolates from 2010 through 2015, resulting in large-scale recalls [119].

How Can WGS Generate Actionable Data?

The channeling of resources into use of whole genome sequencing for public health and hospital infection control investigations is paying dividends in scientific understanding of the spread of resistance and the enormous consequences that can arise from a single introduction of a pathogen to a new environment [27, 40, 47]. A remaining challenge is to identify concrete steps that can be taken in response to real-time sequencing data and that could change the course of an outbreak to reduce hospitalizations and save lives. One example of such a response is the aforementioned use of

GenomeTrakr to detect and rapidly halt transmission of *Listeria* [116].

In the 2011 *K. pneumomiae* outbreak at the NIH Clinical Center, real-time genome sequencing, and analysis of the early isolates directed the investigation away from a point source or multiple independent introductions of the organism, and toward a more complex web of person-to-person transmission. The information prompted several rounds of whole-hospital patient screening for carriage of the outbreak isolate. This large-scale screening identified the last few colonized patients and was associated with interruption of transmission [27]. Although the sequencing output did lead to useful action, the action was application of a blanket measure (screening all inpatients). The granularity of sequencing data merits development of targeted epidemiological strategies that leverage the precise, high-resolution data achievable from WGS.

Mellmann and colleagues attempted to do just that in a prospective study conducted in a large German teaching hospital. The investigators aimed to determine whether actionable data could be gleaned from real-time sequencing of endemic MDROs, and whether acquiring such data would be cost effective [120]. MRSA, VRE, MDR *E. coli*, and MDR *P. aeruginosa* isolates were sequenced and analyzed using core genome MLST over a six-month period. When isolates were found to be nearly identical, epidemiological data were used to confirm or refute the likelihood of transmission. Small clusters of MRSA transmission were identified. Following this baseline analytical period, in which low rates of nosocomial transmission were observed, the investigators discontinued isolation of MDR (but carbapenem-susceptible) *E. coli* on all but the highest risk wards. In a follow-up period under the new isolation conditions, MDRO sequencing demonstrated no increase in documented transmission on those wards, and cost effectiveness analysis suggested a €317,180 savings driven by the reduction in isolation [120].

Bioinformatics Expertise

Although the cost of sequencing continues to decline, and sequencers and automated assembly and analysis programs become more accessible, there remains a human factor that poses a challenge for incorporating the technique into routine infection control and outbreak investigation. Bioinformatics specialists must have the expertise to handle the large, often fragmented data output associated with sequencing, to select and use the appropriate programs, which may vary by organism and platform, to develop computational pipelines and generate interpretations that are accurate and reproducible. In addition, there is pressure to return sequence analyses in real time, especially when they are central to an outbreak investigation. The scarcity and cost of bioinformatics expertise can be a substantial barrier and are growing as a proportion of the total cost of sequencing [121].

Conclusion

As computational and bioinformatics experts confront the challenges posed by massive output of sequencing data, the infection control and public health communities must devise ways to translate real-time sequence data into real-time action that can change the course of an outbreak. Whole genome sequencing combined with epidemiologic data has provided a degree of resolution and certainty in elucidating outbreaks that was unimaginable 15 years ago. Now the epidemiology community must find innovative ways to use this outbreak investigative tool for outbreak control.

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Viral Hemorrhagic Fever Preparedness

21

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Introduction

The 2014–2016 outbreak of Ebola virus disease (EVD) in West Africa marked the 25th such occurrence but was noteworthy in its massive scope, causing more human morbidity and mortality than the previous 24 recorded outbreaks combined. As of April 2016, there were 28,652 cases resulting in at least 11,325 deaths, nearly all in the three nations of Guinea, Liberia, and Sierra Leone [1]. Moreover, the 2014–2016 outbreak was the first in which patients, albeit few in number, were afforded sophisticated intensive care in the United States and in Europe. This 'high-level containment care' (HLCC) was provided in specially designed purpose-built biocontainment units (BCUs). Since the 2014–2016 outbreak and as of this writing, multiple EVD outbreaks have occurred in the Democratic Republic of the Congo as well as a single outbreak in Guinea, emphasizing the need for continued preparedness. In this chapter we explore the history and evolution of biocontainment, discuss its unique engineering and infection control modalities, and offer recommendations for the clinical and operational management of Ebola and other viral hemorrhagic fevers (VHFs).

History of Biocontainment

The modern concept of biocontainment had its birth in 1969 with the convergence of four separate events. In May of that year, Michael Crichton published *The Andromeda Strain* and, while the work was clearly fictional, it debuted amidst a series of discussions leading up to President Nixon's decision in November of that year to abandon the US offensive biological weapons program. Nixon's decision was a prelude to ratification of the 1972 Biological Weapons Convention and to the US ratification, in 1975, of the Geneva Protocols. At the time, Nixon stated that "the United States has decided to destroy its entire stockpile of biological agents and confine its future biological research program to defensive measures". Implicit in that decision was a shift in the focus of US efforts to defensive and medical countermeasure development that would include an emphasis on the management of patients potentially infected with highly hazardous human pathogens. This medical defense program would fall largely upon the newly created US Army Medical Research Institute of Infectious Diseases (USAMRIID), an entity which would inherit its defensive mission from the old Army Biological Laboratory (ABL).

The year 1969 also witnessed the discovery of Lassa virus by Dr. Jordi Casals-Ariet at Yale University [2]. While attempting to characterize the new virus, Dr. Casals contracted Lassa fever himself and fell critically ill, but survived following the administration of convalescent serum from one of his patients. Unfortunately, one of his technicians, Juan Roman, succumbed to the disease while conducting laboratory studies, causing Dr. Casals to move his research to a new maximum-security laboratory at the Communicable Disease Center in Atlanta (now the Centers for Disease Control and Prevention) and ushering in a new era of laboratory safety.

Finally, 1969 saw man's first journey to the moon, aboard Apollo 11. In order to guard against the remote possibility that extraterrestrial pathogens might inadvertently accompany the returning astronauts, a new facility, the Lunar Receiving Laboratory (LRL), was constructed, in consultation with ABL experts, at the Johnson Manned Spaceflight Center in Houston. The facility would receive spacecraft, equipment, and lunar samples from Apollo 11 and from future Apollo missions. Moreover, it would serve as a quarantine facility for the returning astronauts from the Apollo 11, 12, and 14 missions.

Included among the assets of the USAMRIID facility was a novel two-bed high-level containment care unit [3]. This unit, often referred to as "the Slammer", presumably owing

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_21

to the sound produced by the closure of its heavy steel airlock doors, opened in 1971 and included engineering controls analogous to those employed in BSL-4 laboratories. The facility was designed to treat infected patients, but also to provide confidence and a sense of security to scientists and to the community of Frederick, Maryland, in which it was located.

During the period 1972–1985, 20 individuals were admitted to the Slammer following laboratory or field exposure to a variety of BSL-4 pathogens [4]. The 21st patient (exposed to Ebola in the laboratory) was admitted in 2004 [5]. Of note, none of the 21 patients developed clinical evidence of infection. The Slammer was decommissioned in 2012; a new USAMRIID building, slated to open in 2022, will not house a containment care unit.

The intentional dissemination of anthrax via contaminated mail in October 2001, occurring just weeks after the World Trade Center assault and, ironically, attributed to a troubled USAMRIID scientist, convinced some civilian experts to move in the opposite direction and propose the creation of academic medical-center-based HLCC facilities. Outbreaks of Severe Acute Respiratory Syndrome (SARS) and Monkeypox in the spring of 2003 added impetus to these construction projects; SARS because of its high mortality and apparent transmission via droplet nuclei, and Monkeypox owing to a resistance among fearful healthcare providers to treat victims of the disease [6].

During 2004–2005, a two-bed facility at Emory University in Atlanta and a ten-bed facility at the University of Nebraska Medical Center in Omaha opened; the facilities employed some (but not all) of the engineering controls contained within the USAMRIID facility. In 2005, leaders from these facilities, as well as USAMRIID and the Centers for Disease Control and Prevention (CDC), published consensus guidelines for the employment of HLCC units [7].

In that same year, the National Institute of Allergy and Infectious Diseases (NIAID) contracted with Saint Patrick Hospital in Missoula MT to construct the first HLCC unit housed outside of a large university-based medical center in order to care for scientists exposed to BSL-3 and -4 pathogens at the NIAID's Rocky Mountain Laboratories in nearby Hamilton [8]. In 2010, the Special Clinical Studies Unit at the National Institutes of Health adapted its seven-bed clinical research unit in order to provide HLCC. This facility, along with those at Emory and Nebraska, cared for 9 of the 11 victims of the 2014–2016 West African Ebola outbreak managed in the US. One patient was managed under HLCC conditions at Bellevue Hospital in New York, and one patient was managed at Dallas Presbyterian Hospital.

In order to increase preparedness for highly hazardous communicable diseases in the United States following the Ebola outbreak of 2014–2016, the CDC and Department of Health and Human Services (DHHS) developed a tiered system to screen and manage patients with suspected or confirmed EVD. Under this system, there are 10 designated Regional Ebola and Other Special Pathogen Treatment Centers (RESPTC) in the United States, located in each of the 10 DHHS regions. These facilities have demonstrated the enhanced capabilities necessary to manage patients with EVD or other highly hazardous communicable diseases and serve as leaders for other facilities within their region [9]. In addition, facilities with high-level containment care capability are designated as 'Ebola Treatment Centers' (ETC). Other hospitals are designated as 'Ebola Assessment Hospitals' (EAH), and these facilities are able to manage and isolate persons under investigation (PUI) until a diagnosis of Ebola Virus Disease (EVD) can be confirmed or refuted. Finally, remaining hospitals ('Frontline Facilities') would receive training in order to improve their ability to isolate potential Ebola patients until they could be transferred to an EAH or ETC [10]. Within this network, the provision of patient care can be optimized, protocols practiced and improved, and research on investigational drugs and products streamlined. Although this system represents a vast improvement in hospital preparedness in the United States, isolation bed capacity remains limited.

Germany possesses seven HLCC facilities, four of which cared for EVD victims during the 2014–2016 West African outbreak. Some of these units have experience in treating patients infected with Marburg and Lassa viruses as well. Biocontainment units in Britain, France, Spain, the Netherlands, Norway, Switzerland, and Italy also successfully cared for expatriate patients during the recent EVD outbreak, and European nations have been pioneers in the development of HLCC doctrine [11, 12]. Finally, China, at the height of the SARS outbreak in 2003, constructed a 1000-bed infectious disease treatment facility equipped with engineering controls designed to ameliorate the risk of airborne transmission of the SARS-coronavirus [13]. Other nations in the region, such as Singapore and South Korea have since construction of HLCC facilities as well as purpose built surge hospitals, many of which provided care for patients with COVID-19 during the pandemic, which is ongoing as of this writing.

Background: Viral Hemorrhagic Fever (VHF)

The viral hemorrhagic fevers (VHFs) are caused by a heterogeneous group of viruses belonging to four taxonomic families and include:

- The Filoviruses, Ebola, and Marburg.
- The Arenaviruses, which can be divided into Old World (Lassa) and New World (Guanarito, Junin, Machupo, Sabia) agents, the latter causing Venezuelan, Argentinian,

Bolivian, and Brazilian Hemorrhagic Fevers, respectively.
- The Flaviruses, Yellow Fever, Dengue, Kyasanur Forest, and Omsk.
- The Bunyaviruses, Congo-Crimean Hemorrhagic Fever (CCHF), Rift Valley Fever (RVF), and a number of Hantaviruses which cause hemorrhagic fever with renal syndrome (HFRS; Hantaan, Dobrova, Seoul, and Puumala).

Yellow Fever has been known since at least 1647, is distributed throughout tropical Africa, Asia, and South America, and was the first disease shown, by Walter Reed, to be transmitted by mosquitos [14]. The remaining VHFs have, for the most part, been discovered within the last half century and remain quite limited in their geographic distributions.

Although the VHF viruses share certain microbiologic characteristics (all are lipid-enveloped, single-stranded RNA viruses) and derive their name from the fact that some (but not all) patients experience clinically significant hemorrhage, they produce a diverse array of clinical symptoms and vary widely in their virulence. While massive hemorrhage occurs frequently with New World Arenaviral infections, as well as with RVF, CCHF, certain Hantaviruses, and Yellow Fever, it occurs less frequently with infections due to the Filoviruses and rarely in Lassa infections. Renal failure is characteristic of HFRS and Yellow Fever, but otherwise rare. Rash is seen with Dengue, Lassa, and Filovirus infections, but not with most other VHFs. Icterus is prominent with Yellow Fever; tremors with the New World Arenaviruses; and deafness with Lassa. Pulmonary disease is prominent with Kyasanur Forest and Omsk, as well as with certain Hantaviruses.

In addition, laboratory findings vary considerably among the VHFs. New World Arenaviral infections characteristically cause a profound leukopenia, while HFRS patients often exhibit significant leukocytosis. Thrombocytopenia can be marked in most VHFs, but is usually not a prominent feature of Lassa Fever. These notable differences in presentation and symptomatology have implications for clinical care and infection control. The prodigious amount of vomiting and diarrhea seen in patients during the 2014–2016 EVD outbreak, coupled with the very low infectious dose and high quantity of viral particles within these bodily fluids, makes meticulous attention to personal protection imperative. Guidelines for the employment of such protection, as well as engineering and other controls, provide the basis for the remainder of this chapter.

It is important to note that the causative agents of most VHFs need be handled under Biosafety Level 4 (BSL-4) conditions in the laboratory [15]. Exceptions include Yellow Fever, RVF, and the Hantaviruses, which require BSL-3 precautions. Patients harboring any of these agents that present the risk of person-to-person transmission ideally should be managed under HLCC conditions. These agents would include the Hantaviruses, as well all of the BSL-4 agents except RVF, Kyasanur Forest, and Omsk viruses, which are transmitted to humans only via the bite of infected arthropods.

Facility Design

High-level containment care (HLCC) facilities include enhanced engineering controls with the goal of providing safe and effective care to patients while optimizing infection prevention and control procedures. Two consensus efforts have been conducted to develop recommendations for designing HLCC care units: a U.S. consensus workgroup met in 2005 in order to develop standards for the operation of BCUs, and a 2007 European Network for Highly Infectious Diseases (EuroNHID) project [7, 12]. However, formal standards for HLCC facility design features have not been established.

The design of a HLCC unit should serve to minimize nosocomial transmission of infectious diseases by establishing a contained clinical isolation unit capable of housing all facets of patient care. Hallmark HLCC engineering controls include care units that are physically separated from normal patient care spaces and maintained at negative pressure by independent air-handling systems. At least 12 air exchanges per hour in patient rooms are accomplished using dedicated exhaust systems with high efficiency particulate air (HEPA) -filtered effluent air. It is recommended that pressure status of patient care rooms be monitored with audible and visual alarms [16, 17]. Individual patient care rooms should have the equipment necessary to support critically ill patients, self-closing doors, and handwashing sinks [7].

It is important to have established zones for employee donning and doffing, storage of PPE, and staff shower-out capability [7]. Additionally, selection of nonporous and seamless construction materials is an ideal design component of HLCCs that both minimizes the risk of environmental contamination and maximizes the ability to clean surfaces when contaminated.

HLCC units should delineate high-risk areas (“Hot” or “Red” zones: patient room, laboratory), intermediate risk areas (“Warm” or “Yellow” zones: anteroom, decontamination area, waste processing, doffing), and low risk areas (“Cold” or “Green” zones: nurses station, clean supply room, staff egress changing area). Establishment of these designated zones guides healthcare worker flow as well as implementation of protocols for cleaning, packaging of waste or clinical specimens, and decontamination of medical devices, reducing the potential for contamination as personnel and devices move through the HLCC. Inclusion of laboratory

and capability to inactivate category A infectious substances which include the use of steam sterilization within HLCC units are also key features that help minimize the potential of transmission throughout the hospital [18, 19]. A double door pass through autoclave was identified as mandatory for HLCC unit through both consensus efforts [7, 11]. Implementation of telehealth strategies that enable communication with healthcare workers as well as provide a platform for remote patient assessment and safety observation is important in reducing the number of healthcare workers with direct patient contact, thus limiting risk.

Administration and Support Services

The intermittent and sporadic utilization of HLCC units necessitates interprofessional leadership. Ideally, a HLCC leadership team should possess a robust set of diverse skills to include expertise in infectious diseases and critical care, nursing, emergency management, industrial and environmental hygiene, research, laboratory, hospital administration, and public relations and communications This leadership team should meet regularly to strategize and define exercise objectives, plan educational efforts, promote research projects, and synchronize collaborative endeavors [20].

A robust activation checklist should be hardwired and exercised intermittently to ensure that departments can execute essential tasks assigned, and that necessary items can be obtained in a timely fashion. This checklist should address unit supplies, equipment, medications, and notification of departments and key individuals who will be involved in the activation of the unit and the care of the patient(s). Use of a readiness assessment tool can be helpful in ongoing unit validation over time (Fig. 21.1).

Numerous communication strategies are adaptable for use by HLCC team members. An electronic alert system can be used to notify the HLCC team of exercises and activation. An email distribution list can be used for less urgent information sharing. In order to organize the response for arriving patients, a modified Hospital Incident Command System (HICS) can be utilized and the Incident Commander (IC) can support HLCC leaders in completing the Activation Checklist. Moreover, the IC can facilitate coordination among the multiple agencies often involved in air and ground transport of patients to the HLCC unit.

Although each facility may wish to tailor the composition of the HICS team to their own particular needs, and each situation may require adjustment, key team members would typically include logisticians to replenish PPE supply levels and address waste management issues, a public information officer (PIO) for internal and external communications, medical technical specialists to include infectious disease physicians and nurse leaders to manage the clinical care of the patient and staffing within the patient care unit, a laboratorian to address testing logistics and specimen transport, a clinical research expert to facilitate the use of experimental therapies if available, a nurse concierge or other dedicated individual to support family needs, and a behavioral health expert to address staff well-being as well as the psychological and emotional needs of patients and families.

The PIO serves as the point person to respond to media requests, including monitoring and responding to social media posts. Internal messaging within the organization is a very important strategy and should be done prior to release of any external information when possible. Internal messaging may be directed at administration, faculty and staff, and also patients (inpatients and outpatients) and their family members. Press conferences with infectious diseases experts and others involved in patient care should be held to provide timely updates. Establishing an information line staffed by the state or local health department can be useful to answer questions and provide education to the community. Close alignment between public health and healthcare experts is essential for consistent messaging to the public.

During activation, a concierge nurse may prove helpful in the support of families of patients. This individual can assist by making advance contact with family members and arranging services such as airport transportation, accommodations, and meals. They can also serve as the liaison with family in the coordination of meetings to discuss the status of the patient, media information, and various other details. Pastoral Care staff should be available upon request during activation. These personnel resources are pivotal to success and should be engaged in exercises whenever possible in advance of activation.

Staffing: Nursing

The HLCC facilities in the United States that admitted patients infected with Ebola Virus Disease (EVD) all developed teams primarily composed of nurses able to provide skilled and effective patient care within their isolation units. Recruiting and retaining qualified nursing staff willing and able to provide care for patients under emotionally and physically demanding HLCC conditions is the cornerstone for building a successful team. The staffing model must take into account the need for specialized nurses to provide quality care. The virulence of the disease in question, its mortality rate, the advanced levels of PPE required, and the propensity for infected patients to require complex interventions all influence the profile of staff selected to care for patients with VHF or other highly hazardous communicable diseases.

The composition of the HLCC nursing team should reflect these needs. The centers in the United States that provided

NBU readiness Status	
Date	
Person filing report	
NBU Readiness Status	

How to Assign Readiness Status
Any critical factor that is not ready and cannot be fixed within 4 hours is RED
Any critical factor that is not ready but can be fixed within 4 hours is YELLOW
All critical factors operational is GREEN

Notify NBU Leadership on call if NBU status is Red or Yellow

Weekly Nebraska Biocontainment Unit Operational Readiness Report Card					
Readiness Factor	**Ready**		**Inoperative or malfunctioning Readiness Factor can be rectified within 4 hours**		**Notes**
	Yes	**No**	**Yes**	**No**	
NBU is in use for non-NBU reasons					
Autoclave #1 is operational and has passed weekly verification					
Autoclave #2 is operational and has passed weekly verification					
NBU PAPR Level PPE is stocked with enough for 7 days for 1 patient					
NBU High Level PPE is stocked with enough for 7 days for 1 patient					
Staffing schedule for NBU/NQU and coordination with nursing staffing resources					
Omnilert NBU team information is updated (current NBU staff)					
NBU Medical and Nursing leadership is on call					
Essential utilities are functional a. Water b. Lights c. Negative Air Pressure d. Medical gas gauges for pressure					
The biosafety cabinet is in the unit and/or can be ready for verification by assigned personnel					
Synergy software and zoom are operational and functional					
The NBU communication equipment is operational/ functional a. computers b. speakers c. neurons d. printers/fax machine e. phones					
The clinical monitoring equipment is functional					
The Omincell is stocked and functional according to patient population and level of care needed					
The NBU is stocked with age appropriate supplies (Adult or Pediatric)					

Fig. 21.1 Nebraska Biocontainment Unit (NBU) Operational Readiness Report Card. (Adapted from Johns Hopkins Readiness Scale) [83]

care for EVD patients each required that a percentage of their core nursing staff possess critical care experience with some institutions relying solely upon critical care nurses to staff their units. In addition to critical care experience, it is essential to have nurses on the core team who have expertise in infectious diseases and have expressed an interest in caring for patients with highly hazardous communicable diseases [21]. The success of the nursing staff starts with a robust selection process. Utilizing a formal interview process to determine qualifications and interest has been proven to be an effective method of selecting staff. Once the interview is complete, the nursing leadership should contact the employee's current manager to discuss their clinical skills, teamwork skills, adaptability, dependability, and critical thinking skills.

When staffing a unit that is only activated intermittently, an important consideration involves creating a process by which staff members can designate their availability on any given day. This can be accomplished in a multitude of ways; however, maintaining a consistent process is essential to ensuring staff availability when needed. As the provision of nursing care must occur 24 hours a day, 7 days a week, it is important that a schedule be created that accounts for all times. One way to achieve this is to mandate on-call shifts for dedicated staff. The on-call nurses are required to be at the Unit within 60 minutes of being notified of activation. Another option is to have each staff member fill out their availability and maintain a balanced schedule several weeks in advance. This allows staff members a level of autonomy to self-schedule.

Considerations for creating a nursing staff matrix include the design of the unit, the waste management strategy, the disease being treated, the acuity of the patient, the level of personal protective equipment (PPE) required, and the time that could be spent in the PPE [20, 21]. An important consideration is the need to minimize the number of staff that enter into the patient care area. The ability to utilize nursing staff in multiple roles can facilitate effective infection control by minimizing the footprint within potentially contaminated areas. In this effort, nursing staff become responsible for tasks that would typically be assigned to ancillary services within the standard hospital system, including routine cleaning and environmental services, phlebotomy, coordinating care needs, and unit clerk roles.

Consideration must also be given to the nurse-to-patient ratio necessary to provide safe care to a patient with VHF. The number of staff members required for a standard 12-hour nursing shift must take into account the time limitations imposed on each staff member due to the use of advanced PPE. When providing the level of intensive care that these patients can require in addition to wearing PPE, it is necessary to adjust shift times and staffing ratios [22]. The staffing matrix utilized within hospitals that successfully cared for EVD patients differed significantly from standard staffing ratios. Within the Nebraska Biocontainment Unit, six staff members were present on a day shift and five on the night shift (usually 3 nurses along with respiratory therapists and/or patient care technicians). Healthcare staff was scheduled for 12-hour shifts which were broken up into 4 hour blocks to allow for the limitation of not wearing PPE for greater than 3–4 hours at a time. Designation of roles for each staff member on each shift can clarify expectations and ensure consistency within each role. The use of an autoclave for waste processing may necessitate the inclusion of a dedicated staff member to operate the machine [23]. The Serious Communicable Diseases Unit (SCDU) at Emory University utilized 2–3 nurses to staff the Unit at all times when occupied, and it was recommended that nurses remove ('doff') PPE every 4 hours to allow for personal needs and a break. At the highest level of PPE and patient care, three nurses were working in the SCDU at one time, in 12-hour shifts. They rotated in 4-hour shifts between the patient room, the anteroom, and the nursing desk with each having designated responsibilities [24].

Within each treatment facility there are unique circumstances which will dictate the most efficient and safe nursing staffing practices. It is important to consider both staff safety and patient safety when determining which guidelines will be used to operate a unit caring for patients with VHF or other highly hazardous communicable disease. Nurses that join these teams must be individuals able to operate outside their normal routine by utilizing critical thinking skills, flexibility, and autonomy. These nurses are required to take responsibility for a wide array of clinical and nonclinical tasks and perform these in demanding clinical situations, which are skills that require practice, exceptional communication, and teamwork.

Staffing: Physicians

Caring for patients with highly hazardous communicable diseases is a true multidisciplinary effort, and choosing and maintaining an effective physician team illustrates this concept well. Each center should tailor their physician team to fit their needs and the culture of the facility. In general, Infectious Diseases or Critical Care medicine specialists have often led physician teams in the biocontainment setting; however, this may not be appropriate in every facility. Infectious Diseases specialists monitor and manage infectious complications and coinfections and oversee the administration of antimicrobial agents, including experimental products. Specialists in Critical Care medicine are an important asset in the care of patients with VHF, since some of these patients may have critical illness and require ICU-level care, including mechanical ventilation, vasopressors, and

other supportive care measures [25]. Since invasive procedures are often necessary as well, it is critical to ensure that the physician team includes individuals who are experienced and comfortable performing these procedures. This skillset should be assessed by direct consultation with these physicians, since some may not feel comfortable performing invasive procedures in a high-risk isolation environment. Training and drills involving critically ill patients, including performing invasive procedures in PPE, are an integral part of skill assessment and maintenance for the physician team.

It is also important to involve other groups of physicians who may be needed in the care of a patient with VHF. Pediatricians and Pediatric Intensive Care Specialists should be identified in the event that a pediatric patient must be cared for under HLCC conditions. Similarly, obstetricians are an important part of the physician team since it is possible that a pregnant and/or laboring patient with suspected or confirmed VHF will need care in the isolation setting. Nephrology specialists have been involved in the care of patients with VHF who developed renal failure, especially those who required dialysis [26]. Relationships with other physician groups, including but not limited to Surgery, Emergency Medicine, General Internal Medicine, and Pathology, should be established as necessary in case consultative needs arise. It is important to note that some physician consultations can occur via telemedicine without the physician entering the patient care room. This serves to limit the number of physicians required to directly evaluate the patient at the bedside in order to decrease the possibility of exposure.

When considering physician staffing models, it is important to note that physicians providing care to patients with EVD or other VHF in the biocontainment setting may be unavailable for prolonged periods of time. This makes the ability to provide clinical care to other patients very difficult. Thus, it is important to consider backfilling other clinical responsibilities in order to provide dedicated time to the complex processes of donning and doffing PPE, performing procedures, and other aspects of biocontainment care. The most appropriate way to provide 24 hour on-call coverage for patients with VHF must be evaluated, and this will vary depending on the current call structure in the medical facility [27].

The involvement of physicians in training (fellows, residents, etc.) in the care of patients with VHF in the biocontainment setting has been discussed, and generally it is felt that trainees should not be compelled to provide direct care for patients with VHF as a requirement of a clinical rotation due to excessive risk. However, physicians-in-training have entered the biocontainment setting on a volunteer basis to observe and assist in the management of patients with VHF via the telemedicine system, which provides educational opportunity without excessive risk.

Personal Protective Equipment (PPE)

The use of PPE in clinical care to prevent the transmission of infectious diseases is not a new concept, yet in the context of viral hemorrhagic fever PPE became the topic of much debate during the 2014–2016 EVD outbreak. Facilities who were tasked with providing care to infected individuals with EVD faced multifaceted challenges related to the selection, procurement, and proper utilization of PPE, along with changing guidelines.

Personal protective equipment is worn to minimize exposure to infectious material and to protect the skin and mucous membranes from exposure to pathogens. PPE reduces, but does not eliminate, the risk of skin and clothing contamination with pathogens among healthcare personnel [28]. Examples of PPE include items such as gowns, gloves, foot and eye protection, respirators, and full body suits. The Occupational Safety and Health Administration (OSHA) requires that employers protect their employees from workplace hazards that might cause injury. Controlling a hazard at its source is the best way to protect employees. Depending on the hazard or workplace conditions, OSHA recommends the use of engineering or work practice controls to manage or eliminate hazards to the greatest extent possible [29]. Installing negative pressure air handlers to place a barrier between the hazard and the employees is an engineering control; changing the way in which employees perform their work is a work practice control. When engineering, work practice, and administrative controls are not feasible or provide insufficient protection, PPE must be utilized to protect healthcare workers who are providing care to patients with infectious diseases.

There are many variations of PPE available for purchase and selecting the best version for the environment in which care must be delivered can be daunting. The versions of PPE used in HLCC units differed in the individual pieces used; however, the guiding principles remain the same. For healthcare workers caring for patients with EVD, PPE that fully covers skin and clothing and prevents any exposure of the eyes, nose, and mouth is recommended to reduce the risk of accidental self-contamination of mucous membranes or broken skin [30]. Varying levels of PPE are appropriate for use based upon the acuity of the patient, the volume of infectious bodily fluids (blood, vomitus, diarrheal stool) present, and the potential for aerosolization of these fluids [31]. Providing this level of protection often requires that many pieces of PPE be worn; this can lead to an increased risk of fatigue and overheating.

Centers in the United States that treated patients with EVD in 2014 utilized varying levels of PPE based on this stratified risk assessment [23, 24, 31]. In the Nebraska Biocontainment Unit (NBU), the first level of PPE used

Fig. 21.2 First level PPE worn in the Nebraska Biocontainment Unit (NBU) while caring for patients with Ebola in 2014

Fig. 21.3 PAPR level PPE worn in the Special Communicable Diseases Unit (SCDU) while caring for patients with Ebola in 2014

completely disposable and the second level incorporated the use of a powered air purifying respirator (PAPR). First level PPE consisted of fluid impervious Association for the Advancement of Medical Instrumentation (AAMI) level 4 gown, N95 respirator, surgical hood, face shield, knee high fluid impervious boots, three pairs of gloves, and the addition of a second splash resistant apron as needed. (Fig. 21.2) The second level of PPE consisted of fluid impervious coveralls, inner boot liners, outer boot covers, three pairs of gloves, and the PAPR hood with accompanying belt and blower motor. In the Emory University Serious Communicable Diseases Unit (SCDU), varying levels of PPE based upon the risk assessment consisted of a completely disposable ensemble as well as a PAPR ensemble. The disposable PPE included a coverall, apron, booties, double gloves, face shield (goggles if face shield not available), and a surgical mask. The PAPR level of PPE was comprised of a coverall, double gloves, booties, an apron and the PAPR hood (Fig. 21.3). The equipment available for purchase through each institution may have differed; however, making selections based upon disease transmission and risk factors related to patient care rather than brand-specific products helped to ensure healthcare worker protection.

The donning and doffing procedures require both vigilance and attention to detail. While PPE is effective at decreasing exposure to infected bodily fluids among healthcare workers, these healthcare workers are still at risk if this equipment is not removed in a manner that prevents exposure [32]. Detailed guidance with the correct order of donning and doffing equipment should be readily visible on a chart posted within the patient care area. The process used to don and doff PPE should be followed exactly by all personnel every time it is performed and should be guided by a checklist. All staff members, regardless of title or position, are expected to hold one another accountable for adhering to the policies and procedures, including the appropriate use of PPE [33, 34]. The donning and doffing process should incorporate the use of a donning partner who assists the healthcare worker in appropriate placement of PPE, and a doffing partner who assists the healthcare worker in removing their PPE and a trained observer who monitors the doffing process. This doffing partner assists the healthcare worker as needed

to ensure that complex steps in the process are completed with proper technique. The physical exhaustion and emotional fatigue that can accompany the provision of care for patients infected with VHF may further increase the chance of an inadvertent exposure to bodily fluids on the outside of the PPE when performing the doffing process [32]. The CDC also recommends the presence of a trained observer when performing the doffing process [30]. The trained observer is available to provide immediate feedback to ensure that all steps are performed in the proper order and technique and intervene if there is any inadvertent contamination of the healthcare worker. The doffing process can be complex and is considered to be a vulnerable area in which the healthcare providers may be unintentionally contaminated. Simulation studies conducted using donning and doffing scenarios have shown high rates of self-contamination during the doffing process, especially during the removal of the gown and gloves, emphasizing the need for stringent protocols and supervision during this process [28].

Transportation

The safe transport and prehospital care of patients with EVD or other highly hazardous communicable diseases requires enhanced infection control practices, which necessitate sound administrative policies, work practices, and environmental controls implemented through focused education, training, and supervision [35]. HLCC hospitals require partner emergency medical services (EMS) capable of ensuring the safety of the HLCC transport medics and the public through implementation of infection control practices, policies, and procedures [9].

The ambulance environment is defined by confined space with limited air handling and care is provided with reusable medical devices in acute situations. Emergency vehicles have many compartments, shelves, patient care beds, and other high touch areas that are difficult to clean. Ambulance cleaning protocols have been established, but environmental contamination with nosocomial organisms continues to be documented [36–38].

A variety of specialized approaches have been established for HLCC transport. These include specialized truck and trailer ambulances (used in Germany), HEPA-filtered ground ambulance positioned aboard a Hercules C130 aircraft (Sweden), road ambulances with stretcher-based isolators (Italy), and road ambulances draped to minimize contamination potential (United States) [39, 40]. HLCC transport medics should receive enhanced education and training on modes of transmission, the availability of vaccines, pre- and postexposure prophylaxis, and treatment modalities. Competency-based training has also been recommended to develop and maintain PPE donning and doffing competency [32, 35, 41]. The transporting HLCC ambulance is commonly supported by an external transport team with extra supplies which facilitates communication with external support agencies (which may include law enforcement, airport operations, public health, and emergency management) and provides guidance for clinical decision making when required [35, 39]. Transition of the patient from the HLCC transport team to the HLCC unit team should be a highly scripted event, rigorously tested through advanced planning and exercise [35].

Following transition of care, the emergency vehicle should be decontaminated. HLCC facilities have utilized different decontamination methods; however, the general principles of surface cleaning performed by personnel in PPE followed by appropriate waste disposal are maintained. Vaporized hydrogen peroxide, chlorine dioxide, and ultraviolet light have all been used or proposed as adjunct decontamination strategies for emergency vehicles [40, 42, 43].

Clinical Care

The clinical care of patients with VHF is largely supportive, and the ability to provide supportive care varies depending on the capabilities of the individual healthcare facility [44]. Generally, healthcare centers caring for patients with VHF should be ready to provide supportive care and additional aggressive intensive care modalities when necessary and available. Up until recently, little information regarding these care modalities was available given that outbreaks of VHF occurred in resource-limited settings. However, during the 2014–2016 EVD outbreak, patients who were managed in resourced settings in the United States and Europe where aggressive supportive care was available had a much lower mortality rate when compared with that noted in previous reports from Africa [45].

The clinical presentation of VHF may vary according to the etiology, the wide range of clinical severity, and multiple patient factors. It is important to note that the clinical presentation of VHF is nonspecific, therefore it is important to evaluate patients with possible and confirmed VHF for other causes of symptoms, notably including malaria if the patient has a history of travel to an endemic area.

The delivery of aggressive supportive care requires intravenous access, and the availability of this depends on the resource limitations of the healthcare facility. In resource-limited settings, only peripheral IV placement may be feasible, whereas in resourced settings, central venous catheters (CVCs) are generally utilized. The placement of a CVC also enables healthcare workers to obtain blood samples without repeated venipuncture, reducing the risk of sharp injuries and exposure to bodily fluids.

Antipyretic agents have been utilized to manage fever in patients with VHF. Oral rehydration solutions and/or

intravenous fluids may become necessary given the profound volume depletion that can result from vomiting and diarrhea. Pharmacologic controls such as antiemetic and antidiarrheal medications have been utilized to control nausea, vomiting, and diarrhea. Physical controls such as emesis bags and fecal management systems have been employed as well, since controlling these secretions is an important infection control modality in the healthcare setting.

The monitoring and replacement of electrolytes is also an important aspect of supportive care in patients with VHF, since significant electrolyte disturbances have been observed [46]. Nutritional support is often necessary, and when available, total parenteral nutrition has been utilized in patients with anorexia, nausea, and vomiting.

Patients with respiratory symptoms may require supplemental oxygen. Bleeding complications can be treated with blood products and correction of coagulopathy. Cases of encephalitis have been observed, and patients with agitation may require sedating medications. Patients with VHF may also develop secondary infectious complications including bacterial sepsis, and these infections may be managed with antimicrobial therapy, which is often empiric since the availability of blood cultures may be limited [47].

Patients with VHF may present with, or may progress to, critical illness involving multi-organ failure and may require advanced life support including mechanical ventilation and dialysis. These interventions were utilized during the care of patients with EVD in the United States and Europe during the 2014–2016 outbreak [45]. In patients with respiratory failure, airway management was accomplished via intubation by rapid sequence induction and video laryngoscopy [27, 47]. Renal failure was managed with continuous renal replacement therapy (CRRT) in some centers. Vasopressors have been utilized for blood pressure support in patients with VHF. An assessment of the use of other advanced cardiac life support measures like cardioversion and chest compressions should be discussed by healthcare facilities preparing to care for patients with VHF, with consideration of the potential benefits to the patient and the risks to healthcare workers.

Many experimental therapeutic agents were used in the treatment of patients with EVD during the 2014–2016 outbreak; however, as of this writing, there are now 2 FDA-approved drugs for EVD: Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn; a mixture of three monoclonal antibodies) and Ebanga (ansuvimab-zykl; a human monoclonal antibody) [48]. Both of these agents were shown to reduce mortality from EVD in a randomized controlled trial [49]. Convalescent serum has been used in the management of patients with EVD; however, one study did not demonstrate a significant improvement in survival in patients administered convalescent plasma [50]. There are no FDA-approved therapeutic agents for Marburg virus disease. Ribavarin has been shown to be effective in treatment of Lassa Fever [51].

The hospital discharge of patients with VHF is a complicated process and is dependent on many factors, including resolution or significant improvement of symptoms along with correlative virologic laboratory data. Consultation with local and state health authorities and the CDC and/or WHO should occur to determine the recommended disease-specific discharge criteria for patients with VHF.

Laboratory Support

The monitoring of laboratory parameters is a vital part of providing supportive care to patients with VHF, since these patients may have significant laboratory abnormalities on which clinical management is based. This is especially important in patients who are critically ill who require interventions like dialysis where laboratory parameters must be evaluated frequently and closely monitored. The ability to perform laboratory testing in a safe and effective manner requires significant planning prior to implementation.

As a first step, the clinical care team should discuss which laboratory studies are necessary in order to care for the patient with VHF. This potential testing menu should be communicated to laboratory leadership, who should assess each test to determine if the sample can be processed safely. It is essential that the clinical care team has access to a menu of available laboratory tests and detailed information on the collection of specimens, including any special media required or recommended collection times.

Determining the location of the laboratory should take into account the capabilities of the facility. If feasible, laboratory testing should be performed in close proximity to the site of clinical care to eliminate the need for specimen transport, thereby increasing safety and decreasing turnaround time [19, 52]. Point-of-care testing is desirable, but is often not comprehensive and additional testing may need to occur in the core laboratory or a special containment laboratory. It is important to note that some special containment laboratories may not have the equipment necessary to perform routine laboratory studies such as complete blood counts or metabolic panels, so these tests may need to be performed in the core laboratory if point-of-care testing is not available. A careful risk assessment should occur prior to implementation of any testing in order to minimize risk to the instruments and most importantly the laboratory staff [19].

Viral load monitoring is helpful in patients with VHF, as the degree of viremia may predict the initial severity of disease and provide information on progression of disease during the treatment phase. The viral load is generally a component of discharge criteria as well [53, 54]. The transport of samples to the appropriate reference laboratory for viral load testing is a complicated process, and significant preplanning is necessary in order to facilitate this.

Waste Management

The importance of stringent infection prevention and control, including environmental infection control, is heightened when providing HLCC for patients with VHF due to factors such as low infectious dose and potentially large volume of body fluids containing high concentrations of viral particles. These elements contribute to the significant, yet manageable, hazards posed by such care. Perspectives and waste management strategies of two HLCC facilities have been reported [18]. Robust packaging and disinfection procedures were employed by these two facilities in order to process EVD-associated solid and liquid patient waste, contaminated patient linens, healthcare worker PPE and linens, contaminated medical devices, and other general medical waste.

Waste, linens, medical equipment, and other items potentially contaminated with pathogens such as Ebola, Lassa, Marburg, and select other VHFs are categorized as Category A Infectious Substances by the United Nations and US Department of Transportation's Hazardous Materials Regulations [55]. Category A Infectious Substances require enhanced packaging and labeling along with security plans in preparation for transport [56]. Materials that are sterilized by autoclaving or incineration are not required to be packaged and shipped as Category A Infectious Substances.

The quantity of waste generated through HLCC is significant with reports of over 1000 lbs. of waste generated per patient [57]. Management of such large quantities of infectious waste requires scalable strategies for packaging, storage, and security. Solid waste disposal strategies include autoclaving and incineration. It is important to maintain autoclave validation logs to ensure appropriate function. Several strategies have been employed for the transport of waste from the patient care room, including double bagging of waste and disinfecting the outside of waste bags prior to transport. Storage in waste holding containers may be necessary while awaiting transport to the autoclave or incinerator. According to current recommendations, liquid waste can be safely disposed off in the sewer system. However, during the 2014–2016 Ebola outbreak, some facilities utilized pretreatment strategies with a hospital grade disinfectant prior to disposal of liquid waste [18]. Fluid solidifiers were also used at some facilities in order to dispose off liquid waste as solid waste to reduce hazards associated with liquid waste handling. Waste should only be handled by trained individuals in full PPE [58].

Environmental cleaning during and after the care of patients with VHF is an important part of protecting healthcare workers, as well as other patients in the facility by maintaining the highest infection control standards. Environmental cleaning for many VHFs, including Ebola, should only be performed by trained individuals, and full PPE should be worn at all times during this process. Daily cleaning of HLCC facilities generally consists of surface cleaning with an EPA-registered disinfectant approved for use against non-enveloped viruses [59]. The terminal cleaning process varies by facility, but generally consists of disposal of waste followed by surface cleaning with a hospital grade disinfectant and disinfection of medical equipment. Some facilities utilize a final decontamination step involving ultraviolet germicidal irradiation or vaporized hydrogen peroxide [18, 60]. Cleaning and disinfection processes should be monitored and documented by a trained infection control expert using standardized processes to ensure compliance with all procedures.

Care of the Deceased

The remains of a patient with Ebola Virus Disease (EVD) are considered highly infectious. It is important to remember that although the patient is deceased, the viral load may remain very high, and body fluids may remain infectious for an extended period of time postmortem [61]. There is significant risk for those who are handling the body if proper procedures and barriers are not employed. Preparing the body for transportation to the mortuary must be done by trained staff in the patient care room as close to the time of death as possible [62].

When providing care for the deceased in the United States, it is most likely that these patients will be in a hospital setting and more stringent controls can be implemented. In addition to federal laws and guidelines that apply to mortuary workers, mortuary practices may also be subjected to a variety of state, tribal, territorial, and local regulations [63]. CDC recommends close collaboration with public health officials in the state or local jurisdiction, as well as with the licensed funeral director who has agreed to accept the bagged remains, to safely implement each step of the process [62]. The presence of a memorandum of understanding (MOU) with key mortuary care partners can facilitate safe and timely transfer of the remains of deceased patients. It is beneficial for any institution that may provide care for patients with VHF to have an MOU in place with a local mortuary service, crematorium, or cemetery. Mortuary care agencies designated for EVD response should be trained and evaluated for infection control practices as the majority of mortuary care providers report receiving no or little infection prevention training [64].

The highly infectious nature of the remains of a deceased victim of EVD demands the use of increased protection for the healthcare worker. The recommended PPE for handling such remains includes a powered air purifying respirator (PAPR), fluid impervious coveralls, double gloves, and use of an outer apron [30]. Adequate staffing during the care of the deceased is essential for safe execution of the procedures. The patient remains are first prepared and packaged within the patient room (hot zone), transferred out into the hallway

or anteroom (warm zone), and out of the patient care area (cold zone) for transport to final disposition [23]. The body of the deceased should not be washed or embalmed, medical devices should remain in place, and healthcare workers should not attempt to remove them. Autopsies should not be performed unless specifically directed by the state health department and only after consultation with the CDC and state health department officials [62]. Patient remains should be securely contained within the patient care area. The remains should be packaged using established guidance, which currently includes the use of multiple layers [62]. The first layer to form a protective barrier is a standard hospital issued mortuary bag, followed by a heat sealable chlorine-free material and final securement is achieved by the use of a heavy duty morgue bag. Each protective barrier that is added should be thoroughly disinfected before moving to the next step and again before being transported out of the hot zone. The patient remains should be transferred out of contaminated areas with special attention paid to minimizing the potential for environmental cross.

When the remains have been safely processed out of the patient care area, the transport team will assume care of the deceased. The composition of the transport team will vary; however, it is important to consider state requirements for chain of custody when developing protocols. Personnel serving on the transport team may include the servicing mortuary staff, state medical examiner, infection preventionists, and law enforcement personnel. Cremation is recommended [62]. Upon completion of cremation, the ashes may be returned to the family of the deceased as the risk of transmission of infection is no longer present [62]. When providing care for the deceased patient, the utmost level of dignity and respect for the deceased patient and his/her family should be maintained.

Evaluation of Persons Under Investigation (PUI)

During the 2014–2016 Ebola outbreak, many healthcare facilities were faced with caring for patients who presented with symptoms compatible with EVD and met certain epidemiologic criteria as defined by the CDC [65, 66]. These patients were termed ‘Persons Under Investigation’.

In order to properly address quick isolation and care of persons under investigation for EVD or other VHF, a travel and symptom triage tool is needed at check in areas within the healthcare environment [67]. The tool can be a paper instrument with simple questions related to travel history and symptoms. Alternatively, a more robust tool can be built within the electronic health record (EHR) to assess presenting symptoms and then travel history, identifying specific countries and providing decision support prompts that then are correlated with CDC case definitions. Alerts then appear within the EHR to notify caregivers of additional precautions required (e.g., give patient mask to wear, notify Infectious Diseases experts, isolate patient in a negative pressure room, etc.). Whatever tool is used, it must be agile and quickly adapted to meet ever-changing highly hazardous communicable disease threats.

Once a patient screens positive for travel history and symptoms matching the CDC case definition, a process map can be used to provide step by step guidance to healthcare providers using a standardized approach. A protocol should be created for the Emergency Department, as well as for other ambulatory locations (outpatient clinics, laboratories, radiology, etc.) where patients may present with symptoms. A positive screen result for epidemiologic risk and signs or symptoms consistent with viral hemorrhagic fever should trigger escalating personal protective equipment use and movement to a designated isolation area. The choice of isolation area is determined by each individual facility. A predetermined area within the Emergency Department can be utilized since this is often the point of entry for patients [68]. Notification of appropriate personnel should then occur, including Infection Control professionals, area leadership, a designated Infectious Diseases physician, public health officials, and the laboratory.

Once the patient is isolated, security should be summoned to control the area and to maintain a log of staff entering the isolation zone. Staff in PPE then perform an initial assessment of the patient and obtain additional details and history, including confirmation of epidemiologic history. Specialists may be called in to assess the patient as well, or alternatively, this may be accomplished via video technology in an effort to limit the number of individuals who enter the room. Once the exam is completed, a consultation with local public health and CDC should be conducted and testing requirements should be determined. It is important to ensure that the appropriate collection methods are utilized; these should be clarified with the public health laboratory prior to specimen collection [69].

A PUI may require imaging studies. Bedside studies are preferred from an infection control perspective but are not comprehensive, and additional studies that cannot be performed at the bedside may be necessary. Robust predefined plans for patient transport to cardiac catheterization, CT, MRI, and endoscopy should be developed. In addition, a PUI may require surgical intervention. A predefined plan should be created, which outlines the preoperative timeout briefing, intraoperative care considerations to include type of PPE to be used by the surgical team, instrument handling and care, recovery of patient in the operating room, and subsequent cleaning and disinfection of the space, instruments, and waste management [70]. Although there are no formal guidelines for the management of patients with suspected VHF in the operating room, there is information available from the American College of Surgeons, who recommends against

elective surgical procedures, but states that emergency operations can be considered [71]. Development of these processes along with defined drills involving the operating room staff will enhance the capability to successfully navigate through care of PUI's in need of surgical care.

Special Populations

Children differ from adults in myriad ways which potentially impact their vulnerability to the viral hemorrhagic fevers and present challenging management issues. Developmentally, children are likely to be frightened by the sight of caregivers in PPE and may flail, tug, and pull at such equipment, creating additional risk for these caregivers. Similarly, young children are unable to cooperate with their management, and the usual pediatric paradigm of family-centered care, which would enlist parents in assisting with such care, may be prohibitively hazardous in the setting of transmissible VHF such as Ebola, Marburg, or Lassa.

From a policy perspective, multiple factors complicate the care of children. Certain medications that might be used in adults are contraindicated in children, are unavailable in liquid preparations, or are unfamiliar to pediatric practitioners. Similarly, the use of investigational drugs may be more problematic in children. Finally, pediatric-specific equipment, doctrine, and HLCC beds are often lacking.

Despite these apparent disadvantages, children have been consistently underrepresented among Ebola victims. In the 1995 Kikwit outbreak, children accounted for 27 of the 315 cases (9%), despite constituting 50% of the Zairean population [72]. Similar findings were obtained during the 2000 outbreak in Gulu, Uganda, where children represented 20 of the 218 cases (9%) [73]. Moreover, these children had a case-fatality rate of 40%, not dissimilar to the rate among adults. Finally, in a study performed in Guinea during the 2014–2016 outbreak, 147 of 823 cases (18%) occurred in children, again despite the fact that children constitute 50% of the population of Guinea [74]. While these findings raise the possibility that children may be less susceptible to infection with Ebola (and, perhaps, with other VHFs), it is likely that this diminished susceptibility derives mainly from social factors; young children are less likely to function as primary caregivers to dying family members, are thus less likely to have contact with body fluids, and are less likely to participate in intimate funereal preparations.

Management of the pregnant or laboring patient with VHF is similarly problematic; maternal and infant mortality are extraordinarily high in virtually all of the VHFs, although maternal survival has been reported following fetal loss associated with Ebola infection and uterine evacuation has been shown to improve survival of pregnant women with Lassa fever [75, 76]. Fetal and neonatal loss among women with Lassa fever has been reported to be as high as 87% and there are no reports of neonates born to Ebola-infected mothers surviving beyond 19 days [76, 77]. Vertical transmission of Yellow Fever appears to occur very rarely and few reports of affected pregnant women exist for the remaining VHFs [78]. In light of this paucity of information, it is difficult to make specific recommendations for the management of the pregnant woman with VHF. Nonetheless, meticulous planning must be undertaken by facilities that might be called upon to care for pregnant VHF patients. Such planning should address, among others, questions regarding where and when delivery should occur, what equipment is required, and how complications like bleeding should be managed.

The final question raises what is perhaps the most vexing issue associated with the care of newborns and childen with contagious VHFs; which is under what circumstances might parents or other nonmedical caregivers be permitted to remain at the bedside of an infected child. Parents might assist in reducing the anxious flailing of a toddler, thereby diminishing risk to HCWs. They are also afforded the opportunity to participate in family-centered care, thus emotionally benefitting both parent and child. These considerations must be balanced, however, against the reality that parents then become, in a sense, additional patients, requiring assistance in donning and doffing PPE and running the risk of inadvertent breaks in containment by non-skilled individuals. An expert panel met to discuss these considerations, although the subject is likely to remain controversial [79].

Maintenance of Preparedness

Training healthcare workers in the provision of care to patients with VHF presents many challenges. One of the challenges involves maintaining readiness and keeping team members engaged when these specialized patient care areas are not activated. The implementation of a consistent and structured training schedule facilitates staff engagement by incorporating activities of varying intensity. Incorporating complex functional exercises, tabletop exercises, skill focused drills, competency evaluations, and team building activities builds a strong foundation from which the patient care team can further develop. Educational sessions on highly hazardous communicable diseases may also be helpful to maintain readiness and interest. Developing an annual training calendar that is available to team members in advance sets the expectation for the team members and also helps to minimize scheduling conflicts for required attendance. Bringing healthcare workers together to train regularly enables the formation of a cohesive functional team rather than a collection of individuals.

When considering the provision of intensive care to patients with EVD, the challenges are heightened. These patients often require invasive interventions which involve

the skills of anesthesiologists and critical care physicians, as well as nurses proficient in managing the ongoing care of critically ill patients. The interventions must be implemented while wearing advanced levels of PPE, thus potentially limiting the dexterity of the providers. Training regimens for healthcare workers should allow for the development and refinement of specific policies and procedures, addressing critical issues like donning and doffing PPE, waste processing, the insertion of central venous catheters, endotracheal intubation, the use of continuous renal replacement therapy, Advanced Cardiac Life Support (ACLS) and Pediatric Advanced Life Support (PALS) plans and protocols, and the plan for extraction and provision of care for a provider who has a medical emergency in the patient care area. Providing routine training for key personnel ensures the opportunity for healthcare workers to gain confidence in their ability to perform the procedures, as well as to build a firm foundation of processes for many aspects of care [22]. Developing and exercising detailed policies to guide cares within the unit, as well as maintaining an expert staff, are key components to maintaining preparedness.

Training ensures that healthcare workers are knowledgeable and proficient in donning and doffing PPE before caring for a patient with VHF. Comfort and proficiency when donning and doffing are only achieved by repeatedly practicing correct use of PPE. When providing training and assessing competency in PPE, healthcare workers should perform required duties while wearing PPE. This could include inserting an intravenous device, assisting with perineal care after an incontinent episode, processing waste in the patient care area, or charting an assessment. Training should be customized for the intended audience and effectively relay essential information. Healthcare workers who are unwilling or unable to fulfill these requirements should not be included in the patient care team.

In 2019, the FDA approved the first vaccine for the prevention of Ebola virus disease [80]. The rVSVΔG-ZEBOV-GPEbolavaccine(Ervebo)isareplication-competent, live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine, and it has been utilized in an effort to mitigate recent EVD outbreaks in Africa. In 2020, the Advisory Committee on Immunization Practices (ACIP) recommended pre-exposure vaccination with Ervebo for adults who are at potential risk of exposure to Ebola, including those responding to outbreaks of EVD, staff working at biosafety-level 4 laboratory facilities, and healthcare personnel at federally designated Ebola Treatment Centers in the United States. As of this writing, the implementation of this is in process. It is important to note that vaccination does not negate other infection prevention and control measures for healthcare workers; however, the availability of a vaccine provides another level of protection as part of a bundle of risk-reduction strategies.

With regard to maintenance of skills, it is imperative that a culture of safety be fostered within the care team, where the focus is on effective teamwork to accomplish the goal of safe, high-quality patient care [81]. All staff must feel empowered to identify and take action to prevent errors from occurring and to improve the patient care environment. This sense of empowerment can be developed during routine training and preparedness exercises in preparation for the reality of patient care.

Conclusions and Future Directions

The provision of care for patients with EVD or other VHF is a complex process necessitating that close attention be paid to multiple infection control modalities. Engineering and facility controls such as negatively pressurized rooms within designated care areas are ideal; however, the most important assets needed to provide safe and effective care for patients with VHF or other highly hazardous communicable diseases are a trained team and a collection of well-developed and practiced protocols.

The U.S. Department of Health and Human Services, the Assistant Secretary for Preparedness and Response (ASPR), the Centers for Disease Control and Prevention (CDC) and Emory University, Nebraska Medicine, and Bellevue Hospital Center comprise the National Emerging Special Pathogens Training and Education Center (NETEC) [82]. Initiated in 2015, the NETEC program supports the education and training of healthcare facilities in order to enhance preparedness for Ebola and other highly hazardous communicable diseases. Although there remains a significant amount of education and work to be done in this area, this collaborative effort, along with the tiered network of hospitals, represents a significant improvement in preparedness.

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Probiotics and Infection Prevention

22

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Introduction

The World Health Organization accepts a definition of probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [1]. Increasing interest in the clinical use of probiotics in the United States is driven both by consumer enthusiasm for products marketed to have potential health benefits and by researchers inspired by the potential to prevent, treat, and mitigate disease. Some commonly studied applications for clinical use of probiotics include antibiotic-associated diarrhea, traveler's diarrhea, and primary and secondary prevention of *Clostridium difficile* colitis. However, a limited number of studies have examined the use of probiotics as a potential tool in the antimicrobial resistance crisis. These studies include trials using probiotics to eliminate vancomycin-resistant enterococcus colonization and prevent multidrug-resistant organism colonization, necrotizing entercolitis, urinary tract infections, and surgical site infections. These topics, along with the safety of probiotics in the healthcare setting, will be discussed in detail in this chapter. Results have been mixed, leading to ongoing controversy regarding the utility of probiotics in these settings.

The conversation is limited by the quality of published studies. Specifically, there is an overall lack of uniformity in nearly all elements of study design which makes generalizability of results difficult for clinicians. One of the challenges is the breadth of organisms included in the probiotic category. Among many others, frequently studied genera include lactobacilli, bifidobacteria, streptococci, and enterococci. Such organisms have been examined individually and in varying combinations, compared with each other and with placebo, and provided in a wide range of doses and formulations. In addition to the variability of intervention, there is also the heterogeneity of populations. An inherent challenge arises in accounting for differing rates of multidrug-resistant organisms and differences in the microbiome by geographic location and by setting (outpatient to inpatient to intensive care unit). Finally, studies to date have been small and short term.

However, despite the challenges to studying and applying data regarding probiotic use, the potential significance is massive and cannot go understated. The unfortunate effects of the increasing trend of healthcare-associated infections include prolonged hospital stay, increased resistance to antimicrobials, high cost to patients as well as the healthcare system, and death. Over 99,000 deaths in the United States were attributed to healthcare-associated infection in 2002 with an estimated economic impact in 2004 of $6.5 billion [2].

In vitro studies have demonstrated various mechanisms by which probiotics are proposed to take effect. Lactobacilli, in particular, have demonstrated production of both antimicrobial substances which inhibit bacterial growth and short-chain fatty acids that are toxic to various bacteria [3, 4]. In addition, lactobacilli produce hydrogen peroxide which induces an anaerobic environment, thereby indirectly inhibiting bacterial growth [5, 6]. Lastly, studies also have shown lactobacilli to inhibit the adherence of *E. coli*, *Klebsiella*, and *Pseudomonas* in uroepithelial cells [7].

Furthermore, studies have shown that probiotics produce a number of antagonistic metabolites such as organic acids, hydrogen peroxide, low molecular weight compounds, biosurfactants, and bacteriocins that give them antibacterial, anti-biofilm, anti-virulence, antidrug resistance, co-aggregation, and anti-quorum sensing abilities [5]. There is evidence that probiotics also suppress bacterial growth by competitive colonization, by altering intestinal metabolic activity, by altering mucin production, and by binding toxins [5, 8–10]. Probiotics also positively modulate the host immune system by regulating signal transduction mecha-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_22

nisms, which in turn induce cytokines and chemokine production, increase microbicidal activity of peritoneal and spleen macrophages, augment barrier function, and suppress inflammation [5, 11]. Combined, these putative mechanisms position probiotics as a promising nonantibiotic therapy in the forefront of the antimicrobial resistance crisis.

Eliminating VRE Colonization

Beginning with its first appearance in 1988 and growing rapidly in the 1990s, vancomycin-resistant enterococcus (VRE) has been associated with increased morbidity and mortality, particularly in intensive care settings. Risk factors for nosocomial colonization with VRE are prolonged hospital stay, proximity to a patient colonized by VRE, care by a nurse who also cares for patients positive for VRE, longer ICU stay, and exposure to a hospital with higher proportion of patients with VRE colonization [12]. Gastrointestinal colonization is most common, though skin colonization is also frequently present. Animal studies have shown that colonization is more easily established following the administration of vancomycin or other antibiotics and that the continuation of antibiotics causes persistence of VRE [12]. The implications of VRE colonization are dramatically stated, with data demonstrating that patients with VRE bacteremia have a twofold increase in the relative risk of mortality compared to patients who are bacteremic with vancomycin-susceptible enterococcus [13]. This finding was independent of underlying disease. Given the gravity of the burden of VRE, widespread infection control efforts have been implemented to combat VRE colonization, though permanent elimination from a hospital has not been described. Thus, the role for probiotics is of considerable interest. Promising in vitro studies have led to three prominent in vivo trials.

The first study, published in 2007, looked at 27 VRE-positive patients on the renal ward of a tertiary care hospital who were randomly assigned to receive either yogurt containing *Lactobacillus rhamnosus* strain GG (LGG) or standard pasteurized yogurt [14]. Stool was obtained weekly three times and again at 8 weeks to assess for VRE clearance. All 11 in the LGG group who completed the study cleared VRE which was striking compared with 1 of the 12 who completed the study in the control arm. In a second phase of the study, these controls were crossed over and given LGG. Eight of the 11 subsequently cleared VRE within 4 weeks.

Of note, this study did not attempt to culture the stool samples for LGG and did not quantify VRE colonization. In addition, by week 8, three of the subjects in the original treatment group again showed VRE positivity. Lastly, there were a disproportionate number of patients receiving concomitant antibiotics in the treatment group (10 of 14) than in the controls (5 of 13) which included linezolid. These factors may have been at least partially responsible for the very strong initial results of this study.

A second study, published in 2011, also had positive results, demonstrating successful clearance of VRE in children given *Lactobacillus* [15]. The study population was 65 VRE-colonized, inpatient, immunocompetent children (age 0–18), who were randomized to receive 3 billion CFU of LGG or placebo for 21 days. Rectal swabs were obtained for culture at baseline, at weekly intervals for the 3 weeks during intervention, and then at 4 weeks following completion of the intervention. The investigators found a significant difference in the number of children colonized with VRE beginning in week 1. By the third week, 20 of 32 patients in the LGG group were no longer VRE carriers compared with 7 of 29 in the control group ($p = 0.002$). They also observed increased counts of *Lactobacillus* species (though not LGG specifically) in the stool of children receiving LGG. However, at 4 weeks following completion of the treatment, there was no significant difference in VRE colonization.

In contrast to these two studies, a third small randomized, double-blind, placebo-controlled clinical trial found negative results. Conducted to examine the efficacy of LGG for the reduction or elimination of intestinal colonization by VRE, the study included noncritically ill adults who had positive stool culture or rectal swab for VRE within 7 days preceding study enrollment [16]. Strict exclusion criteria were applied. Ultimately, 11 adults were randomized to either a group receiving LGG (five subjects) or placebo (six subjects). The intervention group subjects received one capsule of LGG (1×10^{10}) organisms twice daily. Duration was 14 days and stool samples were collected at days 7, 14, 21, 28, and 56 for quantitative culture of LGG and VRE. No significant differences were observed in VRE colony counts at any time point. LGG was detected by PCR in all samples from subjects in the LGG arm. However, it was only isolated in culture in two of the five subjects in that arm. This was perhaps due to antibiotic administration in this population, leaving dead organisms detectable by PCR but not viable by culture. However, the major finding from this study was the lack of effect of LGG on VRE colonization.

The differing outcome of this third study on VRE elimination may be explained by an inadequately powered study, a shorter course of LGG administration (2 weeks rather than 3 or 4), or a sicker population with heavier burden of comorbidities and higher rate of concomitant antibiotic use. In addition, this study used a different formulation for administration of LGG, using a capsule rather than yogurt.

At this point, there remains hope for an important role of *Lactobacillus rhamnosus* GG in clearing VRE colonization, but questions remain regarding characteristics of the popula-

tion to be targeted, formulation and length of treatment, and the effect of concomitant antibiotic use.

Preventing Multidrug-Resistant Organisms

Colonization with multidrug-resistant organisms (MDROs) poses great risk for hospital complications, including increased length of stay and increased mortality. Risk factors for acquiring MDROs include placement of central lines, administration of broad-spectrum antibiotics, ventilator use, and nasogastric tubes. Infection is often preceded by colonization. Therefore, there is theoretical benefit in an intervention that will prevent or treat colonization and, in doing so, prevent transmission within high-risk healthcare settings such as the intensive care unit.

In particular, studies with Lactobacillus rhamnosus GG (LGG) have demonstrated several behaviors that suggest it may be a promising candidate for clinical application in the intensive care unit. First, its susceptibility profile is key to its success in attaining colonization status of patients in the ICU setting where patients commonly require antimicrobial treatment. While known to be susceptible to penicillin, ampicillin, and erythromycin, as well as to imipenem, piperacillin-tazobactam, erythromycin, and clindamycin in some studies, other studies have demonstrated survival of LGG in the digestive tract of patients treated with such antibiotics [17, 18].

Several in vitro studies suggest putative mechanisms in which LGG may prevent MDROs. One such study, published by Silva et al. in 1987, proposed that LGG may exert a growth inhibition mechanism involving a filterable low molecular weight fatty acid elaborated by LGG that suppresses the growth of *Staphylococcus*, *Streptococcus*, *Mycobacterium*, *Bacillus*, *Clostridium*, *Listeria*, *Escherichia coli*, and *Salmonella* [4]. Later experiments by our lab demonstrated production by LGG of a substance that inhibits and has bactericidal activity against four different strains of VRE as well as five extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* (as determined by pulsed field gel electrophoresis) (unpublished data). One recent study, published in 2020, found that LGG SHA113, a strain isolated from the milk of healthy women, could efficiently inhibit MDR *S. aureus* both in vitro and in vivo by decreasing the number of pathogenic cells, modulating inflammatory and immune response, and repairing structural damage to the intestinal barrier and immune organs [19].

Other studies suggest that other *Lactobacillus* species aside from LGG may also have the ability to prevent MDROs. The first, published in 2005, found that freshly isolated *L. ruminis* can completely inhibit Vancomycin Intermediate *S. aureus* (VISA) and VRE [20]. The second, published in 2016, demonstrated that *L. acidophilus* has moderate inhibitory activity against ESBL-producing *E. coli*, followed by *L. paracasei, L. rhamnosus*, and *L. plantarum* [21]. The third, published in 2018 by Jayashree et al., found that *L. fermentum* could efficiently displace adhered methicillin-resistant *Staphylococcus aureus* (MRSA) via competitive adhesion to Caco-2 cells [22].

Lastly, probiotic cocktails may have the ability to prevent MDROs. A recent study, published by Sun et al. in 2020, found that a probiotic combination of *Bacillus coagulans, L. rhamnosus GG, L. reuteri,* and *L. acidophilus* significantly reduced the population of cocultured VRE and prevented VRE from binding to Caco-2 cells by downregulating several host-adhesion genes of VRE [23]. Putting these data together, Lactobacillus provides a promising modality for colonization and survival in the GI tracts of ICU patients, as well as for inhibition of growth and bactericidal activity against multidrug-resistant organisms.

Nevertheless, some in vivo studies of lactobacillus in ICU patients show contrasting results. One recent randomized controlled pilot study by Kwon et al. looked at LGG versus standard of care in preventing gastrointestinal MDRO colonization in the ICU setting [24]. The study took place at a 1250-bed university-affiliated US hospital in 2012–2013 and included patients over the age of 18, in medical or coronary ICUs, with anticipated lengths of stay greater than 48 h. There were extensive exclusion criteria largely based around immunosuppression, invasive devices, and breakdown of the GI tract, among others. A total of 103 patients were randomized to receive either probiotic or placebo. Probiotic recipients received one capsule of 1×10^{10} cells twice daily for 14 days or until study exit (death or hospital discharge, whichever came first). Stool samples or rectal swabs were obtained for culture at study enrollment, study day 3, and every 3 days until study exit. Included in the outcomes analysis were 70 patients who had at least three specimens available. The primary outcome was the acquisition of gastrointestinal MDRO colonization. Organisms included were ESBL-producing and carbapenem-resistant *Enterobacteriaceae*, VRE, *Pseudomonas aeruginosa*, and *C. difficile*. Secondary outcomes were safety and loss of MDRO colonization. Results revealed that there was no significant difference in acquisition of MDROs between probiotic (10%) and placebo (15%) groups ($p = 0.72$). Similarly, there was no difference in loss of colonization. Of note, randomization was not blinded and the study was limited by size and duration.

Given a trend of multiple small studies frequently with contradictory conclusions, meta-analyses have attempted to synthesize a broader view of the literature. A 2013 meta-analysis published by Barraud et al. compared important outcomes in critically ill patients receiving probiotics [25]. Their group assembled data from nine randomized controlled trials from 2002 to 2013. Sample sizes varied from 28 to 259,

pooling a total of 1119 patients receiving prebiotics, probiotics, and synbiotics (a mixture of probiotics and prebiotics). Primary outcomes were ICU and hospital mortality, and both were found to be uninfluenced by use of probiotics. The quality of the studies was variable. The authors state, however, that their findings with regard to their primary outcomes were robust because heterogeneity was small and findings were consistent among different sensitivity analyses that accounted for the importance of mortality rate and the kind and dose of probiotics used.

Overall, the effects of probiotics on multidrug-resistant organisms in clinical settings, specifically in critically ill patients, are uncertain. While the in vitro data align, creating anticipation for a major role for probiotics in vivo, the clinical data from existing trials have been less conclusive. Trials to date have been small with nonuniform inclusion and exclusion criteria, variable probiotic intervention, and short-term follow-up. Therefore, even systematic reviews of the topic struggle to draw applicable conclusions. Larger studies looking at effects of single-species preparations are necessary to definitively comment on the utility of probiotics in altering the colonization, and thereby outcomes, of critically ill patients.

Reducing Risk of Ventilator-Associated Pneumonia

The use of probiotics to prevent MDROs has the potential to impact the incidence of ventilator-associated pneumonia (VAP) as well. MDROs frequently occur in patients with VAP, as prolonged mechanical ventilation is a major risk factor for contracting resistant infection [26]. Among the most common of healthcare-associated infections (HAIs), VAP affects between 9% and 27% of intubated patients and is associated with increased morbidity, mortality, duration of ICU stay, and ventilator days [27]. In addition to its adverse clinical effects, VAP costs the U.S. approximately $40,000 more per patient compared to those who do not develop VAP. Leading theories suggest that VAP is caused by the aspiration of microorganisms or biofilms from the oropharynx or endotracheal tube, respectively. Subsequently, bacterial translocation and colonization of the aerodigestive and lower respiratory tract with pathogenic bacteria lead to pneumonia [27, 28]. As a result, it is thought that probiotics could play a role in preventing VAP by minimizing virulent colonization or modulating the host immune response [27]. Studies have shown that probiotics increase the frequency of B cells expressing IgA in the colon and lymph nodes and increase both lymph node T follicular helper cells and IL-23-expressing dendritic cells. These changes likely boost host defenses to pathogenic bacteria; thus, this putative mechanism may be one way in which probiotics could prevent VAP [29].

The aforementioned 2013 meta-analysis by Barraud et al. found that probiotic administration reduced the incidence of ICU-acquired pneumonia (OR, 0.58; 95% CI, 0.42–0.79) and was associated with a shorter ICU course (weighted mean difference, 21.49 days; 95% CI, 22.12–20.87 days) [25]. Despite these observations, other secondary outcomes of the meta-analysis yielded negative findings. There was a lack of association between probiotic use and shorter duration of mechanical ventilation (WMD, 20.18 days; 95% CI, 21.72–1.36 days) or shorter hospital stay (WMD, 20.45 days; 95% CI, 21.41–0.52 days).

In comparison, a 2012 systematic review published by Petrof et al. drew somewhat more positive conclusions than Barraud's team based on a larger number of randomized controlled trials [30]. In their analysis, 23 trials met inclusion criteria. Seven of the included studies examined probiotic effect on ventilator-associated pneumonia. When these were pooled, they concluded that risk of VAP was decreased with probiotic use (risk ratio 0.75; 95% confidence interval 0.59–0.97; $p = 0.03$). Petrof's findings were similar but not identical to the Barraud meta-analysis; with probiotics there was a trend toward reduced intensive care unit mortality (risk ratio 0.80; 95% confidence interval 0.59–1.09; $p = 0.16$), but not hospital mortality. Importantly, the authors noted that in their analysis, trials of lower methodological quality observed greater treatment effects than those of higher methodological quality. They acknowledged that recommendations were limited based on clinical and statistical heterogeneity.

Two recent systematic reviews have attempted to elucidate these contrasting results, yet have faced similar challenges. The most recent systematic review, published in 2021 by Zhao et al., included 15 studies involving 2039 patients for analysis [27]. Pooled analysis found that probiotic administration significantly reduced VAP (risk ratio, 0.68; 95% Cl, 0.60–0.77; $p < 0.00001$), but did not significantly affect duration of mechanical ventilation, total mortality, or length of ICU stay. However, the authors concluded that despite statistical significance, there was insufficient evidence to support that probiotics prevent VAP due to the limited number of studies and low quality of evidence. The second systematic review, published in 2020 by Batra et al., evaluated nine randomized controlled trials consisting of a total of over 1127 patients [28]. They found that probiotics had a statistically significant effect in reducing the incidence of VAP ($p = 0.002$). In contrast to results by Zhao et al., they also found that probiotics significantly reduced duration of mechanical ventilation ($p = 0.02$), length of ICU stay ($p = 0.001$), and in-hospital mortality ($p = 0.04$). Nevertheless, authors cited that there were substantial differences in study design, type, duration, and dose of probiotic treatments analyzed – a challenge shared by several reviews to date [29]. Notably, the RCTs included in the review utilized varied definitions of VAP in their trials.

A recent RCT, published by Mahmoodpoor et al. in 2019, randomly assigned 100 critically ill adult patients undergoing mechanical ventilation >48 h to receive either two capsules of probiotic preparation containing a mixture of *Lactobacillus, Bifidobacterium*, and *Streptococcus spp*., or placebo [31]. After 14 days of treatment or placebo, patients in the probiotic group had a statistically lower incidence of microbiologically confirmed VAP and duration of ICU stay. Yet despite the numerical decrease in VAP occurrence, authors concluded that based on nonstatistically significant Kaplan-Meier survival curves for time to first VAP episode, results remained inconclusive.

Given the poor quality of existing evidence, further well-defined, standardized, and multicenter studies are required to draw definite conclusions on the effect of probiotics on preventing VAP. Prevention of VAP has become a growing topic of interest, especially in the era of COVID-19. Recent studies have cited that 31–79% of COVID-19 inpatients receive mechanical ventilation, with 31% of them subsequently developing VAP [32]. While no RCTs exploring probiotic administration to COVID-19 patients on ventilators have been conducted to date, investing in this avenue of research has the potential to improve patient outcomes, reduce healthcare costs, and relieve the burden on healthcare facilities during and following the COVID-19 pandemic.

Reducing Risk of Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a significant cause of morbidity and mortality in preterm infants with low birth weights and gestational ages. First described in the 1960s, the incidence, morbidity, and mortality have remained virtually unchanged since then – in some regions, it has even increased due to the rising survival rate of preterm infants [33]. It is estimated that around 5–7% of low birth weight babies (between 500 and 1500 g) develop NEC, with mortality ranging from 10% to 30%. Risk factors for NEC include prematurity, very or extremely low birth weight, and evidence of intrauterine growth restriction or absent/reversed end-diastolic flow velocities in the fetal aorta or umbilical artery [34]. In addition to increased morbidity and mortality, NEC is also associated with both increased length of hospitalization and risk of microcephaly, neurodevelopmental delays, and short-term bowel syndrome. It is estimated that the disease costs the U.S. between $500 million to $1 billion a year [33].

Intestinal dysbiosis is believed to be a major contributor to NEC. Studies have shown that neonates with NEC have significantly decreased diversity of intestinal and fecal bacteria compared to healthy controls. Delivery by cesarean section and formula-feeding are associated with higher risk of NEC, likely due to the neonate's decreased ability to acquire and become colonized by beneficial commensal bacteria from the vaginal canal or breastmilk [34–36]. When the intestinal microbiome is disrupted, dysbiosis may trigger abnormal apoptotic and inflammatory signaling, barrier function, and bacterial detection mechanisms in the premature intestine, ultimately leading to epithelial damage and necrosis [35]. Given the putative role of dysbiosis in the pathophysiology of NEC, it is important to explore the potential benefits of dietary supplementation with probiotics in restoring beneficial commensal bacteria to the intestinal microbiome and subsequently preventing NEC.

One comprehensive meta-analysis, published in 2019, showed that probiotic administration can prevent the incidence of NEC (3.54%) and gut-associated sepsis (15.59%), and decrease mortality (5.23%) in preterm infants [37]. Leading theories propose that probiotics may reduce incidence of NEC by: (i) producing inhibitory organic acids and antimicrobial compounds that outcompete pathogens for nutrients and limit their growth, (ii) stimulating differentiation and proliferation of enterocytes, (iii) stimulating expression of intestinal digestive enzymes, (iv) strengthening the intestinal mucosal barrier by inducing tight junction protein expression, (v) inducing anti-inflammatory cytokines, and (vi) preventing apoptosis and cell death [38, 39]. In particular, one randomized controlled trial published in 2020 found evidence that *Lactobacillus* and *Bifidobacterium,* two genera naturally present in breastmilk, likely reduce incidence of NEC by inducing anti-inflammatory cytokines [40]. The study compared very low birth weight (VLBW) infants receiving a synbiotic combination of *Lactobacillus rhamnosus* and *Bifidobacterium lactis* in bovine lactoferrin to matched controls receiving placebo from first feed until discharge. Serum levels of interferon-γ, interleukin (IL)-5, IL-10, and IL-17A were measured every 2 weeks from birth. IL-10 levels decreased significantly in the study group compared to the control (p = 0.011). None of the 25 infants receiving probiotic supplementation developed NEC, whereas 3 out of the 25 infants in the control group developed NEC. Of note, sample size was limited. However, this trial demonstrates one likely mechanism in which probiotics reduce incidence of NEC.

Meta-analyses have shown that *Lactobacillus* and *Bifidobacterium* are associated with improved outcomes. A 2021 meta-analysis by Beghetti et al. evaluated the effects of strain and feeding time in preventing NEC in preterm infants [41]. They looked at randomized controlled trials or quasi-RCTs involving preterm infants (<37 weeks) with NEC receiving enteral administration of any probiotic starting within one month of age. Fifty-one trials, including a total of over 15,000 infants total, met inclusion criteria. Thirty-one of these trials included data on human milk versus formula feeding. Findings showed that *Lactobacillus acidophilus* was associated with reduced risk of all stages of NEC, in

addition to *B. longum, L. reuteri*, and the multi-genus probiotic group (odds ratio 0.03; 95% credible intervals (CrIs), 0.00–0.21). Subgroup analysis showed that *Bifidobacterium lactis* was associated with reduced risk of NEC stage ≥2 (OR 0.04; 95% CrIs <0.01–0.49 vs. OR 0.32; 95% CrIs 0.10–0.36). Both organisms showed reduced risk of NEC in both human-milk and formula-fed infants, with higher efficacy in exclusively human-milk-fed infants. Another meta-analysis published in 2017 by Zhu et al. specifically looked at the effects of *Bifidobacterium* in reducing NEC [42]. In an analysis of 22 RCTs including 6155 infants, infants in the *Bifidobacterium* group had decreased relative risk of developing NEC (RR 0.38, 95% CI 0.25–0.58; $p < 0.00001$) and death (RR 0.74, 95% CI 0.60–0.92; $p = 0.006$).

Of note, only 3 of the 51 studies included in the first meta-analysis included data on extremely low birth weight (ELBW) infants [41]. Despite strong evidence that probiotic supplementation can reduce NEC for preterm infants, little information is available on the effects of probiotics on reducing NEC in the highest-risk infants, particularly those who are very preterm or ELBW. One recent meta-analysis by Sharif et al. in 2020 highlights the sparsity of data on these high-risk populations [38]. The analysis included 56 trials including 10,812 infants who were either very preterm (<32 weeks gestation), VLBW (<1500 g), extremely preterm (<28 weeks gestation), or ELBW (<1000 g) who received enteral administration of any probiotic or probiotic combination for at least 1 week compared to placebo. Using the GRADE approach to classify certainty of evidence, they found low certainty that probiotic supplementation may reduce risk of NEC or severe neurodevelopmental impairment in very preterm, extremely preterm, ELBW, or VLBW infants. Low certainty was largely attributed to small trial size (median $n = 149$) and design flaw. In about half the trials, it was unclear whether caregivers or investigators were blinded to the treatment arm, increasing bias. Additionally, reiterating a common theme, probiotic formulation varied by trial. However, they found moderate certainty that probiotics may reduce mortality or late-onset invasive infection. Given the low to moderate level of certainty for these high-risk infants, larger, high-quality RCTs are required to gather sufficient evidence on these high-risk populations.

Further studies have attempted to identify the optimal probiotic formulation and treatment strategy to prevent NEC. One meta-analysis by Sun et al. in 2020 found that probiotic supplementation was most effective in preventing NEC when taken in breast milk, consumed for <6 weeks, administered at a dosage of $<10^9$ CFU/day, and included multiple strains [36]. Another systematic review published in 2020, including 63 trials and involving 15,712 preterm infants, found moderate- to high-evidence that combinations of ≥1 *Lactobacillus* spp. and ≥1 *Bifidobacterium* spp., *Bifidobacterium animalis* subspecies *lactis, Lactobacillus reuteri,* or *Lactobacillus rhamnosus* significantly reduced severe NEC compared to single strains or other combinations of treatments [43]. Lastly, a meta-analysis conducted by Sharif et al. found similar results, with the largest effect size estimates favoring various combinations of ≥1 *Lactobacillus spp., Bifidobacterium spp.*, and *Streptococcus spp*. [38]. Interestingly, the strains that have been found to make up the optimal formulation also dominate the microbiota of human breastmilk [44]. Thus, the ideal probiotic formulation seems to be one that emulates or builds upon the mechanism in which breastmilk confers its protective effects: by introducing specific strains of commensal bacteria to restore the gut microbiome.

Overall, there is strong evidence in favor of the use of probiotic supplementation to reduce risk of NEC in most infants. However, more research is needed to investigate its effects on the highest-risk infants, including very preterm, extremely preterm, VLBW, or ELBW infants. Out of the trials that have examined these high-risk populations, many have highly variable probiotic interventions (timing, dose, and formulation), different feeding regimens, and/or small sample sizes. Interestingly, some studies show differential effects based on geography, with strong evidence that probiotic supplementation during the neonatal period reduces the risk of all-cause mortality (RR 0.80, 95% CI 0.66, 0.96), necrotizing enterocolitis (RR 0.46, 95% CI 0.35, 0.59), and neonatal sepsis (RR 0.78, 95% CI 0.70, 0.86) in low and middle-income countries, particularly in Asian regions [45, 46]. Further studies are required to investigate the protective effects of probiotic supplementation across varying patient populations and geographies.

Preventing Urinary Tract Infection

Urinary tract infection (UTI) is one of the most common conditions worldwide, affecting over 150 million people annually. An estimated 50% of women are expected to be affected in their lifetimes [47]. Risk factors for acquiring UTI include female sex, history of prior UTI, sexual activity, condom/diaphragm/spermicide use, catheter insertion, vaginal infection, trauma/manipulation, diabetes, obesity, and genetic susceptibility/anatomic abnormalities. While most UTIs resolve with treatment, an estimated 22% of children and 30% of women who experience UTI experience recurrent UTI (rUTI) within 1 year [47]. Of note, nearly 15% of all prescribed antibiotics in the U.S. are for the treatment of suspected UTI, rendering it one of the largest contributors to antibiotic overuse and subsequent antibiotic resistance [48]. Thus, there is an urgent need to explore nonantibiotic interventions for treatment and prevention of UTI. In particular, several studies suggest that colonization of *Lactobacilli* in the vaginal microbiome may confer protection against recur-

rent UTI. Since women with rUTI demonstrate an inverse relationship between colonization of *E. coli* and that of vaginal H_2O_2-producting *Lactobacilli*, administration of supplemental *Lactobacilli* may reestablish the balance of beneficial commensal bacteria and reduce risk of rUTI [49]. One in vitro study, published in 2006, shows that *Lactobacillus crispatus* strain CTV-05 strongly adheres to vaginal epithelial cells (VECs), especially cells from women with rUTI [50]. These results may indicate one putative mechanism of action in which *L. crispatus* may reduce risk of rUTI: by outcompeting with *E. coli* for carbohydrate binding sites on the vaginal epithelium. Two key randomized controlled trials demonstrate that *Lactobacillus* may reduce risk of recurrent UTI in both adult women and children.

One study, published in 2018, investigated the effects of probiotic supplementation plus cranberry extract in preventing recurrent UTIs in premenopausal women [51]. The study included women 18–55 years old who had experienced ≥2 episodes of uncomplicated acute UTI in the last 6 months or ≥3 episodes of uncomplicated acute UTI in the last 12 months. Eighty-one women were randomized to receive either a capsule of BKPro-Cyan (cranberry proanthocyanidin (PAC), $>5 \times 10^8$ CFU combined *Lactobacillus acidophilus* and *Lactobacillus plantarum*, and 160 μg/capsule vitamin A) or matching placebo twice daily. Vital signs, urinalysis, and pregnancy tests were checked every 45 days. After 26 weeks, a significantly lower number of women experienced recurrent UTIs with BKPro-Cyan compared to placebo (9.1 vs 33.3%; $p = 0.0053$). Additionally, women in the treatment group experienced shorter time to first UTI (90 vs. 174 days; $p = 0.001$), shorter duration of active UTI (5 vs 12 days; $p = 0.009$), reduced need for antibiotics (3 vs 11 patients; $p < 0.05$), and shorter median duration of antibiotic treatment (4 vs 7 days; $p = 0.09$) [52]. Only three subjects in the treatment group experienced mild abdominal distention or diarrhea, indicating that overall treatment with BKPro-Cyan was safe and well-tolerated.

Several limitations included small sample size and lack of microbiological testing to evaluate ecological impact of the treatment. Of note, BKPro-Cyan was formulated using cranberry PAC and a combination of *Lactobacillus acidophilus* and *Lactobacillus plantarum* due to previous literature indicating their ability to inhibit *E. coli* adhesins and *E. coli* and *E. faecalis* uropathogens, respectively [52]. Future studies investigating the effects of cranberry PAC, *Lactobacillus acidophilus,* and *Lactobacillus plantarum* alone are required to draw more specific conclusions on their individual effects on preventing rUTI.

The second study, published in 2020, looked at children aged 4 months to 5 years with a normal urinary tract after recovery from their first febrile UTI [52]. A total of 181 children were randomly assigned to receive a 500-mg probiotic capsule containing *Lactobacillus acidophilus* (15×10^9 colony-forming units [CFU]), *Lactobacillus rhamnosus* (1.0×10^9 CFU), *Bifidobacterium bifidum* (4×10^9 CFU), and *Bifidobacterium lactis* (15×10^9 CFU) or placebo for 18 months. Participants underwent serial monitoring via urine culture and parents were contacted weekly to inquire about any clinical symptoms of UTI. At 18 months, composite cure, defined as UTI-free survival, was observed in 96.7% of the patients in the probiotic group compared to 83.3% of the patients in the placebo group, demonstrating a statistically significant improvement in the probiotic group.

Of note, this was the first randomized controlled trial to evaluate the role of probiotic prophylaxis after first febrile UTI in children with normal urinary tract. Compared to previous studies, it was also the first trial to use a mixture of *Lactobacillus* and *Bifidobacterium* probiotic strains rather than Lactobacillus species alone. Potential sources of bias included ascertainment bias and lack of inclusion of uncircumcised boys in the study, which may have altered results.

Meanwhile, meta-analyses yield conflicting evidence. One meta-analysis, published in 2018, assessed the efficacy of probiotics in prevention of UTI in children. After evaluating ten studies, they found that probiotic monotherapy does not have any beneficial effects on incidence or recurrence of UTI [53]. However, there was moderate efficacy to probiotic use as an adjuvant therapy to antibiotics. Another study assessed the efficacy of probiotic in prevention of rUTI in adult women [54]. In contrast to the previous study, they found that the pooled risk ratio (comparing probiotic group versus placebo) of at least one recurrent UTI episode during study duration was statistically lower, at 0.684 (95% CI 0.438–0.929, $p < 0.001$). Findings also indicated that intravaginal suppositories containing *Lactobacillus crispatus*, *Lactobacillus rhamnosus*, and *Lactobacillus reuteri* showed the greatest efficacy for UTI prophylaxis compared to oral suppositories. Lastly, two randomized controlled trials found that there was no effect of probiotic supplementation in preventing UTI in people with spinal cord injury or neuropathic bladder [55, 56]. These conflicting results demonstrate the need for further studies that account for the effects of probiotic formulation, combination with other therapies, and route of administration in efficacy of combatting UTI.

While there is some evidence that probiotic supplementation, particularly that of *Lactobacillus* formulation, may have some benefit in preventing UTI in children and adult women, further research is ultimately required to ascertain reliable results. Nearly all studies to date have been limited by small sample size and insufficient methodological detail; in fact, a meta-analysis published in 2015 evaluating probiotics for preventing UTIs in both adults and children found that there was a high risk of bias present in nearly all nine studies included [57]. Based on the last 20 years of research on non-antibiotic approaches in UTI, there is not enough evidence yet to justify complete replacement of antibiotics with non-

antibiotic options. As a result, antibiotics remain the gold standard in treating and preventing UTIs until further well-powered and robust studies are conducted [58].

Preventing Postoperative Complications from Surgical Site Infections

Surgical site infections occur in 9–22% of procedures globally and are associated with prolonged hospitalizations, unscheduled readmissions, extended duration of antibiotic therapy, and increased mortality rate [59]. They are the most costly of all HAIs, with an estimated burden of $3.3 billion to the United States every year [60]. The World Health Organization estimates that SSIs account for up to 60% of all HAIs, with a disproportionate impact on low and middle-income countries [59]. Risk factors include obesity, diabetes, and surgery duration [61]. Of note, up to 60% of surgical patients receive antibiotics postoperatively and 50% are discharged on antibiotics, making SSIs a key contributor to climbing antimicrobial resistance [59]. As a result, it is a priority to look for effective nonantibiotic treatments to reduce incidence of SSIs. While perioperative quality control interventions, mechanical bowel preparation (MBP) for intestinal surgery, and antibiotic prophylaxis have helped reduce rates of infectious complications, these procedures can also contribute to vast disturbances in microbial counts and diversity, which in turn exacerbate the risk of contracting SSI [10, 62, 63]. Thus, probiotics pose a promising option, as there is strong evidence that probiotics can reduce incidence of intestinal dysbiosis, improve patients' immune and nutritional status, and thus reduce postoperative complications and inflammatory reactions. Furthermore, probiotics could serve the two-fold purpose of reducing SSI rate and combatting rising levels of antimicrobial resistance [63].

Multiple studies have found that dysbiosis, intestinal mucosal damage, intestinal local immune system dysfunction, and bacterial metastasis may play a role in causing SSIs [10, 62–64]. Surgical procedures can significantly disturb the gut microbiome by increasing virulent *E. Coli, P. aeruginosa, and E. faecalis* counts, decreasing *Lactobacilli* and *Bifidobacteria* counts, delaying microbiota refaunation, and disrupting bacterial translocation through intestinal barrier damage [62, 64]. Consequently, probiotics may combat these changes by modifying the gut microbiome, competitively adhering to mucous membranes and epithelium, strengthening the bowel epithelial barrier, modulating the immune response, and decreasing intestinal pH to improve intestinal motility [64]. One meta-analysis, which included 35 trials comprising 3028 adult patients, found that probiotics may counteract SSIs by modulating the gut immune response to producing short-chain fatty acids [10]. Patients supplemented with probiotics had significantly decreased levels of C-reactive protein (CRP) and Interleukin-6 (IL-6) alongside elevated concentrations of acetic, butyric, and propionic acid. These patients also had lower relative risk toward surgically related complications (abdominal distention, diarrhea, pneumonia, sepsis, SSI, and UTI) and duration of hospital stay.

One randomized controlled trial, published in 2019, presents robust evidence that probiotics can successfully reduce incidence of SSIs [64]. Since incidence of SSI can be as high as 25% in open colorectal surgery, the study randomized patients with colorectal adenocarcinoma to receive either oral probiotic treatment or no probiotic treatment. The treatment group ($n = 39$) received two probiotic capsules per day (containing *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium breve, and Streptococcus thermophilus*) daily starting 3 days post-op for 30 days, followed by one probiotic capsule per day for 1 year. By the end of the study, patients treated with probiotics had an approximately 1.5 times lower probability of occurrence of SSI and a significant reduction in localization of tumors on the rectum (−33.3%) and the ascending colon (−16.7%). Patients treated with probiotics also had fewer days of postoperative hospitalization ($p < 0.05$). A meta-analysis published in 2021 further supported these results [63]. Analyzing 19 articles involving 1975 patients, the study found that patients receiving pro/synbiotics had reduced total postoperative infections (including both SSIs and non-SSIs) and reduced inflammatory factors, intestinal dysbiosis, noninfectious complications, and systemic symptoms. Of note, strain type (multistrain or single strain) and intervention time (administration preoperatively or pre- and postoperatively) did not affect results.

Fortunately, it appears that the beneficial effects of probiotics are not limited to patients undergoing colorectal surgery. However, most meta-analyses to date compare the relative effects of probiotics, prebiotics, and synbiotics versus placebo, rather than probiotics versus placebo alone. In particular, one meta-analysis, including 31 studies comprising 2952 patients, investigated the effects of probiotic, prebiotic, and synbiotic therapies in reducing postoperative complications in adults [65]. The primary outcome was prevention of SSI, while secondary outcomes were UTI, pneumonia, sepsis, duration of antibiotic administration, length of hospital stay, and mortality. Out of all options, synbiotics ranked highest in reducing pneumonia (RR = 0.28; 95%CI, 0.09–0.90), sepsis (RR = 0.09; 95% CI, 0.01–0.94), length of hospital stay (mean = 9.66 days, 95% CI, 7.60–11.72), and duration of antibiotic administration (mean = 5.61 days, 95% CI, 3.19–8.02). Probiotics ranked highest in reducing length of ICU stay, but were less effective than synbiotics in reducing SSIs. Interestingly, synbiotics demonstrated superior

effectiveness over traditional preoperative antibiotic prophylaxis and MBP, concurring with evidence published in 2018 that probiotics in combination with antibiotics reduced risk of SSI better than antibiotics alone [66]. Thus, switching from antibiotics to pro/synbiotics may combat SSIs with higher efficacy while also combatting multidrug resistance. These findings were consistent with other systematic reviews among patients who underwent elective general surgery, abdominal surgery, and liver transplantation [67–70]. Nevertheless, it is important to note that most of the studies included in this meta-analysis came from Asian and European countries [65]. Further studies are needed to generalize to other populations.

There is robust evidence that pro/synbiotics may reduce incidence of SSI, and in turn, improve patients' quality of life and lower hospital costs [67]. With the rising crisis of antimicrobial resistance, many experts suggest that surgeons should consider the use of pro/synbiotics as an adjunctive therapy to prevent postoperative complications among adult surgical patients [65]. Future avenues of research are needed to characterize the maximally effective pro/synbiotic strain, type, route of administration, and duration of therapy, as well as to investigate efficacy in pediatric populations.

Treating *C. difficile* Infection

C. difficile infection (CDI) is associated with alterations of the gut microbiome. Therefore, there is potential for probiotic supplementation to help in the prevention of primary or secondary infection. Probiotic supplementation may also be a promising adjunctive therapy to antibiotics or fecal microbiota transplantation to treat CDI. For more information, please refer to Chap. 16.

Safety Concerns and Guidelines on the Use of Probiotics

In recent years, amidst ongoing discussion regarding the role of probiotics in the clinical setting, new controversy has developed over the safety of their clinical use. Despite an overall unremarkable record of adverse outcomes over many decades in the world of food and dairy, their evolving applications for more targeted therapeutic use have triggered somewhat of a recategorization by the US Food and Drug Administration (FDA). Because they are not considered drugs in the U.S. or Europe, their regulatory status differs from that of pharmaceutical products [71]. A draft guidance by the FDA in 2010 defined probiotics as biotherapeutic products and therefore mandated an Investigational New Drug (IND) application for all clinical research concerning their use. This has prompted reaction from many in the scientific community who have since recognized new barriers to advancing study in this area. Fallout from the new policy has been a decrease in the number of federally funded human interventional studies. This is due, in part, to reticence of probiotic manufacturers in providing required information to the FDA and also to greater challenges for enrollment given the now-extensive exclusion criteria for these studies [72]. In response, the FDA has maintained its stance in a 2013 guidance that as long as a product is being used for purposes beyond nutritive value, taste, or aroma, it should be considered a drug and therefore held to such higher scrutiny [71].

In a similar vein, a 2011 report released by the Agency for Healthcare Research and Quality (AHRQ) stated that while there is no significant evidence to suggest increased risk, "the current literature is not well equipped to answer questions on the safety of probiotics in intervention studies with confidence" [73]. The report provided a review of the safety of probiotics based on 622 studies and concluded the above citing that interventions, as well as assessment, and systematic reporting of adverse events, in the probiotic intervention studies included were poorly documented. However, the report has been criticized by some who maintain that these data were not reported because they were not, at the time, required nor considered to be relevant. They contend that the long-standing history of safe use carries a substantial weight that is lost in the report's conclusion and further that data do exist from clinical, animal, and in vitro studies that support this presumption.

In 2020, the American Gastroenterological Association (AGA) released guidelines on the role of probiotics in the management of gastrointestinal disorders. In their guidelines, they outlined conditional use of probiotics for treatment of pouchitis for adults and children, treatment of infectious gastroenteritis for children, prevention of CDI *in conjunction with antibiotics* for adults and children, and prevention of NEC for preterm, low birth weight infants [74]. Of note, a 2020 position paper from the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) also recommended conditional use of probiotic supplements to prevent NEC [75]. The AGA does not recommend the use of probiotics for treatment of ulcerative colitis, irritable bowel syndrome, CDI (except as an adjunct), or Crohn's disease outside of the context of clinical trials, citing low-quality evidence [74].

Safety Concerns: Pancreatitis and the PROPATRIA Trial

One of the landmark trials which has raised concern for the safety of probiotics is the *Probiotic prophylaxis in patients with predicted severe acute pancreatitis* (PROPATRIA) trial which was published in 2008 [76]. In a double-blind,

placebo-controlled randomized trial, the study looked at 200 patients in 15 Dutch hospitals with first episode of acute pancreatitis which was predicted at onset to be severe. Subjects were randomized within 72 h to receive either twice-daily multispecies probiotic or placebo via nasojejunal tube for 28 days or until discharge. The primary endpoint was the total number of infectious complications. Secondary endpoints were mortality, necrosectomy, antibiotic resistance, hospital stay, and adverse events. Results were surprisingly striking with no significant difference in infectious complications, but mortality rate of 24 of 152 patients (16%) in the treatment arm versus 9 of 144 (6%) in the placebo group, with relative risk 2.53 (95% CI 1.22–5.25). Nine patients in the probiotic group developed bowel ischemia (compared to zero in the placebo group), of which eight had a fatal outcome. The authors concluded that given the lack of effect on infectious complications and an increased risk of mortality, probiotic prophylaxis should not be administered in patients with predicted severe acute pancreatitis.

Results of this study had been unexpected given that it had been inspired by multiple prior studies, and one randomized controlled trial in particular, that had demonstrated positive results with no significant effect on mortality. Olah et al. had looked at an individual probiotic strain, *Lactobacillus plantarum*, in patients with acute pancreatitis and found infected pancreatic necrosis was significantly decreased in the probiotic arm [77]. The PROPATRIA group had hoped to expand on these findings by broadening to a multispecies probiotic intervention and including patients with biliary etiology of pancreatitis.

Given the unforeseen mortality outcome of the PROPATRIA trial, it was followed by a thorough investigation organized by three Dutch National Institutes in 2009, which ultimately concluded that there were no peculiarities about the way the study was performed to explain the high mortality rate in the probiotic arm [78]. In addition, there have been meta-analyses which have systematically reviewed PROPATRIA among related literature and asserted that the observed outcome could not have been predicted based on evidence published both before and after the trial [79, 80].

A 2016 perspective article, however, published in Nature Biotechnology uses the existing basic science foundation for the use of probiotics to propose a mechanism for the observed findings of PROPATRIA [81]. It forcefully rebuts the notion that future probiotic use in the acute pancreatitis population is contraindicated. Their proposed explanation for the adverse outcome of the study includes delayed initiation of intervention (within 72 h) and excessive delivery of carbohydrates provided by tube feeds in the inherent presence of digestive pancreatic enzymes. They suggest that a lethal combination of proteolytic pancreas enzymes and probiotics may have elevated lactic acid, ultimately leading to a fatal outcome. Their conclusion is that we may expect safe use of probiotics in patients with acute pancreatitis if higher doses of probiotic are used, concurrent enteral nutrition is minimized, and early initiation of probiotic therapy (within 24 h) is achieved.

In any case, acute pancreatitis is one of many populations which are potentially at risk with use of probiotics according to the FDA. Others among this list include those who are pregnant, immunosuppressed, have structural heart disease, or have increased potential for translocation of probiotic across the bowel wall. Inpatients are also considered by the FDA to be potentially a high-risk group.

Safety Concerns: Other Infections

Adverse outcomes of probiotic use have been primarily reported in case reports. There have been over 30 reported cases of fungemia (*Saccharomyces* species), at least eight cases of bacteremia (lactobacilli species), and among these, at least nine cases of sepsis [72, 82–86]. Endocarditis and abscess have both been described, and five reports of D-lactic acidosis have been published. Beyond these proven risks, there is theoretical concern regarding excessive immune stimulation provoking autoimmune response as well as lateral gene transfer of resistance traits via plasmid exchange.

Anecdotal reports of *Lactobacillus*-related central line-associated bloodstream infection in our own institution and others in patients receiving probiotics while in the hospital are the basis for our hospital's policy regarding particular attention to hand hygiene. Providers caring for patients with central venous catheters are advised to change gloves after handling probiotic preparations and before manipulating vascular catheters.

Additionally, while considered safe in immunocompetent adults, there is some evidence that probiotic supplementation may cause bacteremia or fungemia in very preterm or VLBW infants [84]. Nevertheless, a recent systematic review published in 2020 by Navarro-Tapia et al. evaluated 21 clinical trials published in the last 10 years, evaluating the safety of probiotics in pregnancy and during the neonatal period. They found that only one of the studies reported adverse effects – a VRE outbreak attributed by the authors to acquisition of resistant genes of bacteria mediated by probiotic use in combination with vancomycin administration. They concluded that for pregnant women and full-term newborns, probiotics proved a relatively safe option [87].

Undoubtedly, the climate of safety reporting and investigation is changing as probiotics have become more widely recognized as a therapeutic agent. While this poses increased challenges for researchers, the growing body of data will serve to inform on best uses for probiotics. As research con-

tinues, accurate and precise description of adverse events will be critical to their advancement.

Conclusion

While there is increasing interest in the use of probiotics in the treatment and prevention of disease, an abundance of unanswered questions remains. Despite exciting in vitro data, many clinical results have been inconsistent. Randomized trials have been small, and subsequent meta-analyses have been limited in their ability to pool data given the variability of study design with respect to organism, dose, and formulation used for intervention, as well as acuity and population of study subjects.

With regard to the specific question of clearance of VRE colonization, there have been only two small clinical trials suggesting the effectiveness of LGG and a third with contrasting results [14–16]. This third study was undoubtedly small with limited power and was performed in a population with a complicated profile of comorbidities and concomitant antibiotic use. It certainly does not rule out the possibility for future LGG use to clear VRE colonization, but does prompt careful consideration for future study design to determine whom to target, how to administer intervention, and what outcomes are most important. We are left to wonder – particularly given the positive outcomes of the previous two studies – whether there may be other beneficial effects of the presence of LGG which may not be represented by the primary outcome that was assessed here (growth of LGG in stool culture and quantifying VRE colonization). It would be informative to see the effect of LGG on the full profile of the microbiota and on the intestinal immune and barrier functions.

The topic of probiotic use in the critical care setting to prevent disease from MDROs has been examined with many small, varied trials which systematic reviews have subsequently attempted to pool in order to draw meaningful conclusions. Meta-analyses from 2012 to 2013 with differing inclusion criteria seem to agree on a lack of effect on hospital mortality [25, 30]. They also both comment on a potentially reduced risk of ventilator-associated or ICU-associated pneumonia with probiotic use. However, conclusions regarding other endpoints are variable. Given such a widely heterogeneous group of studies, there is room in this topic for a large, randomized trial which examines a single-species probiotic in order to provide more compelling clinical guidance.

In a similar vein, the use of probiotics to prevent VAP has yielded inconclusive evidence. Meta-analyses from 2012 to 2021 find that probiotic administration may reduce incidence of VAP, while it is unclear whether it affects duration of mechanical ventilation, mortality, or duration of hospital stay [25, 27–30]. Among meta-analyses that find statistically significant improvement in incidence of VAP, these studies remain limited by inconsistent study design and lack of standardization of the definition of VAE. Given the CDC's new definition of VAE in early 2020, the stage is set for more robust, standardized studies to be conducted.

Meanwhile, there is promising evidence that probiotics can reduce incidence of NEC and associated complications in preterm, VLBW neonates. While sample size remains limited in randomized controlled trials, several meta-analyses have attempted to summarize existing evidence. Six meta-analyses published between 2017 and 2021 have found that *Lactobacillus* and *Bifidobacterium* administration are associated with reduced risk of all stages of NEC in both human-milk and formula-fed infants, with increased benefits in human-milk-fed infants [36–38, 41–43]. Nevertheless, ELBW neonates, one of the highest-risk groups for developing NEC, remain underrepresented in these studies. Further studies call for investigation of probiotic usage in ELBW neonates, as well as exploration of maximally efficacious timing, dose, and formulation of probiotic.

Regarding the use of probiotics to prevent UTI, two landmark randomized controlled trials, published in 2018 and 2020, respectively, found that probiotic supplementation in children or probiotic supplementation plus cranberry extract in adult women successfully reduced incidence of recurrent UTI [51, 52]. In contrast, two randomized controlled trials found that these effects did not apply to patients with spinal cord injury or neuropathic bladder [55, 56]. Meta-analyses find conflicting evidence as well due to high risk of bias and small sample size [54]. Due to the high prevalence of UTI and its contribution to rising antibiotic resistance levels, it remains crucial to investigate nonantibiotic options, such as probiotics, as an alternative strategy to treatment and prevention.

Lastly, there is strong evidence that pro/synbiotics may reduce incidence of SSI and associated complications. A recent randomized controlled trial, published in 2019, found that administration of probiotic capsules daily for 1 year lowered colorectal patients' probability of occurrence of SSI by 1.5 times compared to those receiving placebo [64]. Seven meta-analyses corroborate these results, demonstrating probiotic and synbiotic efficacy in reducing incidence of SSI, length of hospital stay, and mortality, in patients undergoing colorectal, general, abdominal, and liver transplantation surgeries [10, 63, 65, 67–70]. While the field would benefit from more research in clarifying strain, type, administration, and duration of prophylactic probiotic therapy, data so far indicate that probiotics could significantly improve quality of life while reducing antimicrobial resistance and hospital costs.

The call for further investigation now comes with the critical requirement for increased vigilance regarding safety data. While in the past there has been inconsistent reporting of safety outcomes, their use has been generally regarded as safe given the overall widespread use without major adverse events. However, the landscape is evolving as the FDA now recognizes probiotic preparations as drug rather than food [71]. Increased scrutiny, perhaps in part inspired by the noteworthy PROPATRIA trial, means that all probiotic studies now require an investigational new drug application to proceed [76]. This has been met with some resistance by critics who argue that the larger body of historical practice and limited body of reported evidence should carry a greater significance than a single trial. There is a need to balance potential risk versus protection – one that can only be informed by more robust evidence. Regardless, a new standard has been set as we seek to answer the outstanding questions necessary to guide clinical application of probiotics in the prevention and treatment of disease.

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Animals in Healthcare Settings

23

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Introduction

Animals may be present in healthcare facilities for multiple reasons. Although specific laws regarding the use of service animals in public facilities were established in the United States in 1990, the widespread presence of animals in hospitals, including service animals, animals used to assist in patient therapy, and research animals, has resulted in the increased presence of animals in acute care hospitals and ambulatory medical settings. The role of animals in the transmission of zoonotic pathogens and cross-transmission of human pathogens in these settings remains poorly studied. Until more definitive information is available, healthcare facilities should establish policies and procedures to prioritize patient and healthcare provider safety and to use standard infection prevention and control measures to prevent animal-to-human transmission in healthcare settings. This chapter is based on published consensus recommendations from a panel of experts, representing the Society for Healthcare Epidemiology of America (SHEA), regarding the management of animals in healthcare (AHC) [1]. However, this chapter aims to review the controversies related to animals in healthcare with respect to infection prevention, identify potential steps for mitigation of risks and areas for future study, and provide updated information where available, including the implications of SARS-CoV-2 infection in animals. Any opinions noted beyond the consensus SHEA guidance document reflect the opinions of only the authors of this document.

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Background

Contact with animals by people is increasing and can occur in a variety of settings including households (pets), occupational exposure (veterinarians, farmers, ranchers, and forestry workers), leisure pursuits (hunting, camping, and fishing), petting zoos, and travel to rural areas in the US or abroad. Pet ownership is common in the United States. Surveys of US pet owners from 2017–2018 and 2019–2020 revealed that 67% of US households included a pet (representing approximately 84.9 million households); dogs and cats represented over 70% of household pets (dogs 40%, cats 34%, respectively) [2, 3]. Patients in healthcare facilities come into contact with animals primarily through the use of animals for animal-assisted activities (animal-assisted activities encompass "pet therapy," "animal-assisted therapy," and pet volunteer programs) and the use of service animals such as guide dogs for the sight impaired. Other reasons for contact with AHC include the use of animals in research or education, and personal pet visits to their owners in the hospital (personal pet visitation). Risks to patients from exposure to animals in the healthcare setting may be associated with transmission of pathogens through direct or indirect contact or, less likely, droplet/aerosol transmission (Table 23.1). However, insufficient studies are available to produce generalizable, evidence-based recommendations, and as a result, substantial variations exist in policies and practice across healthcare institutions [1].

Although limited published literature exists on this topic, the SHEA document offers specific guidance on the management of AHC in four categories: animal-assisted activities (AAA), service animals as defined under the Americans with Disabilities Act (ADA), research animals, and personal pet visitation, and recommends that institutions considering

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_23

Table 23.1 Selected diseases transmitted by dogs stratified by transmission route

Transmission route	Selected diseases
Direct contact (bites)	Rabies (rabies virus) *Capnocytophaga canimorsus* infection Pasteurellosis (*Pasteurella* spp.) *Staphylococcus aureus*, including methicillin-resistant strains *Streptococcus* spp. Infection
Direct or indirect contact	Flea bites, mites Fungal infection (*Malassezia pachydermatis, Microsporum canis, Trichophyton mentagrophytes*) *Staphylococcus aureus* infection Mites (*Cheyletiellidae, Sarcoptidae*)
Fecal-oral	Campylobacteriosis (*Campylobacter* spp.) Paratyphoid (*Salmonella* spp.) Giardiasis (*Giardia duodenalis*) Salmonellosis (*Salmonella enterica* subsp *enterica* serotypes)
Droplet	*Chlamydophila psittaci*
Vector-borne	Ticks (dogs passively carry ticks to humans; disease not transmitted directly from dog to human) Rocky Mountain spotted fever (*Rickettsia ricksettsii*) Ehrlichiosis (*Ehrlichia* spp.) Fleas *Dipylidium caninum* *Bartonella henselae*

these programs should have policies that include well-organized communication and education directed at healthcare personnel (HCP), patients, and visitors. Table 23.2 represents an overview of the key recommendations from the SHEA expert guidance document.

Risks of Animals in Healthcare

Reasons for concern about AHC stem mainly from general knowledge of zoonotic diseases, case reports, and limited research involving animals in healthcare facilities. Scientific studies addressing the potential risks of animal-to-human transmission of pathogens in the healthcare setting are limited in number and, because animals have generally been excluded from hospitals, the experience gained to date has been mainly from case reports and outbreak investigations [1]. For example, human strains of methicillin-resistant *Staphylococcus aureus* (MRSA) have increasingly been described in cats, dogs, horses, and pigs, with animals potentially acting as sources of MRSA exposure in healthcare facilities [4]. MRSA is just one of many potential pathogens; a wide range of pathogens exist, including common healthcare-associated pathogens (e.g., *Clostridioides diffi-*

Table 23.2 Summary of animals in healthcare classification and selected recommendations

	Animal-assisted activities	Service[a]	Research	Personal pet
Program				
Written policy recommended	Yes	Yes	Yes	Yes
Federal legal protection	No	Yes	No	No
Animal visit liaison	Yes	No	IACUC	Yes
Infection Prevention and Control notification of animal visit/session	Yes	Yes	Yes	Yes
Infection Prevention and Control consultation for restricted areas	Yes	Yes	Yes	Yes
Visit supervised	Yes	No	Yes	Yes
Visit predetermined	Yes	No	Yes	Yes
Animal and handler/owner				
Performs trained tasks	As indicated for goal-directed interventions or recreational/social purposes	Yes	N/A	No
Specially trained handler	Yes	Yes	Yes	No
Health screening of animals and handlers	Yes	N/A	N/A	No
Documentation of formal training	Yes	No	N/A	No
Animal can be a pet	Yes	No	No	Yes
Animal serves solely for comfort or emotional support	Includes recreational/social purposes	No	N/A	Yes
Identification with ID tag	Yes	Not required	N/A	Yes/No
Animal required to be housebroken	Yes	Yes	N/A	Yes
Permitted animals				
Dogs	Yes	Yes	N/A	Yes
Other animals	Not recommended	Miniature horses	N/A	Not recommended (case by case exceptions may apply)

Adapted from 2015 SHEA guidance document [1]
IACUC Institutional Animal Care and Use Committee
[a]Policy to reflect ADA and regulatory compliance. Inquiries limited by ADA to tasks performed for patient

cile, multidrug-resistant enterococci), emerging infectious diseases (e.g., carbapenem-resistant *Enterobacterales {CRE}*), common zoonotic pathogens (e.g., *Campylobacter*, *Salmonella*, and dermatophytes), rare but devastating zoonotic pathogens (e.g., rabies virus), and pathogens associated with bites and scratches (e.g., *Pasteurella* spp., *Capnocytophaga canimorsus*, and *Bartonella* spp.) [4–8].

The SHEA document was developed from an analysis of available data and was intended to provide a set of practical, expert-opinion-based recommendations for the management of animals in acute care and ambulatory medical facilities. Except where clear regulatory or legislative mandates exist related to the topic and are noted (e.g., Americans with Disabilities Act (ADA)), adoption and implementation of the recommendations is expected to occur at the discretion of individual institutions. In addition, these recommendations have been endorsed by, and incorporated into, animal-assisted therapy training modules by Pet Partners [9].

The following definitions are used in the SHEA document as well as in this chapter:

1. Animal-assisted activities (animal-assisted activities): pet therapy, animal-assisted therapy, and other animal-assisted activities. While these practices and their purposes may vary because these animals and their handlers are (or should be) specifically trained, they will be referred to as animal-assisted activities in this document.
2. Service animals: specifically defined in the US under the ADA.
3. Research animals: animals approved for research by the facility's Institutional Animal Care and Use Committee (IACUC).
4. Personal pet visitation: defined as a personal pet of a patient that is brought into the facility specifically to interact with that individual patient.

In this chapter, we address select controversies (Table 23.3) related to AHC with respect to infection prevention, including those identified in the SHEA document as well as others, and suggest potential steps for mitigation of risks as well as potential areas for future study.

Table 23.3 Controversies related to animals in healthcare and potential resolutions

Topic	Argument for	Argument against	Practical resolutions
Benefits of animal-assisted therapy	Improved physical well-being Improved emotional well-being Relief of boredom in the healthcare facility	Risk of physical injury (e.g., bite) Risk of interference with care (e.g., damage to indwelling device) Risk of zoonotic pathogen via director or indirect contact, or droplet transmission Acquisition of healthcare-associated pathogen (e.g., MRSA) Precipitation of allergies	Institutional policy modeled after SHEA Guidance document Use of specifically trained and evaluated dogs Use of specifically trained and evaluated handlers
Role of animals used for emotional support as "service animals"	Possibly improved physical well-being Possibly improved emotional well-being	Not covered by the ADA Unlike ADA, animals are not limited to dogs or miniature horses Unlike ADA-specific requirements by owner not delineated (e.g., ADA animals must be housebroken and owner is responsible for care) Impossible to define specific role for the animal, thus potentially allows any person to bring any animal into the facility	Either exclude or require approval by institution designee Require same conditions as ADA animals (i.e., limit to dogs and miniature horses; housebroken; owner responsible for care, etc.) Include in institutional policy
Cats	Large segment of pets Some patients prefer cats	Cannot be trained to reliably provide safe interactions with patients Concerns for increased potential allergenicity Potential increased risk of bites and scratches Lack of data to demonstrate advantages over dogs	Avoid any direct contact Assure no allergies Consider for compassionate use visits only Require transport in an pet container (i.e., not carried)
Pets	Strong bond between pet and owner Possible positive impact on patient Possible lower risk of adverse events due to patient-pet bond (such as bites and scratches)	No formal training of owner/designee Inability to reliably restrict to individual patient (potential for pets to encounter healthcare personnel, visitors, and patients while at facility) Pets not temperament tested Do not typically undergo the same degree of health assessment or exclusion practices (e.g. age), as compared to AAT animals	Do not allow pets (including healthcare personnel pets) Consider for compassionate use visits only (e.g. terminally ill patients) Dogs only Outline expectations for owner/guardian for hygiene and safety Establish facility policy with oversight and restrictions to pet visitation

(continued)

Table 23.3 (continued)

Topic	Argument for	Argument against	Practical resolutions
Research, veterinary, zoo animals	Allows use of equipment/ facilities already used for humans Mitigates logistics and cost of acquiring separate equipment Access to new technology for diagnostic and therapeutic use in animals	Risk of pathogen transmission to humans (patients or healthcare providers)	Oversight by IACUC Restrictions as appropriate to prevent disease transmission from ill animals Environmental disinfection Ensure surgical instruments and other medical devices not be used on both animals and humans. Use single use disposable devices where feasible Medical devices that require disinfection or sterilization should be used exclusively for animals.
Leeches	Prevention of acute venous congestion Future potential uses (i.e., osteoarthritis pain reduction)	Wound infection with *Aeromonas* species and possible sepsis especially in patients with immunosuppression Multiple side effects including thrombotic microangiopathy, anemia, and allergy	Use only FDA-approved leeches (regulated as devices) Antibiotic prophylaxis to decrease infection risk Avoid use in contraindicated cases Disposal as regulated medical waste (i.e., they contain human blood)
Maggots	Exclusively debride necrotic tissue leaving viable tissue intact Antimicrobial, anti-inflammatory, and promote healing Low side-effect profile	Pain Infection Social stigma	Use only FDA-approved maggots Analgesics for pain and physical discomfort Follow disinfection protocol to decrease infectious risk Disposal as regulated medical waste
Aquarium	Visually appealing	Potential reservoir for pathogens that can cause infection during routine cleaning and maintenance	Ensure protocols for appropriate tank hygiene and secure maintenance Prohibit from patient care areas Keep covered; prevent access by patients Ensure professional maintenance
Petting zoo	Enjoyable experience for children	Potential reservoir for pathogens High level of interaction provides increased infection risk	Prohibit from healthcare facilities
SARS-CoV-2	No evidence at present of pet-to-human transmission	Dogs and cats may become infected with SARS-CoV-2. While most commonly asymptomatic, pets have died as a result of infection	Handlers of dogs used for AAT should be fully immunized with a COVID-19 vaccine Animals with symptoms consistent with COVID0-19 should be excluded from the facility and be evaluated by a veterinarian for infection

Benefits of Animal-Assisted Therapy

Background

Animal-assisted activities (AAA) therapy (also known as "animal-assisted therapy (AAT) or "pet therapy") is defined as an animal-assisted activities animal that, as a personal pet with its owner or handler, provides comfort to patients in healthcare facilities [1]. Dogs are almost exclusively utilized in AAA; however, cats, miniature horses, and occasionally other animals have been used for AAA. The use of AAA in hospitals is now well established [1, 10]. In a 2013 survey of the SHEA Research Committee, 337 SHEA members responded and provided information regarding their institutions' policies for AAA. Overall, 89 percent of US facilities and 67% of non-US facilities provided AAA for their patients [1]. Of the facilities that permitted AAA, all allowed dogs, with 21% of facilities also allowing cats, 5% allowing miniature horses, and 2% allowing primates. This survey also noted that animals were prohibited from visiting in an intensive care unit (73%) and step-down units (39%).

Benefits/Risks

The SHEA Guidance documents a review of selected references on AAA (See Table 23.2 in Ref. [1]). Multiple studies have demonstrated benefits of AAA including enjoyment of

canine-assisted ambulation for patients with heart failure (hospital) [11], decreased loneliness (long-term care) [12], improved social functioning (psychiatric ward) [13], decreased fear and anxiety in electroconvulsive therapy (hospital) [14], reduced anxiety in psychiatric patients (hospital) [15], improved nutritional uptake in Alzheimer's disease with contact with fish aquariums [16], improved depressive symptoms in patients with dementia, depression, or psychosis (nursing home) [17], and decreased perceived pain in children (pediatric hospital) [18]. However, the benefits of AAA in general hospitalized patients have not been adequately assessed in high-quality comparative trials.

The general risks of animals in the hospital have been described above. Additional concerns regarding AAA, especially for immunocompromised patients or patients with host defects, include local infection or seeding of proximal prosthetic joints following licks by a dog [19] and peritonitis in patients with peritoneal dialysis catheters [20].

Mitigation

Recommendations from SHEA and APIC should be followed to reduce the risk of adverse patient outcomes from participating in AAA [1, 10]. The evidence suggests that adherence to these recommendations allows AAA to be safely used in hospitals.

Key recommendations for a safe AAA program include the following: (1) Facilities should develop a written policy for animal-assisted activities. (2) Only dogs should be used. (3) Animals and handlers should be formally trained and evaluated. Facilities should consider use of certification by organizations that provide relevant formal training programs (e.g., Pet Partners, Therapy Dogs Incorporated, Therapy Dogs International). (4) Animals and animal handlers should be screened prior to being accepted into a facility of animal-assisted activities program. (5) Instruct the animal-assisted activities handler to restrict contact of his or her animal to the patient(s) being visited and to avoid casual contact of their animal with other patients, staff, or the public. (6) Require that every animal-assisted activities handler participates in a formal training program and provides a certificate confirming the training.

Future Research Needs

The great majority of studies claiming benefits of AAA have been low-quality studies and focused on specific patient populations (e.g., psychiatric patients, older patients). Additional high-quality comparative trials, especially in general hospital populations, should be undertaken. Further, most studies did not specifically comment on possible adverse events (e.g., precipitation of allergies, injuries, etc.). It would be useful for additional studies to be specifically designed to collect information on possible adverse events.

Conclusions

AAA is widely used in US hospitals. Many benefits of AAA have been demonstrated in published studies, although many used low-quality designs. However, the weight of evidence suggests properly managed AAA programs are both safe for patients and beneficial. Hospitals should adhere to the published recommendations to protect patient safety when implementing an AAA program.

ADA: Role of Animals Used for Emotional Support as "Service Animals"

Background

The Americans with Disabilities Act (ADA) is a US Federal law that was passed in 1990 and has been subsequently updated [21]. This law established certain legal rights for persons with disabilities including the need to use service animals and defined the minimum access required by law. Healthcare facilities must comply with the ADA. Under the ADA, "service animals" are defined as "dogs that are individually trained to do work or perform tasks for people with disabilities" [22]. Legal protection extends only to individuals who are disabled, as defined under the ADA; not all patients with medical or psychological conditions are covered. In brief, disability is generally defined by the statute as (1) a physical or mental impairment that substantially limits one or more major life activities, (2) a record of such an impairment, or (3) being regarded as having such an impairment. Guidance provided by the Department of Justice makes clear that service animals under the ADA are "working animals" and not pets, and they are trained to perform specific duties or tasks. "Examples of such work or tasks include guiding people who are blind, alerting people who are deaf, pulling a wheelchair, alerting and protecting a person who is having a seizure, reminding a person with mental illness to take prescribed medications, calming a person with Post Traumatic Stress Disorder (PTSD) during an anxiety attack, or performing other duties.

Service animals are working animals, not pets. The work or task a dog has been trained to provide must be directly related to the person's disability. *Dogs whose sole function is to provide comfort or emotional support do not qualify as service animals under the ADA*" [22]. Thus, healthcare facilities are not legally required to allow animals into the hospi-

tal that provide comfort or emotional support to visitors, patients, or healthcare provides.

The Fair Housing Act (1968, revised 1974 and 1988) provides protection against disability discrimination for tenants and renters [23]. The Act also prohibits housing providers from refusing residency to persons with disabilities, or placing conditions on their residency, because they require reasonable accommodations. Included in the Act is the requirement to allow disabled persons to use an assistance animal (i.e., an animal that works, provides assistance, or performs tasks for the benefit of a person with a disability). The Act differs from the ADA in several ways. First, an assistance animal must be accommodated if it "provides emotional support that alleviates one or more identified symptoms or effects of a person's disability." Second, unlike the ADA which only allows dogs or miniature horses, the Fair Housing Act states "while dogs are the most common type of assistance animal, other animals can also be assistance animals." Finally, for purposes of reasonable accommodation requests, neither the Fair Housing Act nor Section 504 requires an assistance animal to be individually trained or certified. The Fair Housing Act does not extend to hospitals, but does include independent living and assisted living facilities. It is unclear whether the Fair Housing Act includes nursing homes.

Although allowing emotional support animals into a hospital is not required by the ADA, hospitals may choose to allow patients and/or visitors to bring such animals into the hospital.

Benefits/Risks

The physical (e.g., lower blood pressure) and social (e.g., improved self-esteem, reduced levels of stress, reduced anxiety) benefits of human-animal interaction have been reported [24]. As most of the studies were uncontrolled and compared pet owners with non-pet owners, substantial bias and/or confounding may have been present in the studies. As noted by Peacock and colleagues "few controlled studies have been conducted to provide empirical support for positive physical or mental health outcomes gained from interacting with companion animals. Previous research has been largely descriptive and conducted with specific populations of convenience such as the aged" [24].

Despite the limitation of the existing research, there are multiple studies which have reported the benefits of pet ownership. For example, Shoda and colleagues performed a series of studies to assess the positive consequences of pet ownership [25]. They reported the following findings: (1) Study 1 found in a community sample that pet owners fared better on several well-being (e.g., greater self-esteem, more exercise) and individual-difference (e.g., greater conscientiousness, less fearful attachment) measures; (2) Study 2 assessed a different community sample and found that owners enjoyed better well-being when their pets fulfilled social needs better, and the support that pets provided complemented rather than competed with human sources; and (3) Study 3 brought pet owners into the laboratory and experimentally demonstrated the ability of pets to stave off negativity caused by social rejection.

The risks associated with the use of animals in healthcare facilities to patients, visitors, and HCP have been described above and include physical injuries (e.g., bites and scratches), allergies, and zoonotic infections. Importantly, emotional support animals are unlike service animals in that there are strict criteria that define a service animal (i.e., ability to perform work) that can be observed while there are no strict observable criteria that define an emotional support animal. Thus, a healthcare facility that allows the use of emotional support animals might find a large number of patients and visitors requesting the use of such animals with an increased risk of physical injuries, zoonotic infections, and/or precipitating allergies. Adoption of the Fair Housing Act standards would also permit the use of a variety of animals (e.g., primates, birds, etc.) which may increase the risk of injuries and zoonotic infections and preclude requirements for training or certification of the animal.

Mitigation

Since there is no legal requirement that hospitals allow the use of emotional support animals in the facility, most hospitals should include a prohibition of such animals in their policy. Hospitals wishing to allow the use of emotional support animals should consider applying the same standards as defined in the ADA for service animals. Such standards would include the following: allowing only the use of dogs or miniature horses; requirement that the animal be housebroken; statement that the care of animal is responsibility of the owners or his/her designee (not HCP); statement that use of such animals be approved by the patient's physician, primary care nurse, legal, and infection preventionist; and that animals that are disruptive or impair patient care are excluded.

Future Research Needs

Two key evidence gaps are the preponderance of anecdotal reports and cross-sectional research designs and failure to control for a host of known influences on human health [26]. Thus, there is a need for well-designed studies to assess the benefits, if any, of companion animals on the physical and emotional well-being of humans. The potential benefits of

emotional support animals in specific populations (e.g., persons with anxiety, depression, attention deficit order, etc.) need to be rigorously examined.

There is virtually no research on the benefits, risks, and impact of emotional support animals in healthcare facilities. Hospitals that allow such animals should review and publish the benefits and risks of allowing emotional support animal use. In the longer run, well-designed studies should be undertaken which assess the benefits and risks of emotional support animals in healthcare facilities. These should focus on use of such animals in psychiatric units, rehabilitation and geriatric units, hospice units, and potentially among long-term patients.

Conclusions

In conclusion, there is no legal requirement that hospitals allow the use of emotional support animals by patients, visitors, or HCP. Allowing such use might lead to substantial increase in the number of animals in the hospital with increased risks of physical injury, allergies, and zoonotic diseases. The evidence supporting the use of emotional support animals is weak and more rigorously designed studies are required to define the benefits. Hospitals choosing to allow emotional support animals should follow similar requirements as allowed under the ADA.

CATS

Background

As noted above, animals may be present in healthcare facilities for multiple reasons including serving as service animals, animal-assisted therapy (AAT), "pet" visitation, and research. In this section, we will explore whether domestic cats (*Felis catus*) should be allowed in healthcare facilities in one of the capacities listed above.

As of 2017–2018, 35.4% of households ($N = 31,896,077$) owned at least one cat [2, 3]. Since, on average, households owning a cat have 1.8 cats, there are ~58,400,000 pet cats in the US. Importantly, 76% of cat owners consider their cats to be family members [2, 3]. Another 20% of cat owners consider their cats to be pets or companions. Surveys have reported that average amount spent on veterinary care per year per cat is either $335 or $890 [2, 3].

Benefits/Risks

Over the centuries, cats have provided benefits to humans including pest control (e.g., reducing numbers of rats and mice) and companionship. Studies have reported that the ownership of cat is useful in maintaining or slightly enhancing activities of daily living in older people [27].

The lifetime risk of having at least one emergency room visit due to a cat bite or scratch was 1 in 60 based on a incidence study in North Carolina, 2008–2010 [28]. The overall incidence rate of emergency room visits related to cat bites or scratches was 18.8/100,000 person-years (p-y) [28]. The rate of injuries was more than twofold higher for females than males (26/100,000 p-y vs 12/100,000 p-y). The incidence rose with increasing age being highest in persons >79 years of age.

Approximately, 5–15% of cat bites or scratches become infected [29]. The most common types of infection are a non-purulent wound with cellulitis, lymphangitis, or both (42%), followed by a purulent wound without abscess formation (39%) and abscesses (19%) [8]. Most cat-related wounds yield a mixture of aerobic and anaerobic organisms. The most common genera isolated from cat bite wounds are *Pasteurell*a (75%), followed by *Streptococcus* (46%), *Staphylococcus* (35%), *Neisseri*a (35%), *Moraxell*a (35%), *Corynebacteriu*m (28%), *Enterococcu*s (12%), and *Bacillu*s (11%) [8]. *Pasteurella multocida* is the most common pathogen isolated from cat bite or scratch-related infections, which most commonly causes a rapidly evolving cellulitis [30]. As cats have sharp pointed teeth, cat bites may directly inoculate pathogens in deeper tissues resulting in tenosynovitis, septic arthritis, osteomyelitis, and meningitis [30]. Several features of cat-related *P. multocida* infection are relevant to the potential use of cats in healthcare facilities [30]. First, immunocompromised patients (e.g., leukemia) are at higher risk of serious infection. Second, cat licks of open wounds or bites/scratches of limbs may result in septic arthritis of more proximal joints if they have been damaged (e.g., rheumatoid arthritis) or the patient has had a joint replacement. Third, cat bites or scratches of tubing used for peritoneal dialysis may result in peritonitis. Finally, transmission by contaminated fomites (e.g., baby's pacifier which was used by a cat as a toy) may lead via indirect transmission to severe infection in patients with host defense abnormalities (e.g., extremes of age, immunocompromised). Cat bites or scratches may also cause an infection by *Bartonella* (cat-scratch disease), *Bacillus anthracis* (anthrax), *Erysipelothrix rhusiopathiae, Francisella tularnesis* (tularemia), *Yersinia pestis* (plague), and *Sporothrix schenckii* (sporotrichosis) [31]. A number of pathogens may be transmitted to humans from cats including Q fever (direct exposure, inhalation of infected material from parturient or aborted tissue), plague (cat bite/scratch, inhalation), bordetellosis (inhalation), and flea-borne spotted fever and murine typhus (via cat flea) [31]. Fecal-oral transmission from cats may occur with *Campylobacter jejuni* (campylobacteriosis), *Helicobacte*r (helicobacteriosis), *Toxoplasma gondii* (toxoplasmosis), *Cryptosporidia* (cryptosporidiosis),

Salmonella (salmonellosis), *Toxocara cati* (toxocariasis), and *Giardia lamblia* (giardiasis) [31]. Direct contact transmitted diseases include dermatophilosis, scabies, *Cheyletiella* mite infestation, and dermatophytosis [31]. Rabies in domestic animals such as cats is rare in the United States. During 2014, domestic animals accounted for 47.9% of all animals submitted for testing, but only 7.37% ($n = 445$) of all rabies cases were reported [32]. Cats accounted for 61.1% (272/445) of the rabid domestic animals reported in 2014, a 10.12% increase compared with the 247 reported in 2013.

Importantly, methicillin-resistant *Staphylococcus aureus* (MRSA) may colonize companion animals including cats which may be transmitted to humans [31]. An outbreak of epidemic MRSA occurred on a rehabilitation geriatric ward [33]. Intensive screening of patients and staff revealed an unusually high carriage rate in the nursing staff (38%), thought to be related to a ward cat which was heavily colonized from the environment. Other healthcare-associated infections or outbreaks due to contact with cats have occasionally been reported. A case of Q fever in a long-term nursing home resident was linked to cat exposure [34]. An outbreak of nosocomial ringworm involving five infants in a neonatal intensive care unit was linked to a nurse infected with *Microsporum canis* by her cat [35].

Mitigation

As per the US Department of Justices, "Beginning on March 15, 2011, only dogs are recognized as service animals under titles II and III of the ADA. A service animal is a dog that is individually trained to do work or perform tasks for a person with a disability" [36]. In addition to the provisions about service dogs, the Department's revised ADA regulations have a new, separate provision about miniature horses that have been individually trained to do work or perform tasks for people with disabilities. (Miniature horses generally range in height from 24 inches to 34 inches measured to the shoulders and generally weigh between 70 and 100 pounds) [36]. Thus, healthcare facilities do not need to allow cats into the facility even if a person claims they provide a service function.

Cats, in general, should not serve as an AAT animal [1]. This is because of their temperament (i.e., bite or scratch moving objects); lesser ability to be trained compared to dogs; multitude of potential pathogens that they can transmit via direct contact, bites or scratches, inhalation, fecal-oral exposure, or indirect exposure (i.e., ectoparasites); occasional reports of nosocomial outbreak associated with cats; and lack of protocols for safe use as AAT animals. For similar reasons, cats should, in general, not be allowed in hospitals for "pet" visits. Exceptions for a single "pet" visit may be considered for terminal patients for compassionate reasons (to say good bye to their pet cat) under strict supervision and with the approval of the patient, the attending physician, and infection prevention.

One potential mitigation strategy would be to allow the use of a declawed cat. However, many people are opposed to declawing because of the pain inflicted on the cat, complications of the procedure, interference with the ability of cat when out of doors to escape predators, and impairment of natural cat behavior. Recently, New York State became the first state to pass legislation banning the practice of declawing of cats [37].

Future Research Needs

A recent review of pet ownership and physical health concluded that "most research on pet therapy/ownership has focused on dogs and to a lesser extent, cats. Essentially all of the laboratory research has been with dogs" [38]. Additional research including clinical trials is warranted to determine whether cat ownership is beneficial, especially to older persons. Similarly, almost all the research on the benefits and risks of animal-assisted therapy has focused on dogs. Additional research on the benefits and risks of using cats in AAT is warranted. Healthcare facilities that use cats for AAT should publish their policies and protocols for the safe use of cats and describe whether any adverse events were associated with use of cats.

Conclusions

Domestic cats are the most prevalent pets in the United States. Although less studied than dogs, some studies suggest that cats improve the well-being of older adults. Cats may be source of many infectious diseases transmitted to humans by bites, scratches, and licks (e.g., *P. multocida*); direct contact (e.g., MRSA); fecal-oral transmission (e.g., toxoplasmosis); inhalation (e.g., Q fever); or via ectoparasites. Cats are not recognized under the ADA as approved service animals. Due to their temperament and lesser ability to be trained, in general, cats should not be permitted to serve at AAT animals. Additional research should be undertaken to assess the benefits and risks of using cats as AAT animals.

Research Animals

Background

The advancement of human health through research in basic science as well as clinical and translational science often requires the application of sophisticated equipment and clin-

ical techniques for research animals. Many health-science centers may not be able to dedicate some equipment items and facilities solely for animal use due to the logistics and expense-associated. Therefore, healthcare institutions may need to consider using equipment and facilities used for humans to also study research animals. In addition, zoos and veterinary facilities may also appeal to human healthcare facilities to diagnose or treat sick or injured animals. In order to accommodate these situations, where applicable, acute care hospitals should establish comprehensive policies and procedures in order to ensure patient and public safety, while enabling safe, effective, and efficient evaluation and treatment of animals.

Benefits/Risks

Animals can serve as a reservoir and vehicle for potentially infectious pathogens; as such, potential pathogens can be transmitted from research animals to humans. Though the focus of this document is on transmission of infectious agents, given the variety of animals that may be used in research settings [39], it should be noted that some animal species may pose additional threats, such as physical injury from large animals or envenomation.

Potential routes of inoculation and the range of pathogens associated with research and veterinary animals are illustrated below.

1. Direct inoculation from percutaneous or mucosal membrane exposure: Blood and body fluids of research and veterinary animals may harbor a variety of pathogens and reports of transmission to laboratory workers or healthcare providers have been documented. Examples include *Streptobacillus moniliformis* (rat bite fever) resulting from the bite or scratch of laboratory rodents [40]; Herpes B virus encephalitis, transmitted by the bite of certain nonhuman primates [41]; skin and soft tissue infection due to *Pasteurella multocida* from cat bites and scratches, and dog bites [42]; and infection due to lymphocytic choriomeningitis virus, associated with exposures to laboratory rodents [43].
2. Inhalation: *Coxiella burnetii* (Q fever) and *Chlamydophila psittaci* (psittacosis) are examples of pathogens that have been spread from laboratory animals to humans [44, 45].
3. Direct contact: Infected mammals may transmit zoophilic dermatophytes (*Microsporum canis*, *Trichophyton mentagrophytes*) to humans through direct contact [46]. Similarly, MRSA has been noted to colonize various domestic animal species and may pose a risk of transmission to humans through contact [3].
4. Fecal-oral: Laboratory animals may carry a large number of pathogens subclinically in the gastrointestinal tracts that can potentially be transmitted via the fecal-oral route. Examples include *Salmonella sp.* (many animal species), *Campylobacter sp.* (mammals, birds, reptiles), and *Cryptosporidium sp.* (mammals, reptiles, primates).
5. Indirect transmission via vectors: Laboratory animals may occasionally harbor ectoparasites (e.g., fleas) that may serve as vectors for transmission of various pathogens to human laboratory personnel or HCP.
6. Indirect contact: Animals may be infected with prions, leading to potential risk for transmission via surgical instruments or medical devices if the same instruments are subsequently used on humans.

Mitigation

In order to minimize the risk of transmission of pathogens to humans, institutions should formulate thorough procedures to safely conduct diagnostic and therapeutic procedures on research animals and animals from veterinary or zoological sources. In doing so, healthcare facilities must ensure that human safety takes priority over research project goals. Although accredited healthcare research centers expend significant efforts to ensure research animal well-being and to minimize the likelihood that research animals harbor human pathogens, the risks cannot be eliminated as many potential pathogens are part of the normal microbiota of animals. At a minimum, the institution's IACUC must have approved all research involving animals, with supervision and monitoring by the institution's Comparative Medicine Department or Infection Prevention Department to ensure minimal exposure to potentially ill animals and optimal prevention measures are in place for animal and human interactions, including environmental cleaning protocols for any equipment used in common. Since animals may be infected with prions, surgical instruments and other medical devices should not be used on both animals and humans. Medical devices that require disinfection or sterilization should be used exclusively for animals. Alternatively, single use disposable devices could be used.

Conclusions and Future Research Needs

As advances in medical research to benefit humans continue to develop, healthcare facilities are increasingly likely to use advanced diagnostic and therapeutic facilities for patients as well as research animals, and possibly for zoo and veterinary animals. Healthcare facilities that use research animals should publish their policies and protocols for their safe use and monitor whether any adverse events were associated with their use. Single-use disposable devices are preferred for animal use, or instruments or devices that are exclusively

dedicated for animals. Future research is needed in this area to assure safe use of facilities at acute care hospitals for research animals.

PETS

Background

For the purposes of this document, 'pet' refers to a 'personal pet', namely a domestic animal that is owned by an individual patient which is neither a service animal nor an animal used for animal-assisted activities.

Over 67% of American households [2] own at least one pet (dogs 38.4%, cats 25.4%, birds 2.8%, and horses 0.7%), representing an estimated total of over 157 million companion animals [3]. The benefits associated with pet ownership, brief exposures to pets in various types of clinical and laboratory settings, and as an augmentation to traditional therapy are being increasingly realized and acknowledged [38, 47]. However, the safe management of pet visitation in healthcare facilities has not been systematically studied.

Benefits/Risk

Visitation of patients in healthcare facilities by their own pets potentially offers benefits and challenges. The potential benefits of pet ownership have been discussed in another section [27] and though no studies have specifically addressed the impact of pet visitation when the pet owner is in the healthcare setting, some of the described benefits, such as reduced levels of stress and reduced anxiety, may occur when the pet owner is a patient in the healthcare setting. While pets are less scrutinized and would not necessarily fulfill the requirements for animal-assisted activities visitation programs, the potentially strong human-animal bond and corresponding potential positive impact on the patient lead many facilities to permit this activity. The stronger bond with the pet could accentuate the positive impacts on the patient, and the preestablished relationship between pet and person could reduce the risk of adverse events such as bites and scratches.

However, pets and their owners typically do not undergo the same (or any) form of training and scrutiny as compared to animal-assisted activities teams. Pets do not typically undergo the same degree of health assessment or exclusion practices (e.g., age) as compared to animals used in animal-assisted activities. Further, while visitation with pets can be restricted, in theory, to only the individual patient, in practice, this may not be the case, as pets could encounter various HCP, visitors, and patients during their time in the facility. Therefore, it cannot necessarily be assumed that the implications of visitation of a personal pet are guaranteed to be restricted to an individual patient. Additionally, pets have typically not been temperament-tested, resulting in inconsistency in their behavior in an unfamiliar healthcare environment. Especially concerning would be young animals who may not be housebroken, are generally more excitable, and more likely to bite or scratch.

Mitigation

Healthcare facilities should have a policy regarding the admittance of pet animals into the facility and an individual that oversees the program. Pets in general should be prohibited from entering healthcare facilities, including pets of HCP, patients, and visitors. Exceptions can be considered when the healthcare team determines that visit with a pet would be of benefit for the patient and can be performed with limited risk to the patient, other patients, and for the healthcare facility as a whole. Examples of such exceptions may be for compassionate or clinical care purposes (such as terminally ill patient, a patient hospitalized for prolonged period of time, or where the healthcare team determines that a visit with a pet may improve the patient's physical or mental health). Pets of HCP should not be allowed in a healthcare facility since they may place other HCP and patients at risk (i.e., bites or scratches, allergies).

Risks associated with pet visitation should also be mitigated by limiting pet visitation to dogs, in particular to dogs at least 1 year of age and that are housebroken. Additionally, written information must be provided to the animal's owner/designee outlining the details of the visit, limited duration (1 h), expectations for acceptable and unacceptable practices, and supervisory and hygiene responsibilities of the owner/guardian. Visitation should be restricted for high-risk settings (e.g., patients on isolation precautions or in intensive care, or immunocompromised patients).

Future Research Needs

A recent review of pet ownership and physical health concluded that the value of pet ownership as a nonpharmacological treatment modality, augmentation to traditional treatment, and healthy preventive behavior is starting to be realized [38]. However, more investigations, including clinical trials and investigations that more closely examine the underlying mechanism of the pet-health effect, such as oxytocin, are needed. Finally, research is warranted on benefits and risks of pet interactions in the acute care setting.

Conclusions

Pets should in general be excluded from visiting their owners in the healthcare setting. Though pets are prevalent throughout the United States, little data are available to clearly demonstrate that benefits outweigh potential risks associated with pet visitation in the healthcare setting. Unlike animals used in AAT, pets and their owners typically do not undergo the same (or any) form of training and scrutiny as compared to animal-assisted activities teams, nor are they subject to the same degree of health assessment or exclusion practices (e.g., age) as compared to AAT animals. Exceptions may be considered for pet visitation for compassionate reasons on a case-by-case basis at the discretion of the healthcare facility, with close supervision. Additional research should be undertaken to assess the benefits and risks of allowing pets into healthcare facilities.

Medicinal Leeches

Background

Medicinal leeches are used in modern medicine to sustain circulation in the management of acute venous congestion in patients with replantation of digits and ears and in reconstruction using cutaneous or muscle flaps [1]. Evidence has also demonstrated that leeches might provide therapeutic pain reduction in patients with osteoarthritis [48]. Leech therapy most commonly uses *Hirudo medicinalis* and usually lasts around 2–6 days. Leeches may remove 5–15 mL of blood in this period to prevent congestion, keeping the tissue perfused until venous capillary return is established. Leech saliva released during feeding contains biologically active substances that act as vasodilators, anti-inflammatory mediators, anticoagulants, and analgesics. The most important component of leech saliva is the anticoagulant and bactericidal agent hirudin [49].

Benefits/Risks

Leech therapy (hirudotherapy) is generally considered safe and well-tolerated, but contraindications include arterial insufficiency, hematologic disorders, and allergy to leeches. Additionally, infection is a major complication. *Aeromonas hydrophila* is one common pathogen found in the gut of leeches which has been implicated in an incidence of sepsis after leech therapy [50]. Infections from *Vibrio fluvialis* and *Serratia marcescens* have also been reported [51, 52]. In addition to infection, other potential complications that can arise following hirudotherapy include thrombotic microangiopathy, anemia, and continued bleeding [53].

Mitigation

Antimicrobial prophylaxis with trimethoprim-sulfamethoxazole or ciprofloxacin appears to be equally effective for prevention of leech-associated infection of *Aeromonas* spp. [54]. However, antibiotic-resistant *Aeromonas hydrophila* infection following leech therapy has been reported.

Guidelines for using leeches include general storage protocols. Leeches should be stored in a refrigerator or cool, dark place in a glass or plastic container with bottled or distilled, non-chlorinated water as well as a salt additive. Tap water, direct sunlight, and temperatures above 20 °C are contraindicated for leech storage [55]. Unused leeches should be maintained by a pharmacy. Used leeches should never be reused even on the same patient or returned to the pharmacy. They should be disposed of by placement in a labeled, screw capped jar of 20 mL of 8% ethanol for 3 min, have 50 mL of 70% methylated spirit added, and disposed of as regulated (i.e., hazardous) medical waste [1, 56].

Future Research Needs

Further research is needed to understand the role of prophylactic antibiotic therapy to decrease risk of infection. Additionally, it is important to determine conditions in which leech therapy is contraindicated and improve prevention against adverse effects.

Maggot Debridement Therapy

Background

Larval debridement therapy, also known as maggot debridement therapy (MDT), uses sterile larva of the fly *Lucila sericata* and is implemented around the world to treat wounds that are resistant to conventional therapy. Maggots preferentially digest and remove necrotic tissue, leaving behind healthy tissue. The antimicrobial and anti-inflammatory properties of MDT therapy may also aid in wound healing through disinfection and tissue growth stimulation [57, 58].

Benefits/Risks

MDT has been shown to effectively treat chronic ulcers in diabetics and wounds in patients with malignancies [59, 60]. The most common complaint after MDT in patients is pain due to the hook-like teeth of maggots used for locomotion, but it can be controlled with analgesics [61]. While many clinical uses for MDT have been identified, contraindica-

tions include dry wounds, wounds close to large blood vessels, and patients allergic to fly larvae [62].

Mitigation

Before the use of larvae, external disinfection of the fly eggs is necessary to reduce the chance of introducing new bacteria into the wound. One study has yielded a protocol that requires immersing fly eggs for 10 min in 3% Lysol to provide high disinfection efficacy as well as maximum egg survival [63]. Larvae should be bred in a sterile and moist environment. After hatching, larvae should be stored in a refrigerator at 8–10 °C in an insulated box with oxygen and a humid atmosphere or used within 8 h [64]. Used maggots should be disposed of as regulated (i.e., hazardous) medical waste (i.e., placed in a tight-fitting bottle) and incinerated.

Future Research Needs

Large controlled clinical trials assessing benefits, risks, and cost-effectiveness of MDT need to be performed [65]. Further research needs to assess whether single or episodic debridement has better clinical benefits and whether MDT enhances wound healing after debridement is achieved. In order to decrease the social stigma of MDT, further studies should assess if the antimicrobial or anti-inflammatory properties of MDT can be concentrated in a medication or cream.

Aquariums/Fishtanks

Background

There are many infections that can be acquired in water either by trauma or animal-inflicted injury. Pathogens that can cause these infections include *Aeromonas hydrophila, Erysipelothrix rhusiopathiae*, *Mycobacterium marinum*, *Vibrio vulnificus*, *Staphylococcus* species, *Streptococcus* species, and *Sporothrix schenkii* [66].

Benefits/Risks

While aquariums and fish tanks are found by many to be visually appealing, infections pose a serious concern. *M. marinum* infections have been shown to be associated with cleaning fish tanks [67]. One study identified *A. hydrophila* in a patient's goldfish tank as the cause of peritoneal dialysis-related peritonitis [68]. Another study investigated an outbreak of *Salmonella paratyphi* in which 33 of the 53 patients owned aquariums and purchased tropical fish weeks before exhibiting symptoms. Furthermore, more than half of the pet shop aquariums where the fish were purchased tested positive for *Salmonella* serotypes [69]. Additionally, one public aquarium was found to be the source of an outbreak of Legionnaires' disease [70].

Mitigation

Because fish tanks can be a reservoir for many pathogens, fish tanks should be generally excluded from healthcare facilities, including nonclinical areas; however, aquariums may be permitted if maintained by trained personnel, utilize a closed system, and are implemented with water pumps designed to prevent aerosalization [1]. Patients should never have direct access to the aquarium.

Future Research Needs

Further studies into methods to improve tank hygiene are important to decrease potential for infection.

Petting Zoos

Background

Animal exhibits such as petting zoos provide a popular, managed learning environment that involves interaction with animals such as feeding and other physical contact. Conrad et al. compiled a review of the principal causal organisms of human illness associated with petting zoos and farm environments which include *Campylobacter*, non-0157 Shiga toxin-producing *Escherichia coli* (STEC), *Yersinia enterocolitica*, *Salmonella*, and Cryptosporidium [71]. Transmission risk of enteric infectious diseases and parasites may be higher in children where high risk behaviors may contribute to pathogen transmission, such as contact with manure and hand-to-mouth behaviors such as thumb sucking. Controlling transmission is difficult as livestock can shed pathogens such as *E. coli* O157:H7 intermittently, can shed due to stress from confinement, transport, and human interaction, and can carry infectious organisms in their fur, saliva, and hair due to fecal contamination [71]. Additionally, non-typhoidal *Salmonella* species are found in live poultry including baby chicks and ducklings [72]. Lastly, infections spread to humans from pet reptiles have been identified, with 90% of captive reptiles estimated to carry *Salmonella* [71].

Mitigation

As petting zoos and other animal exhibits have been associated with infectious outbreaks, such activities should be prohibited from healthcare facilities [1]. If any exceptions are made for special situations, they should not be conducted as an activity of the healthcare facility to avoid confusion about the healthcare facility's responsibility for legal and regulatory requirements and to protect the patients from possible acquisition of a zoonotic disease.

Future Research Needs

Further research should examine methods of animal vaccination and decontamination. Additionally, facilities should assess allowing children to view animals in an active and enjoyable experience without direct contact.

SARS-CoV-2 Infections in Animals

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of coronavirus disease 2019 (COVID-19), an emerging infection caused by the introduction of a novel coronavirus into humans late in 2019 (first detected in Hubei province, China) [73]. As of 26 April, SARS-CoV-2 had spread to greater than 200 countries with ~147,000,000 cases of COVID-19 reported worldwide leading to ~3,100,000 deaths [74]. The United States has reported ~32,000,000 cases of COVID-19 with ~572,000 deaths [74].

It appears that all human coronaviruses originated as bat viruses [73]. There are currently four endemic coronaviruses that cause human disease (229E, NL63, OC43, and HKU1). Over the recent decades, there have been three outbreaks caused by epidemic coronaviruses: SARS-CoV-1 (2003–2004), Middle East Respiratory Syndrome (MERS virus) (2012-present), and now SARS-CoV-2 (2019-present).

Challenge studies on animals have demonstrated that SARS-CoV-2 can infect the upper respiratory tract (mice, ferrets, nonhuman primates, mink, cats and bats), lower respiratory tract (mice, hamsters, ferrets, and nonhuman primates), and other organs such as the central nervous system (mice) and gastrointestinal tract (hamsters, ferrets, and nonhuman primates [75]. Challenge studies have demonstrated that ferrets and cats are more susceptible to infection with SARS-CoV-2 than dogs, pigs, chickens, and ducks [76]. To date, SARS-CoV-2 transmission from humans to animals has been reported in companion animals (dogs, cats, ferret), zoo animals (tigers, lions, snow leopards, cougars, pumas, gorillas), and farmed animals (minks) [77–80]. Infections typically appear asymptomatic in dogs, while clinical signs of respiratory and/or gastrointestinal disease tend to be mild to moderate in cats [78]. It is important to note that domestic dogs and cats are not easily infected under natural conditions, and there is no evidence that these animals spread SARS-CoV-2 to other animals or to people [81, 82]. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans has been described [83, 84].

Mitigation

Recommendations from the American Veterinary Medical Association with regard to SARS-CoV-2 and animals are as follows [82]: (1) Animal owners without symptoms of COVID-19 should continue to practice good hygiene during interactions with animals. (2) Do not let pets interact with people or other animals outside the household. (3) Keep cats indoors, when possible. (4) Walk dogs on a leash, maintaining at least 6 feet from other people and animals. Avoid dog parks or public places where a large number of people and dogs gather. (5) Those ill with COVID-19 should restrict contact with pets and other animals, just as you would restrict your contact with other people. (6) Routine testing of animals for SARS-CoV-2 is NOT recommended. Veterinarians are strongly encouraged to rule out other, more common causes of illness in animals before considering testing for SARS-CoV-2. (7) Human outbreaks are driven by person-to-person transmission and, based on the limited information available to date, the risk of animals spreading COVID-19 to people is considered to be low. Accordingly, there is no reason to remove pets from homes, even if COVID-19 has been identified in members of the household, unless there is risk that the pet itself is not able to be cared for appropriately. The Centers for Disease Control and Prevention (CDC) also has provided recommendations regarding SARS-CoV-2, and pets and other animals (CDC). The CDC has provided specific guidance on the management of SARS-CoV-2 companion animals and service animals [85]. Based on naturally occurring infection in companion animals to date, clinical signs likely to be consistent with SARS-CoV-2 infection in mammalian companion animals include: Fever, coughing, difficulty breathing or shortness of breath, sneezing, nasal discharge, ocular discharge, lethargy, vomiting, and diarrhea. We recommend that if domestic animals present in healthcare facilities (e.g., service animals) demonstrate these symptoms, the animal should be excluded (in consultation with the legal department) and owner should be encouraged to have the animal evaluated by

a veterinarian for COVID-19. Ideally, the handlers of animals used for animal-assisted therapy (AAT) should be fully immunized with a COVID-19 vaccine and ill animals should not be allowed to provide AAT.

Future Research Needs

Future research should focus on whether pet-to-human (i.e., dogs and cats) transmission can occur, and if so, how frequently. In addition, if pet-to-human occurs, it would be useful to assess the risk factors for such transmission including duration of contact, type of contact, and underlying comorbidities of the person that may place them at risk for such transmission (e.g., advance age, host defense abnormalities, and immunocompromising conditions or medications). The risk to farmed animals (e.g., pigs, cattle, chickens/turkeys, etc.) and to zoo animals, and the subsequent risk of animal-to-human transmission should be assessed. Finally, mitigation efforts to protect mink and their handles should be implemented and evaluated.

Conclusions

Recommendations for the safe oversight and management of AHC should comply with legal requirements and minimize the risk of transmission of pathogens from animals to humans when animals are permitted in the healthcare setting. Accordingly, healthcare institutions should ensure appropriate policies and procedures are implemented regarding the management of AHC and provide education to staff, patients, and visitors as indicated.

As the role of AHC evolves, research is warranted to establish evidence-based guidelines for their management and for that of emerging pathogens. Carefully designed and conducted studies are needed to better define the benefits and risks of allowing animals in the healthcare setting for specific purposes.

Additionally, there is a need for the systematic evaluation of risks of animals in healthcare based on the category of use (e.g., animal-assisted activities, service animal, research, and personal pet visitation). Prospective tracking of adverse outcomes associated with AHC facilities will help to refine and clarify the approaches to managing the controversies related to AHC. In addition, publication of any outbreaks, clusters, or infections attributable to the presence of AHC facilities should be encouraged. Finally, prospective studies on optimal infection prevention practices for management of animals in healthcare are needed.

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Decolonization Strategies for Infection Control of Gram-Negative Bacilli

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Background

Extended spectrum beta lactamase-producing Enterobacterales (ESBL-E) and Carbapenemase-producing Enterobacterales (CPE) have recently been classified by World Health Organization as the most critical priority pathogens for research and development [1]. The human gastrointestinal tract is a significant reservoir for gram-negative bacilli, including some of these antibiotic-resistant organisms. Eradication of the carriage of these gram-negative bacteria from the gastrointestinal tract is emerging as a therapeutic option, a strategy described as decolonization. In addition to reducing the risk of an individual carrier developing an infection caused by an antibiotic-resistant organism, decolonization can also prevent cross transmission, which is the spread of bacteria to other individuals. Further, decolonization can limit the possibility of horizontal gene transfer which confers resistance to the other bacteria in the gastrointestinal tract [2].

Although much of the published literature focuses on decolonization of gram-positive organisms, such as *Staphylococcus aureus*, there is a growing interest in the decolonization for gram-negative bacilli, particularly multidrug-resistant organisms. There are two main infection prevention and control approaches in which decolonization can be integrated: vertical and horizontal strategies. Vertical strategies target individual pathogens and are based on active surveillance and detection of colonization with organisms of interest such as multidrug-resistant gram-negative bacilli. This approach also implements strategies like isolation precautions when caring for patients infected or colonized with these organisms. An example of vertical infection control strategy is universal screening for methicillin-resistant S*taphylococcus aureus* (MRSA) colonization. Horizontal strategies are nonpathogen specific and include standard precautions such as hang hygiene, universal decolonization, antimicrobial stewardship, and environmental cleaning. An example of this strategy is chlorhexidine bathing. In this chapter, we will describe both approaches to decolonization but focus mainly on horizontal approaches with regards to gram-negative bacilli including topical and oral systemic antibiotics along with strategies focused on the use of probiotics and fecal microbiota transplantation.

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Skin Decolonization of Gram-Negative Bacilli

Human skin is considered a reservoir for pathogens associated with infections, particularly in the healthcare settings, and has been suggested as a potential target for decolonization to reduce bacterial burden and subsequent risk of infections. Although much of the focus of topical decolonization lies in preventing infections caused by gram-positive organisms which compose the majority of the skin microbiome, some studies have evaluated the impact of this strategy on the reduction of infections caused by gram-negative bacteria, including multidrug-resistant organisms. Nasal mupirocin is the most widely used topical antibacterial agent used for decolonization for *Staphylococcus aureus*. Povidone iodine is another widely used agent with activity against both gram-positive and gram-negative organisms. Triclosan is an antimicrobial agent with gram-negative activity incorporated into household soaps and skin care products [3]. Its role in decolonization for the control of gram-negative bacilli is not established, and its benefit over traditional soap and water in hand hygiene has also not been well-established. Overall, there is limited to no specific evidence to support the use of these products in topical decolonization of gram-negative organisms.

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_24

Chlorhexidine Gluconate

The agent with the most experience in topical decolonization of gram-positive and gram-negative organisms is chlorhexidine gluconate (CHG). CHG has been used widely for infection control purposes including hand washing, procedural skin preparation, and bioburden reduction (body washes). CHG is available in varying formulations, most commonly as a 2–4% concentration solution. CHG has a broad spectrum of activity against gram-positive and gram-negative organisms by binding to bacterial cell walls and altering the osmotic equilibrium. Studies evaluating its effectiveness in the prevention and control of infections caused by gram-negative bacilli have yielded mixed results.

Daily bathing with CHG has been suggested as an effective intervention to reduce the risk of healthcare-associated infections during an intensive care unit stay. A single-center randomized controlled trial (RCT) by Pallotto et al. recently performed in Perugia, Italy, showed evidence for daily bathing with 4% CHG in reducing blood stream infections. Approximately 450 patients were enrolled in the study and then randomized to the treatment arm which consisted of daily bathing with a soap-like solution of 4% CHG followed by a water rinse. In contrast, patients in the control arm were bathed with water and standard soap. Overall, the incidence of hospital-acquired infections, including bloodstream infections (BSI), central line-associated BSI (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP), was found to be 40.4% less frequent in the treatment arm compared to the control arm [4].

A number of other studies have evaluated CHG along with other infection control strategies such as hand hygiene and isolation precautions as part of a bundle program that may be effective in controlling infection outbreaks with gram-negative bacilli. One study by Hayden et al. demonstrated that daily 2% CHG bathing as part of a bundled intervention was associated with decreased skin colonization with *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales (KPC-E). In this study of long-term acute care patients, there was a statistically significant reduction in the rate of isolation of KPC-E from any clinical culture and a reduction in bacteremia caused by KPC-E [5]. Another study published by Cassir et al. evaluated an intervention of daily skin cleansing with CHG-impregnated cloths compared to soap and water in two six-month periods in the ICU in preventing healthcare-associated infections (healthcare-associated BSI, UTI, and VAP). In the two cohorts, 29 patients in the CHG group developed a healthcare-associated infection versus 56 patients in the control group. In subgroup analysis, there was a statistically significant decrease in the incidence of healthcare-associated infections caused by gram-negative bacilli in the CHG group [6]. Another study performed by Noto et al. evaluated the impact of CHG on the reduction of healthcare-associated infections. This was a crossover study of nearly 10,000 patients admitted to 5 adult intensive care units of a tertiary medical center in Nashville, Tennessee, from July 2012 through July 2013. This prospective crossover study did not demonstrate a reduction in healthcare-associated infections such as CLABSI, CAUTI, and VAP caused by all organisms including gram-negative bacilli [7]. A large, cluster-randomized trial along with an interrupted time series study performed in 13 different ICUs across Europe, daily CHG combined with a hand hygiene intervention, showed reduced acquisition of antimicrobial-resistant bacteria, particularly MRSA, associated with CHG. In subgroup analysis, this study did not demonstrate any decrease in the acquisition of ESBL-producing Enterobacterales after the implementation of CHG bathing [8].

Overall, the majority of current evidence supports the use of horizontal approaches of universal decolonization such as using CHG bathing as an effective strategy to prevent healthcare-associated infections. However, more information is needed to evaluate the impact of this strategy in preventing infections caused by gram-negative bacilli. Notably, CHG bathing does not target the gastrointestinal tract where the majority of gram-negative bacteria reside. Additionally, the concern of the impact of topical CHG on the emergence of CHG-resistant organisms has been expressed, which will need to be monitored closely in the future.

Selective Decontamination

A finding published by Waldemar Johanson in 1969 described that the pharyngeal flora of patients changed mostly from gram-positive to gram-negative bacteria just a few days after hospitalization. Later, they identified gram-negative organisms as the major cause of hospital-acquired infections such as pneumonias [9]. Selective decontamination is a strategy used to prevent or minimize the risk of developing infections by administering prophylactic antibiotics that target the digestive tract. Selective oropharyngeal decontamination (SOD) is the application of topical antibiotic paste to the oropharynx only, without enteral or intravenous antibiotics. Chlorhexidine is widely used as part of the routine oral care in ICU settings. Selective digestive decontamination (SDD) consists of enteral application of nonabsorbable antimicrobial agents, such as colistin, aminoglycosides, and amphotericin B, to eradicate aerobic gram-negative bacteria and yeasts, often followed by a short course of intravenous systemic antibiotic such as a third-generation cephalosporin. This practice is more readily accepted in European countries, such as the Netherlands, and is considered standard of care for patients admitted to the intensive care unit in many

centers. Further surveillance is carried out by following up on throat and rectal cultures. In most situations, SDD does not include antimicrobial activity against all possible organisms and excludes anaerobes, enterococci, and the multidrug-resistant Enterobacterales. The evidence for SDD dates back to as early as 1982, and to date, over 60 randomized control trials are published [10]. A summary of the more recent individual trials and meta-analyses will be presented in this section.

One large meta-analysis undertaken by Silvestri et al. was published in 2007. In this study, 51 RCTs conducted between 1987 and 2005 including over 8000 patients across several ICUs were included. SDD had a significant effect in reducing rates of mortality, bloodstream infections, and infections caused by gram-negative organisms. There was no significant effect on reducing infections caused by gram-positive organisms [11]. This analysis had several limitations; hence, a follow-up analysis was performed that evaluated the efficacy of SDD in reducing the rates of infections and colonization between the gram-positive and gram-negative organisms. Data from 54 RCTs were included with nearly 10,000 patients. SDD was associated with statistically significant reductions in oropharyngeal and rectal carriage of gram-negative organisms. Further, SDD was found to significantly reduce the rates of lower respiratory infections, bacteremia, and overall infections caused by gram-negative organisms [12]. As noted in the prior analysis, SDD did not significantly reduce either carriage or infection rates in patients with gram-positive organisms. These investigators then further looked at 21 RCTs with a total of 4902 patients that looked at the use of SDD/SOD with a parenteral component identified as the full 4 component protocol of the decontamination strategy. Overall, mortality as well as late mortality was significantly reduced. However, early mortality and mortality specifically attributed to infections were not reduced [13].

Many variations of the original decontamination strategy protocol have been incorporated into clinical practice and modified, as feasible. In 2018, the Dutch guidelines on selective decontamination in the ICU patients were revised to recommend use of SDD over SOD. This change from the 2014 guidelines was based on two large studies that showed lower mortality in the SDD group. One study by Oostdijk et al. performed in 16 ICUs in the Netherlands from 2009 to 2013 compared 12 months of SDD to SOD. The 28-day mortality was 25.7% during SOD and 23.8% during SDD. ICU and hospital mortality were also lower with SDD [14]. Plantinga et al. performed a large individual patient data meta-analysis to look at the randomized and cluster-controlled trials on selective digestive and oral decontamination published between 2000 and 2016. Six studies were included in the analysis which included 16,528 patients. Hospital mortality was found to be 29.5% for SDD patients compared to 31.5% for SOD and 32.4% for the control group. Similar results were reported for ICU mortality (20.8% for SDD, 22.9% for SOD, and 24.2% in the control groups), but no difference was noted in the subgroup analysis between the medical and surgical patients. Overall, the study concluded that SDD is more effective at improving hospital and ICU survival than SOD. One limitation to this meta-analysis is that these studies were performed in countries with a low prevalence of antimicrobial resistance which limits the generalization of these findings [15].

Recent randomized control trials have been published that further support the use of selective decontamination in special populations such as prior to colorectal surgeries and organ transplant. However, there is not sufficient evidence to support the use of SDD in lowering the risk of multidrug-resistant gram-negative organisms. In the recently published SELECT trial, it was concluded that SDD reduces infectious complications after colorectal cancer resection but did not significantly reduce the incidence of anastomotic leakage. This was a multicenter open-label RCT in six centers in the Netherlands. A total of 485 patients were enrolled from 2013 to 2017 and randomized to SDD arm who received oral suspension of amphotericin B, colistin, and tobramycin four times daily starting at 3 days before surgery along with a single preoperative dose of cefazolin and metronidazole. The control group received the preoperative antibiotics only. Thirty-four (14.9%) patients in the SDD group had one or more infectious complications compared to 61 (26.9%) in the control group. There were fewer surgical site infections in the SDD group but no difference in other infections such as pneumonia, urinary tract, or other intravascular catheter-related infections. Anastomotic leakage was seen in 14 (6.1%) in SDD group and 22 (9.7%) in the control group. The 30-day mortality rate did not differ between study arms. The SELECT trail was discontinued early as it was determined that no superiority was achievable in the SDD arm for prevention of anastomotic leak [16]. Smaller studies demonstrate similar results of SDD decreasing infectious complications in various gastrointestinal surgeries including esophageal and gastric resections for both benign and malignant disease [17].

Another large population in which the question of intestinal decolonization has been repeatedly studied is the immunocompromised population, including patients with leukemia and bone marrow transplant recipients. Studies over the past two decades cite the use of prophylactic antibiotics against gram-negative bacteria in leukemia patients while preserving the protective anaerobic flora by avoiding antibiotics such as penicillin [18]. A study performed by Stoma et al. evaluated the efficacy of oral colistin in eradicating the intestinal carriage of multidrug-resistant bacteria in patients with hematological malignancies in Belarus. A short-term positive outcome was observed after 14 days of treatment with oral colistin in eradication of multidrug-resistant gram-negative

bacteria; however, eradication was not significant at day 21 (61.3% versus 32.3%). Further, a small reduction in the incidence of blood stream infections was seen in the treatment group compared to controls in the first 30 days while receiving chemotherapy [19]. Some of the limitations of this study include a small sample size of only 62 patients involving only one center, which may not be reflective of the general population.

The emergence of further antimicrobial resistance is appropriately raised as a concern with both of these decontamination strategies. Most of the evidence to date, however, does not report increasing level of resistance with any of the selective strategies. In a large meta-analysis performed in the Netherlands which looked at 38 intensive care units for 4 years, 17 of which continuously used SDD/SOD strategies, there was no statistically significant resistance among the 637 blood isolates [20]. Similarly, in a single-center evaluation, 21 years of SDD use was not associated with an increase in antibiotic resistance in ICU [21].

Few studies have looked at the impact of SDD on the composition and diversity of the microbial flora. In one study, SDD was associated with an increase in the abundance of resistance genes carried by anaerobic gut bacteria in 12 patients [22]. In a subsequent study, the same investigators analyzed the gut microbiome in 10 ICU patients that received SDD and compared it to 10 healthy subjects at 1-year interval. The intestinal microbiota of the ICU patients differed from those of the healthy subjects and was characterized by lower microbial diversity, decreased level of *Escherichia coli* and of anaerobic gram-positive bacteria, and increase of Bacteroidetes and enterococci. Four types of resistance genes conferring resistance to aminoglycosides, macrolides, disinfectants, and tetracycline were significantly more abundant among the ICU patients when compared to healthy subjects [23]. At this point, the impact of SDD on the intestinal microbiome remains an important area of further study.

Systemic Antibiotics

Based on the existing observational data, there is a growing interest in evaluating the use of systemic, absorbable antibiotics in decolonization of gram-negative bacilli with or without oral or digestive decontamination. A small, single-center study from Germany described a potential association between duration of shedding of Shiga toxin-producing enteroaggregative *E. coli* (STEC) and the receipt of azithromycin during an outbreak of STEC [24]. In this study, azithromycin was given for meningococcal prophylaxis in the setting of administration of eculizumab used in the setting of hemolytic uremic syndrome. In retrospective analysis, azithromycin was associated with lower frequency of STEC 0104:H4 carriage. A review of five liver transplant recipients in the setting of an outbreak of ESBL-producing *E. coli* included the administration of norfloxacin for 5 days as a component of an outbreak control strategy. In this study, a transient reduction of ESBL-producing *E. coli* carriage was identified [25]. Based on the limited data available, coupled with significant potential adverse effects, including the risk of *C. difficile* infection, the use of systemic antibiotics to reduce colonization with gram-negative organisms is not recommended.

Investigational Agents for Decolonization

The gastrointestinal microbiome consists of thousands of bacterial species, including gram-negative bacilli. As knowledge about the microbiome increases, strategies to restore homeostasis within the complex microbiome have been explored. Circumstances in which enteropathogens, including multidrug-resistant gram-negative bacilli, dominate the microflora may be directly addressed through attempts at restoration of a healthy, diverse intestinal microbiome. Two potential strategies that may be incorporated in the decolonization for gram-negative bacilli include reconstitution of a healthy intestinal microbiome through fecal microbiota transplantation and the use of probiotics.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is the administration of healthy donor stool into the patient's gastrointestinal tract. This can be performed via colonoscopy or enema into the lower gastrointestinal tract or via endoscopy or swallowed capsules into the upper small intestine. This form of intervention is considered safe and is recommended for use in recurrent infections with *Clostridioides difficile*. There have been various studies that used FMT as a method of decolonization with a mix of outcomes.

One multicenter randomized controlled trial published by Huttner et al. was undertaken in Switzerland, France, Israel, and the Netherlands. Thirty-nine patients that were colonized with ESBL-producing Enterobacterales (ESBL-E) (n = 36) and/or carbapenemase-producing Enterobacterales (CPE) (n = 11) were included in the study from year 2016 to 2017. The intervention group received 5-day course of oral antibiotics including colistin and neomycin followed by FMT. The control group received no intervention. The conclusion was that nonabsorbable antibiotics followed by FMT slightly decreased ESBL-E and CPE carriage by 41% in the treatment group compared to 29% in the control group, with an odds ratio for decolonization success of 1.7 [26]

Another single-center study by Bilinski et al. studied the use of FMT for eradication of multidrug-resistant gram-negative bacteria in 20 patients with hematologic malignancies in Poland. The patients were colonized with CPE, ESBL-E, and other multidrug-resistant organisms. Complete decolonization was achieved in 70% (15/20) at 1 month after FMT and in 13 out of the 14 (93%) of patients followed at 6 months [27]. There are several other smaller case studies published in the recent years that demonstrate benefit of FMT in decolonization of gram-negative bacilli, including multidrug-resistant organisms; however, there are limitations in terms of follow-up, and it remains unclear whether the benefit is noted from antibiotic pretreatment versus FMT [28–30]. Large, well-designed trials are needed to assess the short- and long-term impacts of FMT for intestinal decolonization of multidrug-resistant gram-negative bacilli.

Probiotics

Probiotics are live microbial food supplements with health benefits. They may have a role in changing the gut microbiota as a method to counteract the existing colonization by gram-negative bacteria. Some of the other ways that probiotics may work include production of toxins and acids to inhibit the growth of pathogens and improvement of intestinal barrier function.

A recently published randomized placebo-controlled trial conducted in Sweden in a small population of 80 patients did not show the superiority of a probiotic which contains a mixture of eight different living bacterial strains when compared to placebo in eradication of ESBL-producing Enterobacterales. Successful intestinal decolonization was achieved in only 12.5% of patients in the probiotics group compared to 5% in the control group, which was not statistically significantly different [31]. Another pilot study performed in patients of a long-term care facility in Austria evaluated the effects of a multispecies probiotic on intestinal and skin colonization by multidrug-resistant gram-negative bacteria (MDR-GNB). Patients colonized with MDR-GNB received a 12-week oral course of a multispecies probiotic that contained 12 different bacterial strains. The prevalence of intestinal colonization by MDR-GNB decreased to 75% at week 12, followed by a reduction to 42% at weeks 20 and 24. Further analysis with the fecal microbiome suggested an increase in the enterococcus at week 12 during the probiotic treatment phase, but this was not demonstrated after this time. During follow-up at week 36, two patients that tested negative at weeks 20 and 24 for MDR-GNB were found to be positive, suggesting that decolonization may be transient and the local environment of the facility may play a role in new colonization [32].

There is mixed evidence on the use of probiotics for reduction in healthcare-acquired infections such as pneumonia and ICU length of stay and very limited evidence on its utility for reduction in infections caused by gram-negative bacilli, including multidrug-resistant organisms. Overall, more studies are needed to better understand the role of probiotics in intestinal decolonization of gram-negative bacteria.

Conclusion

Decolonization may be an effective strategy to reduce infections caused by gram-negative bacilli and reduces healthcare-associated transmission of these organisms. Topical decolonization with chlorhexidine as well as selective oral and digestive decontamination of the gastrointestinal tract with various antibiotics has shown effectiveness in some limited studies. However, the data are not conclusive, and no consensus has been reached regarding the optimal decolonization strategy and the most appropriate setting for its use. Although the concerns for emerging antibiotic resistance remain, most of the studies have not demonstrated such risks. Ongoing studies are needed to recommend alternative methods such as fecal microbiota transplantation and routine use of probiotics for decolonization. This is an important area for further research to determine whether such strategies can be useful to prevent the transmission of multidrug-resistant gram-negative organism.

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Testing Water for *Legionella* Prevention

25

Brooke K. Decker and Cornelius J. Clancy

Legionellosis consists of two distinct clinical syndromes, a mild flu-like illness called Pontiac fever [1] and a more severe disease that disproportionately affects immunosuppressed hosts, referred to as *Legionella* pneumonia or Legionnaires' disease [2]. Both diseases stem from infection with the waterborne bacteria *Legionella*, in particular *L. pneumophila*, the species most pathogenic to humans [3]. Infection is acquired after aspiration or inhalation of contaminated water. Aspiration is the primary mode of infection in healthcare-associated cases [4].

Approaches to prevention and control of Legionella infection in Allegheny County (PA) health care facilities, one of the first comprehensive recommendations on *Legionella* control in healthcare, was published in 1997. Early in the document, the authors state "It became apparent that there was no uniformity in the evaluation and monitoring of Legionella in hospital water systems…" [5]. Despite the importance of *Legionella* as a cause of human illness and the widespread publicity given to disease outbreaks in healthcare and community settings, this statement regarding controversies in *Legionella* management remains largely true 25 years later. In this chapter, we will review current practices for testing healthcare water systems for *Legionella* prevention, highlighting areas of controversy and uncertainty. We focus on the management of healthcare water systems because these facilities are likely to be most relevant to the interests and professional practices of readers. Healthcare facilities house persons who are most vulnerable to Legionnaires' disease. Not uncommonly, hospitals and healthcare campuses are large, built over decades, and consist of multiple additions and sites of reconstruction. As a result, buildings typically contain highly complex water systems, for which inventory and mapping may be incomplete or inaccurate. The challenges in *Legionella* control presented by these systems are manifold and made more pressing by a particular responsibility to protect the health and safety of patients, visitors, and employees.

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How to Test for *Legionella*

Culturing Methods

Environmental testing for *Legionella* most commonly includes swab testing and water cultures. Less commonly, air sampling is performed to explore the association between positive water sources and the potential for nosocomial infection [6, 7]. Water systems may also be cultured for amoebas that carry *Legionella* intracellularly, but such efforts are more of a research tool than standard infection prevention practice.

Legionella bacteria reside in biofilms coating the interior of pipes and fixtures or as free-floating planktonic cells. Fixtures with complex surfaces or mixing of hot and cold water are more likely to harbor *Legionella* [8], since warm water provides an ideal temperature for growth [9]. Aerators [10] and electronic faucets (magic eye faucets) [11, 12], in particular, provide additional interior surfaces on which biofilms can develop. The US Centers for Disease Control and Prevention (CDC) recommends the use of swabs in the investigation of *Legionella* cases [13], based in part on the theoretical consideration that they improve *Legionella* detection within biofilms and subsequently in water samples. While this hypothesis is intuitively appealing, it has not been borne out in testing [14]. In some studies, swabs have been demonstrated to be less sensitive than water cultures [15]. If swab testing is performed, CDC recommends briefly running the water to wet the interior of the fixture. A dacron or polypropylene-tipped swab should be inserted as far as possible into the fixture followed by a vigorous attempt to

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_25

disrupt the resident biofilm [13]. Swabs should be stored in water from the same fixture and transported to the lab as soon as possible. Depending on the fixture sampled, some creativity is needed to determine the best location to swab. Aerators, moving parts amenable to biofilm, or areas of turbulent or stagnant flow represent good targets for swab collection. Certain point-of-use fixtures (such as those in behavioral health units or some shower heads) may require partial disassembly to access with a swab. Collaboration with plumbing or facilities staff can significantly improve collection process efficiency.

Water collected for the detection of planktonic *Legionella* may be directly plated or filtered. Direct plating is best reserved for non-potable water with a known or suspected high bacterial count. Filtering is superior to centrifugation for improving yield [14] and is most appropriate for water from areas with lower bacterial counts, such as potable water sources where screening a larger volume of water is needed to detect *Legionella*. CDC recommends the use of a 0.2 micron polycarbonate filter. After filtration, the filter is vortexed in a 50 mL centrifuge tube with 5 mL of sterile water, which is plated [6]. If source water has been treated with chlorine, 0.5 ml of 0.1 N sodium thiosulfate per liter should be added in order to neutralize the potential for the inhibition of *Legionella* growth. If samples cannot be plated immediately, prompt refrigeration at 4 °C is recommended [6]. For areas without in-house testing, significant error does not appear to occur when samples are appropriately packaged and promptly shipped [16].

Specific guidance for *Legionella* air sampling has been described [6, 17]. Matching sequence types of *Legionella* have been detected in the air and water of healthcare facilities [7]. However, the sensitivity of air sampling and the validity of negative results are not established. As such, air sampling may serve as a complementary approach to water studies in certain situations, but it is not a standard component of healthcare facility *Legionella* testing.

Legionella Growth Requirements

Legionella bacteria require longer incubation time and special media and conditions for detection compared to routine bacterial cultures. *Legionella* media typically include 0.1% alpha-ketoglutarate, which may be more important in limiting oxygen toxicity than in direct metabolism [18]. Both clinical and environmental cultures can be grown on buffered charcoal yeast extract (BCYE), a "non-selective" *Legionella* growth media. Additional supplementation with bovine albumin (ABCYE-BCYE with 1.0% albumin) may increase the detection of certain strains, including *L. micdadei* and *L. bozemanii* [19].

Since bacteria other than *Legionella* grow on BCYE, "selective" *Legionella* media with antimicrobial supplementation are useful for water sources with higher bacterial counts. Polymyxin B, cycloheximide, and vancomycin are components of both PCV (polymyxin, cycloheximide, vancomycin) and GPCV/GVPC media ("G" denotes the addition of glycine to PCV). These selective media reduce the growth of non-*Legionella* bacteria, as well as non-pneumophilia *Legionella* species. They are best used for water from areas with high bacteria contamination such as non-potable sources, air sampling, or plating in parallel with "non-selective" media to ensure both sensitivity and the ability to interpret culture results if heavy growth occurs. Colonies that grow on BCYE or PCV media should be inoculated onto media without L-cysteine (BCYE- or PCV-). Growth on BCYE but not on BCYE- is consistent with *Legionella* spp. and should prompt further identification [6]. Additional *Legionella* media include glycine, vancomycin, polymyxin B, and natamycin (GVPN), which substitutes natamycin or anisomycin for cycloheximide as a fungal inhibitory agent that is less toxic to laboratory personnel. Selective *Legionella* agar containing bromocresol purple and bromothymol blue (BCYE with DVGP (dyes, glycine, vancomycin, and polymyxin B)) or MWY (the medium of Wadowsky and Yee [20]) may aid in the visual identification of *Legionella*.

In addition to special media, selection in a population of bacteria can be improved by exploiting *Legionella*'s relative resistance to low pH. Acid treatment of the specimen before plating reduces overgrowth by non-*Legionella* bacteria. Procedural guidance can be found on the CDC website [6]. There may be little difference in *Legionella* recovery between selective and non-selective media when acid washing is used [14, 21].

After inoculation, *Legionella* plates should be placed in a humidified, 2.5% CO_2 incubator at 35 °C. CDC recommends incubation for 7 days [6], but growth of *Legionella* can take up to 2 weeks [22]. For hospitals with in-house *Legionella* detection capability, it may be reasonable to hold plates longer than 7 days. Ten-day incubation periods are recommended by the International Organization for Standardization [23] and frequently cited [21, 24]. Incubation longer than 7 days should be considered in circumstances where detection of non-pneumophila *Legionella* species is sought (such as surveillance in an area housing immunosuppressed patients or in the investigation of non-pneumophila cases.)

Elite certification is provided by CDC to laboratories that perform to an adequate standard in culturing *Legionella*. Healthcare facilities with the capacity to support in-house *Legionella* culturing should become Elite-certified. In-house *Legionella* surveillance allows for faster notification of positive results and simplifies the collection of strains for typing or other follow-up analyses. Many commercial enterprises perform *Legionella* testing for facilities without in-house

capabilities. Hospitals should contract with an Elite Laboratory; infection prevention leadership should be aware of specific culture methods and the duration of incubation and whether these can be modified if desired.

Legionella Burdens Within Positive Water Cultures

Quantitative cultures for *Legionella* hold intuitive appeal as measures of burden within a water system. However, the value of determining *Legionella* concentrations in assessing risk has not been established. Indeed, nosocomial cases of legionellosis are commonly encountered when counts within culture-positive samples from healthcare facilities are below thresholds for water system treatment proposed by the Occupational Safety and Health Administration (OSHA) for cooling towers [25, 26]. Moreover, an analysis of Elite-certified labs revealed that quantitation of *Legionella* by colony count varied extensively [27]. Therefore, utilizing a threshold for *Legionella* growth or comparing colony counts between samples has no established clinical value. CDC recommends against using strict CFU/mL thresholds in designating a healthcare facility water system as safe or in triggering remediation [27].

Amoeba Culture

Legionella frequently exist intracellularly in amoeba, and their coexistence within amoeba has been linked to persistence in the setting of adequate biocide levels [28]. Amoebic culture is a sensitive detection method, but effort-intensive [15]. A correlation between increased sensitivity of *Legionella* detection with amoeba culture and increased patient risk in the setting of this detection has not been established.

Additional Detection Methods

Alternative water testing methods have been suggested, including qPCR and immunomagnetic separation [29]. These strategies aim to better detect *Legionella* in the water, including what has been called viable but non-culturable (VBNC) [30] *Legionella*. It is less clear what risk, if any, *Legionella* that is detectable, but not cultivable, poses to patients.

Which Water to Test

Legionella prefers relatively high temperatures with an optimal growth range between 32 and 42 °C [9], and strains are more commonly isolated in hot water systems that do not maintain recirculating temperatures greater than 122 °F (50 °C) [9]. Accordingly, most attention in healthcare facilities has focused on sampling hot water systems. CDC recommends testing only hot water [13]. In contrast, the United Kingdom Health and Safety Executive Guidance [31] and the United States Veterans Health Administration [32] require routine sampling of both hot and cold water in healthcare facilities. Areas of increased risk to patients, such as wards that house immunosuppressed hosts or locations that have undergone recent additions of new plumbing into an established system, are reasonable targets for testing. Maintenance or construction involving a water system can result in the disruption of biofilm and the release of planktonic *Legionella*. Construction is a risk factor for *Legionella* outbreaks [25, 33].

A less obvious source of potential water exposure in the hospital setting is the non-potable water systems involved in heating and cooling. Outbreaks occurring in the absence of potable water system positivity should prompt investigation of cooling towers as a potential source [34]. Open cooling towers have been associated with *Legionella* cases [35]. Closed-loop cooling systems can also harbor *Legionella*, but patient exposure is less likely outside of a breach of the cooling system (such as in a cold winter if an incompletely drained system freezes). In facilities with open cooling towers, the orientation of the air intake for air handling systems should point away from the cooling tower and be as separated in distance as possible to reduce the potential for inflow of possibly contaminated aerosols.

When to Test

Environmental *Legionella* testing should be performed routinely after the detection of a possible or definite hospital-associated case. Such "case-based" testing is recommended by the CDC and allows for the identification of facility sources of *Legionella* risk requiring remediation. Surveillance *Legionella* testing and water system remediation in response to positive cultures have been advocated in the absence of hospital-associated cases, as a means of reducing the risk of nosocomial infections, but remain controversial [36]. Surveillance testing can be further divided into two categories, defined by O'Neill et al. as primary and secondary prevention [37]. Primary prevention is defined as environmental sampling and remediation at institutions without a previous history of nosocomial cases. Secondary prevention occurs in facilities that have had previous cases of *Legionella*, when testing and remediation are performed outside of an immediate investigation into patient cases.

Case Investigation

One or more healthcare-associated cases of *Legionella* warrant investigation of hospital waterworks. Investigations must be multidisciplinary to be complete, including an

evaluation of the consistency of engineering controls (pH, biocide levels, temperature), as well as *Legionella* culturing from potential sources of water exposure. Sites of exposure, such as relevant patient care unit(s), restrooms, or showers that might have been used, and any other additional water sources encountered (baths, therapy pools, fountains, etc.) during the incubation period are appropriate targets for sampling [3, 38].

Specific guidance on water system sampling varies greatly by agency, and a recent summary by Parr et al. highlights the differences in primary prevention recommendations [39]. A summary of selected guidance is presented in Table 25.1. For water samples, the first draw of the initial flow of water from the fixture is referred to as "before-flush." The before-flush sample reflects what the patient might experience were they to access the sink. A sample in which the water is allowed to flow for a period of time (e.g., to achieve the maximum temperature) is referred to as "after-flush."

In the absence of consensus on how to obtain samples for testing, it is most reasonable to proceed in a manner consistent with the reasons for sampling. First-draw samples are the logical choice when investigating a patient case. First draw best represents the patient's exposure and includes the fixture as a potential source of *Legionella* colonization. In a study of samples obtained at 0, 5, 10, and 15 minutes of flushing, the first-draw sample demonstrated the highest yield of *Legionella* [21]. Post-flush samples make sense when the water system is suspected in situations of inadequate engineering control or to validate a remediation of the water system. Institutions investigating an outbreak should consider both "first-draw" and "post-flush" samples in order to ensure that the risk associated with a potentially colonized fixture and the central potable water system are both evaluated. Fixture samples are more sensitive in identifying *Legionella* than hot water return line testing [40].

Surveillance

Routine environmental surveillance for *Legionella* in the absence of definite or possible healthcare-associated cases is controversial. As of this writing, surveillance testing for *Legionella* (in the absence of clinical cases) is not universally required. Routine surveillance testing is resource-intensive and insensitive, and the same goals might be accomplished by assuming universal positivity and instituting mitigation strategies in settings where vulnerable patients reside [41]. As mentioned, CDC recommends case investigation environmental testing in lieu of surveillance strategies. Rather than recommending routine surveillance, the most recent American Society of Heating, Refrigerating and Air-Conditioning Engineers document (ASHRAE, 188–2015) advocates thoughtful evaluation of water system risk and the generation of a facility-specific water safety plan [42]. Routine surveillance, rather than a case-based approach to environmental detection, has been recommended due to the potential severity of infection, susceptibility of hospitalized populations, and the advantage of prevention if *Legionella* is detected [5, 43, 44].

Appropriate consideration of patient risk, waterworks complexity, and facility history is necessary before deciding to perform surveillance cultures for *Legionella*. Healthcare facilities contemplating surveillance water testing should first consider if patients at greatest risk for *Legionella* infection are housed at the facility. According to the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) guidance, patients at greatest risk include transplant patients and those requiring protective environments [38]. CDC/HICPAC guidelines from 2003 state that "water samples from the potable water in the solid-organ transplant and/or PE (protective environment) unit can be performed as part of an overall strategy to prevent Legionnaires disease in PE units." The guidelines suggest that healthcare facilities

Table 25.1 Summary of selected guidance on environmental testing for *Legionella*, requirement, and approach

Guideline	Primary surveillance required	Water culture minimum	Swab cultures	First draw	Post-flush	Hot water	Cold water	Hot water tanks/ recirculating loops
OSHA 2003 [26]	No	250 mL	Yes	Yes	Yes	Yes	Yes	Yes
WHO 2007 [9]	No	1 L	Yes	Yes	Yes	Yes	Yes	Yes
EWGLI 2011 [58]	No	1 L	Yes	Yes	Yes	Yes	Yes	Yes
UK HSE 2013 [31]	Yes	200 mL	No	Yes	Yes	Yes	Yes	Yes
VHA 1061 2014 [32]	Yes	250 mL	No	Yes	No	Yes	Yes	No
ACHD 2014 [57]	No	1 L	Yes	Yes	Yes	Yes	Yes	Yes
CDC June 2015 [6]	No	1 L	Yes	No	Yes	Yes	No	Yes

OSHA Occupational Safety and Health Administration, *WHO* World Health Organization, *EWGLI* European Working Group for Legionella Infections, *VHA* Veterans Health Administration, *ACHD* Allegheny County Health Department, *CDC* Centers for Disease Control and Prevention

use periodic potable water culturing as a basis to recommend diagnostic testing to clinicians if positive water cultures are found.

Per the most recent ASHRAE, appropriate high-risk groups include patients with burns, those receiving chemotherapy for cancers or medications that impair immune functioning, solid organ and bone marrow transplantation recipients, and persons with renal disease, diabetes, or chronic lung disease [42]. ASHRAE stops short of recommending *Legionella* testing of water from locations where patients with these conditions are housed. Rather, the guidelines state that the decision of whether to test for *Legionella* should consider the presence of immunosuppressed patients, success in maintaining control limits (biocide, temperature, etc.), and prior history of facility nosocomial legionellosis [42].

A threshold for environmental site positivity was first proposed in a 1983 study, in which the authors suggested that the risk for nosocomial legionellosis within a hospital increased significantly when >30% of sampled sites were culture positive for *Legionella pneumophila* [45]. Based on these data, 30% positivity had been used at many centers as an action threshold for remediation [38]. This practice, however, is controversial. A review of data from peer-reviewed studies reported that the sensitivity and specificity of a 30% threshold relationship for nosocomial legionellosis were only 59% and 74%, respectively. During an outbreak of *Legionella* pneumonia at a Pittsburgh hospital, cases were diagnosed when positivity rates were as low as 4%. The perception that *Legionella* was under control because of positivity rates below the threshold was concluded to have contributed to the duration of the outbreak.

In summary, surveillance testing for *Legionella* is most reasonable in settings with high-risk patients, inadequate environmental controls, and a history of nosocomial legionellosis. In the absence of these factors, decisions on the need for surveillance testing should consider if adequate clinical *Legionella* testing is performed and the risks, benefits, and feasibility of initiating a water sampling program. There is no threshold level of water positivity that signifies a facility is safe from nosocomial acquisition of *Legionella*.

Some jurisdictions and healthcare systems mandate *Legionella* testing. In 2005, New York State required quarterly testing of areas serving patients with transplants or receiving chemotherapy [46]. After a 2015 outbreak of legionellosis in the Bronx, New York City enacted legislation mandating cooling tower registration, testing, and treatment, as well as hospital water surveillance and action based on positive results [47]. After a 2011–2012 outbreak at a VA hospital [25], the Department of Veterans Affairs Veterans Health Association released comprehensive requirements for maintaining the safety of hospital water systems. These requirements include quarterly surveillance of ice, hot, and point-of-use water in all buildings in which patients or employees stay overnight [32]. As of this writing, similar legislation is being discussed in Michigan, in response to a significant increase in legionellosis cases in Genesee County [48].

The tragedy of acquiring a severe, preventable infection like Legionnaires' disease in a healthcare facility is undeniable. Though *Legionella* outbreaks may inspire legislation designed to protect vulnerable citizens seeking medical care, the likelihood of acquiring *Legionella* from a hospital visit is far less than that of acquiring a more mundane (but no less potentially severe) infection related to a catheter or surgery. As healthcare resources are limited, the most rational approach is to develop water system management guidelines that match a hospital's risk and history.

What to Do with Surveillance Results

If *Legionella* surveillance is performed, appropriate responses to positive and negative results are essential. The response a facility will have to positive results is best defined before testing. A decision on how to respond, or change in the planned response, after *Legionella* has been detected has the potential to be perceived as motivated by cost rather than patient safety. Some hospitals have adopted a zero-tolerance policy, remediating water in response to any culture positivity. Such hyper-vigilant approaches are not feasible at all facilities, nor are they likely to be necessary. Infection prevention programs should strive to maintain burdens of *Legionella* as low as possible at all times. However, *Legionella* is a ubiquitous waterborne organism, and long-term sterilization of potable water in endemic areas is not feasible. Where acceptable water positivity thresholds fall will differ at individual centers, as dictated by factors discussed in the previous section. The need to perform potentially costly remediation is frequently cited as a reason to avoid testing in the absence of documented or suspected cases, provided adequate clinical testing is performed.

Typical immediate strategies to remediate positive *Legionella* cultures include fixture remediation, biocide treatment of the water, thermal treatment (heating the water to 160 °F), and flushing each fixture for 5–30 minutes. These treatments may be followed by a maintenance strategy such as continuous or intermittent prophylactic biocide treatment. Whatever strategy is considered, validation of the effectiveness should follow. In its most basic form, validation includes re-testing the fixture after remediation, allowing at least 48–72 hours of use to ensure residual biocide does not remain.

L. pneumophila causes approximately 90% of disease [49], but other types of *Legionella* can infect immunosuppressed patients and have been associated with nosocomial

cases [50]. Therefore, it is important to consider how non-pneumophila species will be addressed if detected prior to sampling. In locations with immunosuppressed patients, a policy of remediation regardless of *Legionella* species is most conservative. At this time, it is not known if the factors allowing for growth of non-pneumophila species portend future detection of *L. pneumophila* or if they fill a distinct biological niche.

Typing of isolates, if available, is epidemiologically useful and typically performed as part of an outbreak investigation. Sequence-based typing [51–53] has been the gold standard in *Legionella* identification, and more than 2000 sequence types have been described thus far [54]. Finding identical strains both in a facility location and in the patient's clinical sample implies an association. However, similar *Legionella* sequence types can be found in both the community and a healthcare facility supplied by the same water distribution system. Whole genome sequencing (WGS) has been used in the characterization of outbreak and environmental *Legionella* strains [55]. WGS will likely provide increased granularity for *Legionella* typing compared to SBT, but adequate clinical association between cases and environmental strains will still be needed to differentiate a shared community reservoir vs. facility acquisition in patients spending only part of the incubation period in the positive facility.

For all indications of testing, finding no positive cultures is the ideal and most reassuring finding. Even with negative testing results, however, infection preventionists must maintain vigilance and take care to ensure that water remains safe. *Legionella* is most frequently found from water systems with imperfect engineering control, such as cold water that is too warm, hot water circulating loops that are too cold, infrequently used (stagnant) fixtures, and plumbing dead-legs and run-outs. Sampling sites should target areas with engineering risk factors. *Legionella* is a highly seasonal organism, which is more frequently detected in the summer and fall [56]. Case-based sampling should be performed as proximate as possible to the time of exposure, but primary and secondary surveillance is best performed throughout the year. Many sources have recommended quarterly sampling protocols [32, 57]. Additional considerations in the setting of negative surveillance testing might include ensuring that first-draw samples were obtained, obtaining 5-minute flush samples in addition to first-draw [26], and sampling both hot and cold water sources.

Controversies

The work-up of healthcare-associated *Legionella* is rife with controversies; major controversies are listed in Table 25.2. Debate is not limited to just simple concepts such as when, where, and how to perform water sampling. *Legionella* is almost universally found in water systems (manmade or natural), but no level of detectable *Legionella* is considered safe, incentivizing those without nosocomial cases to avoid testing. The location where water sampling must occur, central waterworks or point-of-use fixtures, is a subject of debate. It is not generally agreed upon if first draughts of water from the tap should be tested or if the water should be allowed to "equilibrate" prior to collection. Further high-quality data are sorely needed to resolve these controversies on water testing for *Legionella* in the healthcare setting.

Table 25.2 Major controversies in *Legionella* environmental testing

Major controversies	
Surveillance testing for primary prevention	Surveillance testing is not universally recommended, and the detection of *Legionella*, especially non-pneumophila species, in the absence of cases is of unclear significance, and remediation is costly
30% cutoff	The percentage of total cultures found to be positive has been suggested as a threshold for concern, but significant outbreaks of Legionnaires' disease have occurred where less than 30% of cultures were positive
Quantitative cultures	Action thresholds using colony-forming units exist, but they are of uncertain validity and demonstrate poor reproducibility

Table 25.3 Take-home points

Take-home points
Facilities should develop a considered water safety plan based on local risk assessment
The decision to perform primary or secondary surveillance should be justified based on the above
Even a single possible or definite nosocomial case associated with a facility should prompt environmental testing

Conclusions and Perspectives

All appropriate regulations and requirements should be followed, but in the absence of mandate, the decision to perform primary or secondary *Legionella* surveillance testing should be related to the risk and history of each healthcare facility. A summary of take-home points is listed in Table 25.3. The development of a water safety plan based on a considered facility risk assessment is the recommended first step to approaching hospital water systems [42]. In the absence of standardized guidance, consideration of the reason for testing and system being tested should guide the type, location, and frequency of testing performed and interpretation of the results.

There is a critical need for evidence, free of industry bias and scientifically rigorous, to protect the safety of hospitalized patients and promote the rational development of guidelines.

Legionella literature is relatively sparse and plagued with limitations, most significantly the retrospective nature of most reports occurring after an outbreak of a seasonal organism. For example, it is not surprising that interventions and retesting of a system would appear successful if undertaken in January–March following an outbreak in June–September. Unbiased evaluations of *Legionella* prevention systems and treatments across a full year are needed, ideally evaluating *Legionella* control outside of large, highly politicized outbreaks. The rapid initiation of unvalidated requirements and the potential for misappropriating limited resources, in response to political or public relations pressures rather than scientific reasoning, must be avoided.

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The Importance of *C. difficile* Colonization in Infection Prevention

26

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Clostridioides difficile infection (CDI) has become one of the most common healthcare-associated infections in the United States [1]. Initially identified in 1980 as the etiologic agent of antibiotic-associated diarrhea among hospitalized patients, interest in its epidemiology surged in the early 2000s with the emergence of an epidemic strain variably referred to as BI by restriction enzyme analysis, North American PFGE type 1 (NAP1) by PFGE, or PCR ribotype 027 [2]. The strong association of CDI with hospital exposure led to the investigation and recognition of transmission in the hospital setting and recommendations for infection control strategies to limit transmission [3–5]. Although the rates of CDI in the United States increased between 2005 and 2010, there has been an 18% decrease in healthcare-associated CDI cases from 2018 to 2019. This decrease in healthcare settings, however, has been countered with an increase in community-associated cases [6–8]. There were over 220,000 cases, resulting in 12,800 deaths in 2017, leading the CDC to name *Clostridioides difficile* an urgent "drug-resistant threat to the United States" [7, 9].

Current CDI prevention strategies largely focus on *C. difficile* transmission from symptomatic patients. Similar to other epidemiologically significant organisms in the hospital setting such as MRSA, VRE, and multidrug-resistant gram-negative bacteria, asymptomatic colonization with *C. difficile* has been reported in several studies as described below. However, unlike other organisms, active surveillance for such asymptomatic colonization is not routinely recommended [4, 5]. The links between asymptomatic *C. difficile* colonization and hospital transmission and between asymptomatic *C. difficile* colonization and subsequent infection continue to remain actively debated topics [10, 11]. In this chapter, we discuss various aspects of *C. difficile* colonization to help readers understand the basis for this controversy.

Prevalence of and Risk Factors for Asymptomatic Colonization with *C. difficile*

Although there is no formal definition, at least one author suggests that asymptomatic colonization with *C. difficile* occurs when the bacteria are present in stool of an individual without CDI symptoms over a period of 7 days [12]. Several studies have described the frequency of asymptomatic colonization in acute care settings, ranging between 4% and 29% among hospitalized or institutionalized patients [12–27]. While some of this variability relates to true variation driven by geographic- and patient-related factors, some differences in estimates may be related to the time elapsed from admission to the time when the prevalence study was performed, the testing method (whether culture-based testing, molecular testing, or toxin assay was used to identify colonization), and the inclusion of toxigenic vs. non-toxigenic strains in studies using culture-based detection [13].

The presence of *C. difficile* bacteria in the absence of symptoms has also been associated with the presence of a protective immune response against *C. difficile*. Kyne et al. described a significantly greater detection of IgG serum antibodies against toxin A in asymptomatic carriers than CDI symptomatic patients [28]. Similarly, Loo et al. also associated the presence of serum antibodies against toxin B with healthcare-associated *C. difficile* colonization compared with symptomatic CDI [29].

C. difficile asymptomatic carriage has been associated with recent hospitalization, chemotherapy, and use of acid-suppressive medication (both PPI and H2 receptor blockers) in several studies [14, 27, 29–34]. A recent meta-analysis of risk factors for *C. difficile* colonization reported previous hospitalization in the preceding 6 months increased the odds

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_26

of colonization over twofold (OR = 2.18; 95% CI, 1.86–2.56) [32]. In contrast to symptomatic CDI, studies have been unable to associate antibiotic use with *C. difficile* carriage [14, 32]. In addition, the *C. difficile* strain or ribotype may play a role in determining if the patient remains asymptomatic after colonization. Loo et al. found 63% of CDI patients in Canadian hospitals carried ribotype 027 compared to 36% of asymptomatic carriers [35]. Similarly, Alasmari et al. reported similar findings among hospitalized patients in St. Louis, Missouri (25% CDI patients vs. 3% asymptomatic carriers had ribotype 027) [14].

Detection of *C. difficile* Carriers and Its Impact on CDI Rates

The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA), the American College of Gastroenterology, and the American Medical Association recommend either nucleic acid amplification testing (NAAT) alone or part of a multistep laboratory algorithm including the detection of glutamate dehydrogenase (GDH), a constitutive enzyme produced by all *C. difficile* strains (regardless of toxin production), and testing for toxin production using an enzyme immunoassay (EIA) [4, 5, 11, 36, 37]. Culture is cumbersome and generally not performed outside of research studies. Although NAAT is considered to have a higher sensitivity and specificity than EIA [36], as well as a shorter turnaround time than culture or CCTA, NAAT detects the toxin-encoding gene rather than the toxin itself, essentially picking up the presence of toxigenic *C. difficile*, but does not distinguish between CDI symptomatic and asymptomatic individuals [38, 39].

In 2014, 44% of acute care hospitals participating in the National Healthcare Safety Network reported using PCR alone or in combination with other tests for the diagnosis of CDI [40]. The implementation of this more sensitive test has led to 50–100% increases in CDI-reported rates. Considering that colonization with *C. difficile* is five to ten times more common than CDI and that *C. difficile* is responsible for only ~20% of all nosocomial diarrheas, it is likely that some patients diagnosed as CDI positive using a PCR test have diarrhea of a different etiologic origin [40, 41]. Therefore, appropriate identification of only symptomatic patients for CDI testing is essential to avoid "false-positive results" from *C. difficile* carriers.

Association of *C. difficile* Colonization with Subsequent Symptomatic CDI

There is evidence suggesting that asymptomatic *C. difficile* colonization has a protective effect and is associated with a reduced risk of CDI [11]. Shim et al. reviewed four longitudinal studies describing that asymptomatic carriers develop CDI between 0% and 3.9% of the time, while non-colonizers were more likely to develop CDI (1.7–8.0%) [42].

More recently, however, Zacharioudakis et al. reported the contrary after completing a systematic review and meta-analysis on the topic. Patients colonized with *C. difficile* upon hospital admission had six times higher risk of developing CDI than non-colonizers [43]. In a study of over 3000 consecutively admitted patients, 6% were determined to be *C. difficile* carriers, and the risk for the development of CDI was 4 times higher among these patients [44]. This difference might be related to the unknown incubation period for CDI. It is possible that those individuals that go on to develop long-term carriage are protected, while other asymptomatic carriers with more recent acquisition might still remain susceptible to the development of symptomatic CDI.

Recent research has also focused on the risk of subsequent development of CDI among hematopoietic stem cell transplant (HSCT) recipients [45–47]. In this population, colonization led to infection in 75–88% of studied patients, though it remains unclear if this represents conversion to active disease versus other causes of diarrhea. Limited data among solid organ transplant patients did not find a strong association between colonization and subsequent active infection [48]. Although further research is needed to better understand this association, these studies highlight the need for developing preventive measures toward *C. difficile*-colonized patients.

Contribution of Asymptomatically Colonized Patients to In-Hospital CDI Transmission

While several studies have evaluated the prevalence of asymptomatic colonization, fewer studies have investigated hospital-based transmission from these colonized patients and particularly whether such transmissions contribute to active CDI. In one of the earliest studies looking at the role of asymptomatic patients in *C. difficile* transmission in the pre-hypervirulent strain era, Clabots et al. (1992) cultured 634 stool samples and used restriction endonuclease analysis to distinguish between strains. They found that hospital acquisition of a *C. difficile* strain was preceded by the introduction of that strain to the ward by an asymptomatic admission in 84% of cases [18]. In contrast, when Walters et al. (1982) conducted a study during an outbreak of pseudomembranous colitis in an ICU, investigators traced the outbreak to a single symptomatic patient and associated environmental contamination [49]. No asymptomatic carriers were found among patients or staff during that outbreak.

More recently, studies have been able to take advantage of more sophisticated techniques such as MLVA (multiple locus variable number tandem repeat analysis) or whole genome sequencing to evaluate the relatedness of strains

and improve the understanding of transmission [50, 51]. Curry et al. used MLVA to determine the genetic relationship between isolates of asymptomatic carriers and CDI cases after screening 3006 patients at the University of Pittsburgh Medical Center Presbyterian in 2009 [50]. Of 59 incident nosocomial CDI cases identified, 30% were associated with previous CDI cases and 29% with asymptomatic carriers. Eyre et al. applied whole genome sequencing to 1223 strains from 1250 cases with symptomatic CDI in either healthcare or community settings in Oxfordshire, UK, between September 2007 and March 2011 [51]. In their analysis, 45% of cases were genetically distinct from all other cases preceding that case. The authors concluded that the presence of a reservoir of asymptomatically colonized patients was a potential explanation for this finding [51, 52]. However, the study was limited by the inclusion of only toxin-positive CDI cases detected by EIA. Given that EIA has low sensitivity in CDI diagnosis, it is possible that a significant proportion of CDI cases were not considered as sources of subsequent cases. In follow-up to the above, the investigators conducted a small prospective study to assess the potential for transmission from asymptomatically colonized patients in the hospital setting. Stool cultures were performed at admission and sequentially every 3 days between February and June 2012 at two hospitals in the United Kingdom. They were able to enroll 132 of 227 patients hospitalized during the study period. They found an initial, at-admission colonization prevalence of 14/132 (11%), and an additional 4 patients developed colonization over the course of the study [53]. Using whole genome sequencing, only two patients on the same ward were found to be asymptomatically colonized with similar isolates. The authors concluded that this could be due to either transmission from one asymptomatic patient to another or transmission to both patients from a third common source that had not been cultured. The relatively small sample size, short follow-up time, and lack of culturing of nearly half the patients were important limitations of this study.

Similarly, Durham et al. estimated the effect of hospital- and community-based transmission of *C. difficile* using a mathematical CDI transmission model [54]. The investigators reported that hospitalized patients with CDI transmit *C. difficile* at a rate 15 times that of asymptomatic patients. However, as the authors pointed out, despite the lower transmission rate from asymptomatic patients, these transmissions have a substantial effect on CDI because of the relatively larger reservoir of hospitalized *C. difficile* carriers. Likewise, Lanzas et al. (2011) developed a compartmental mathematical model of CDI transmission using data from six medical wards and published literature [55]. Their results suggested that transmission within the ward solely from patients with symptomatic CDI could not sustain the new *C. difficile* colonizations.

HCW and Environmental Contamination Related to Asymptomatically Colonized Patients

Evaluation of HCW and environmental contamination related to asymptomatically colonized patients is also important to better delineate the potential role played by asymptomatic carriers in CDI transmission. Several studies have been conducted in this regard. Faden et al. conducted a study in a neonatal intensive care unit (NICU); investigators identified asymptomatic colonization among 9/35 (26%) neonates [56]. A total of 150 cultures of various environmental surfaces were obtained in the NICU and in infant, adolescent, and hematology/oncology units; none of the included units had any identified cases of CDI during the study period, and units other than the NICU were not assessed for asymptomatic colonization among patients. None of 91 surfaces sampled in non-NICU locations were positive. Seven (12%) of 59 surfaces in the NICU were positive for *C. difficile* (five diaper scales, one infant scale, and a refrigerator). The authors concluded that overall environmental contamination was low in the pediatric setting.

At a Veteran Affairs Medical Center, Guerrero et al. (2013) performed rectal swab, skin, and environmental cultures among 149 of 160 patients in 8 wards as part of a point prevalence survey in order to identify asymptomatically colonized patients [57]. The prevalence of skin and/or environmental contamination was significantly lower in asymptomatic carriers (3/18, 17%) compared to patients with CDI (5/6, 83%; $p = 0.007$) [40]. However, 18 of 149 (12%) patients were found to be carriers of toxigenic *C. difficile*, while 6 patients (4%) were identified with active CDI [40]. This suggests again that even with lower rates of environmental contamination, because *C. difficile* carriers outnumber CDI patients, they may have a greater overall potential to influence *C. difficile* transmission.

Furthermore, in a similar study conducted among residents of a long-term care facility, 35/68 (51%) asymptomatic patients were found to be colonized with toxigenic *C. difficile* [58]. Skin and environmental contamination was found to occur for 61% and 59% of asymptomatic carriers. Using PFGE, 13/15 (87%) of *C. difficile* isolates recovered from the skin and 11/19 (58%) of isolates from the environment were found to match the patient's isolate. In addition, *C. difficile* was transferred to hands (donning sterile gloves) after contact with the skin of 8 (57%) of 14 patients who had positive skin culture results.

Together these results suggest that there is high potential for *C. difficile* to be transmitted from asymptomatic patients to both HCW skin and the environment, creating the potential for onward transmission and infection in susceptible patients. However, because environmental contamination appears more strongly associated with symptomatic patients

and can persist for long periods, the relative contribution to new cases from asymptomatic carriers via the environment remains unquantified.

Impact of Strain Type on the Role of Asymptomatic Colonization

The major difference between *C. difficile* and other antibiotic-resistant microorganisms is that *C. difficile* produces spores. Since these spores are resistant to antibiotics and most hospital-used disinfectants, they become an additional challenge for CDI control and prevention [59]. Among patients with CDI, hypervirulent strains such as ribotype 027 have been shown to produce greater amount of spore than non-hypervirulent strains [60]. Furthermore, although this topic has not been fully explored, some early evidence suggests that certain strains may be more likely to be associated with symptomatic CDI and greater environmental contamination. Samore et al. (1996) prospectively obtained stool cultures from selected epidemiologically linked contacts, as well as cultures of the environment of index cases with symptomatic CDI over a 6-month period. *C. difficile* isolates were analyzed by PFGE or by restriction enzyme analysis if unclear by PFGE. The investigators identified 98 index cases of *C. difficile* toxin-associated diarrhea, including 26 outbreak-related cases. Transmission to personnel or patient contacts of the strain cultured from the corresponding index case was strongly associated with the intensity of environmental contamination [61]. A total of 31 index strains were found; however, a single strain was predominant among isolates associated with heavy environmental contamination, with personnel carriage, and with development of symptomatic illness among prospectively identified contacts suggesting that strain type has an important role in environmental contamination, transmission, and disease.

Recently, Eyre et al. developed a *C. difficile* transmission model using their dataset from Oxfordshire, UK, for 2007–2011 that integrated sequence type (ST) [62]. The strains associated with the highest rates of acquisition from a known case were ST1 (ribotype 027), ST42 (ribotype 106), and ST3 (ribotype 001). These STs were also associated with transmission via environmental contamination.

Effect of Targeting Asymptomatically Colonized Patients for Infection Prevention Interventions

Contact Precautions and Active Surveillance

The use of gloves when providing care to CDI patients has been shown to reduce CDI rates. Johnson et al. evaluated the impact of the implementation of an intensive education program regarding glove use during CDI patient care in two hospital wards [63]. A significant decrease in the incidence of CDI was observed from 7.7 cases/1000 patient discharges before the intervention to 1.5/1000 during the 6 months of intervention. Moreover, the point prevalence of asymptomatic *C. difficile* carriage was also reduced significantly on the intervention wards in the post-intervention period (from 27% to 9.3%). Although there is insufficient evidence showing the effectiveness of gown use to reduce CDI, its use is recommended as part of "contact precautions" [64]. Current guidelines for symptomatic CDI patients suggest contact precautions until diarrhea resolves [5]. However, research has shown prolonged shedding continues beyond resolution of symptoms. Sethi et al. reported recurrent shedding up to a month after CDI treatment [65]. These results provide support to recommend continuation of contact precautions until hospital discharge.

To date, limited studies has evaluated the use of active surveillance and contact precautions for asymptomatic *C difficile* colonization [66–68]. Longtin et al. conducted a quasi-experimental study in a Canadian acute care facility between November 19, 2013, and March 7, 2015 [66]. Admission screening was conducted by detecting the *tcdB* gene by PCR on rectal swabs. Three hundred sixty-eight out of 7599 (4.8%) screened were identified as carriers and placed under contact precautions. The authors detected a significant effect of the intervention, represented by a gradual progressive decrease in the healthcare-associated CDI (HA CDI) by an overall magnitude of 7.2 HA CDIs per 10,000 patient-days. Barker et al. evaluated an agent-based model of *C. difficile* transmission, which included 9 interventions and 8 intervention bundles [68]. Besides regular cleaning with sporicidal disinfectant, screening for *C. difficile* at hospital admission was one of the most effective intervention strategies, reducing hospital-onset CDI by 35.7%. The authors concluded that actively managing the reservoir of asymptomatic colonization could help optimize control of CDI. Several studies have focused on active surveillance in high-risk patient populations [69, 70]. A study at the HSCT unit of Mayo Clinic Hospital in Arizona actively screened and placed *C. difficile*-positive patients on contact precautions and reported a significant decrease in hospital-onset CDI post-intervention (72.5/10,000 patient-days to 14.4/10,000 patient-days, $p = 0.035$) [70].

Although these studies assist in exploring this topic, there are still notable limitations. Interventions were non-randomized and single centered, and compliance with isolation precautions was not assessed. In addition, the authors did not report the strain relatedness between carriers and CDI cases or the proportion of *C. difficile* carriers that progressed to CDI. Therefore, as Crobach et al. pointed out, it is hard to distinguish if the observed reduction is due to less

progression from colonization to symptomatic disease, less spread from carriers, or less spread from symptomatic CDI cases [71].

Treatment of *C. difficile* Asymptomatic Carriers

Antibiotic therapy is a primary risk factor for CDI, and treating *C. difficile* asymptomatic individuals may lead to CDI development and transmission to others. Lawley et al. described the effect of clindamycin treatment on asymptomatic carriers using a mice model [42]. According to the authors, antibiotic treatment triggers a highly contagious supershedding state, which is described by *C. difficile* overgrowth and spore shedding, parallel to a decrease of the gut microbiota diversity. Similarly, Kundrapu et al. reported that among patients diagnosed with CDI but that did not meet the clinical criteria for testing ($n = 30$), skin and environmental contamination was common only in those who had prior antibiotic exposure in the previous 90 days. None of those who were not previously exposed to antibiotics had skin or environmental spores [72]. These studies highlight the importance of antibiotic stewardship not only on development of disease but also on potentially decreasing shedding from asymptomatic carriers and preventing further transmission.

Antimicrobial therapy has also been shown not to be effective in decolonizing *C. difficile* carriers. Johnson et al. conducted a randomized study where 30 asymptomatic *C. difficile* carriers were assigned to receive vancomycin, metronidazole, or placebo as treatment [73]. Although vancomycin treatment was temporarily effective to reduce shedding, it was associated with a higher rate of *C. difficile* carriage after 2 months of treatment in comparison to individuals that received the placebo. Furthermore, metronidazole was not effective in eliminating carriage even immediately after treatment.

There is very limited research specifically on the intervention of treating *C. difficile* carriers as a measure of preventing and reducing CDI [64]. In one of the oldest studies reported in 1987, Delmée et al. observed that after completely renovating and cleaning a leukemia unit and treating all *C. difficile* carriers with vancomycin, their positive toxin assays went from 9.9% to 1.2% [74]. However, this does not take into account the potential impact of environmental cleaning and less detection of *C. difficile* rather than true reduction of symptomatic CDI. In contrast, Bender et al. (1986) observed no effect of treating *C. difficile* carriers with metronidazole on the incidence of new CDAD cases at a chronic care facility during an outbreak [75]. These results are in agreement with Johnson et al., who also observed no effect of metronidazole treatment of asymptomatic carriers [73].

Recently, small retrospective studies have employed "primary prophylaxis," mostly in patients identified to be asymptomatically colonized with *C. difficile* [76–79]. Ganetsky et al. studied the use of oral vancomycin prophylaxis in HSCT patients [78]. They determined it was highly effective with 0 cases of CDI in the prophylaxis group compared to 11 in the control group. This study was extremely limited in sample size and provided limited data on other risk factors or exposure. Johnson et al. conducted a randomized open-label trial of oral vancomycin in high-risk patients (those 60 years of age or older) to determine the risk of development of CDI [80]. Among the 100 patients that were studied, there were 0 CDI cases in the intervention group compared to 6 cases in the control group. Patients did not have to be colonized to be included in this study. Overall, evidence to date is extremely limited and does not support for treating asymptomatic *C. difficile* carriers.

In summary, asymptomatic colonization with *C. difficile* is prevalent in healthcare facilities. Further research of the role played by *C. difficile* carriers in *C. difficile* nosocomial spread and the most effective management of these individuals to prevent *C. difficile* transmission is essential to inform and improve CDI *Clostridium difficile* infection (CDI) prevention and control guidelines.

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Mandatory Influenza Vaccination of Healthcare Personnel

27

Bryan D. Harris and Thomas R. Talbot

Introduction

Healthcare-associated transmission of influenza has been documented in many different patient populations and clinical settings [1] including neonatal intensive care units [2–7], pediatric wards [8–11], adult and pediatric transplant units [12–15], infectious diseases units [16, 17], general medical wards [18–20], geriatric wards and long-term care facilities [21–25], oncology units [26, 27], pulmonary rehabilitation centers [28], and emergency departments [29]. In many of these outbreaks, infections occurred in unvaccinated healthcare personnel (HCP), and HCP were linked epidemiologically to further transmission of influenza. The "chain of transmission" (Fig. 27.1) from an infected HCP can occur in several pathways: in an asymptomatic HCP prior to symptom onset, in a pauci-symptomatic HCP who may attribute symptoms to a non-influenza illness due to their milder nature, and from a symptomatic HCP who has come to work while ill ("presenteeism") [30]. Such outbreaks may result in increased patient morbidity, mortality, length of hospitalization, and costs and may disrupt the essential services of a healthcare facility during a season when the patient census and HCP absenteeism are high [18].

Recognizing that there is no perfectly effective measure to prevent the nosocomial transmission of influenza, a multifaceted approach is needed. Such practices should include appropriate surveillance for acute respiratory illness symptoms, isolation of infected patients, high patient vaccination rates, and dedication to basic infection prevention measures such as handwashing, restriction of ill visitors and HCP, and respiratory hygiene and cough etiquette. One practice that has grown in use and support in many jurisdictions over the past decade is the strategy of mandatory vaccination of HCPs as a condition of employment. This chapter will discuss some of the controversial aspects of mandating influenza vaccines for HCP by addressing frequently cited reasons for rejection of such policies. The legal framework for mandatory vaccination is outside the scope of this chapter, but some excellent reviews on this topic are recommended [31, 32].

History of Mandatory Influenza Vaccination for HCP

At the start of this century, despite efforts to promote HCP influenza vaccination by government agencies, regulatory groups, professional societies, and visible vaccine champions, influenza vaccination rates among US HCP remained low. Prior to the 2009–2010 influenza season, despite increased awareness of the importance of HCP influenza vaccination and large-scale, resource-intensive voluntary vaccination campaigns at most healthcare facilities, vaccination rates remained around 45% [33]. A combination of several factors has led to an increased focus on HCP influenza immunization and the use of various strategies (including mandatory vaccination +/− masking of unvaccinated HCP) in order to improve vaccination rates. Namely, the perception of HCP immunization, and specifically HCP influenza immunization, has evolved from that of an employee health benefit to an important measure of a healthcare facility's quality and patient safety program. In addition, the emergence of novel influenza (e.g., the 2009 H1N1 influenza pandemic) and the importance of preventing healthcare-associated transmission of such pathogens helped alter the approach to and perceptions of the importance of HCP influenza vaccination.

Since 2005, an increasing number of facilities have considered HCP immunization as a mandatory condition of employment. The move to mandate HCP influenza immunization gained traction in 2005, when Virginia Mason Medical Center (VMMC) revised its institutional policy to require influenza immunization as a condition of employment [34]. This innovative program was implemented despite vaccination rates well above the national rate. The Washington State Nurses Association (WSNA) filed a grievance against

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_27

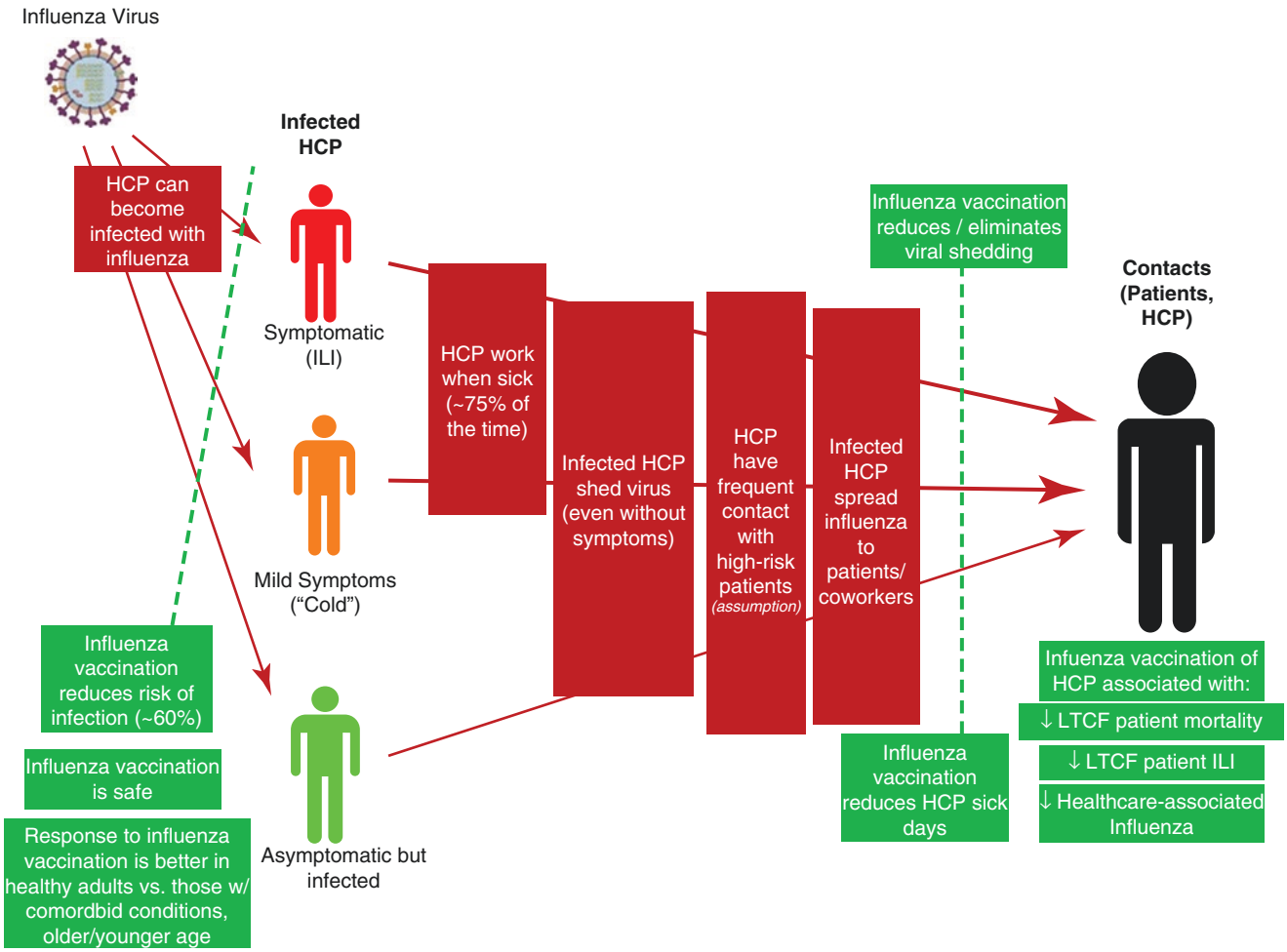

Fig. 27.1 Causal transmission pathway for the development of healthcare-associated influenza. HCP healthcare personnel, ILI influenza-like illness, LTCF long-term care facility. (From Perl and Talbot [30], epublished; reprinted by permission of the publisher)

VMMC arguing that the decision to alter a policy that resulted in the termination of employment violated the collective bargaining agreement. An arbitrator found in favor of the WSNA, but VMMC's subsequent implementation of mandatory masking for unvaccinated employees was upheld after WSNA challenge. With the mandate, influenza immunization rates of VMMC employees rose to 98.9%, and, notably, the rates in the unionized nurses, who were exempt from the vaccination mandate, rose to 95.8%.

Subsequently, more institutions and healthcare systems have implemented similar programs. Every facility/system that has implemented a mandatory HCP influenza immunization program and has reported their experiences has noted rates above 85% (and above 90% in most instances) following the mandate [35–42], with several noting sustained high rates for a decade after policy implementation [41, 43].

Not all "mandatory" programs are the same. Variation exists regarding the requirements of unvaccinated HCP to wear a mask during the influenza season, exemption allowances and review (e.g., only medical vs. allowances for personal belief exemption), and the consequences for non-compliance. Some facilities have also moved to use of the less-punitive term "universal" to describe their still-mandatory program in which HCP are required to either receive an annual influenza immunization or meet specified exemptions (which may include medical, religious, and/or personal belief exemptions).

The use of policies where influenza immunization is a condition of employment is increasing in the USA, based on an annual survey of HCP conducted by the CDC. The percent of respondents who reported working at an institution where there was an employer vaccination requirement (with no specific mention about masking policies) increased from 20.9% during the 2011–2012 influenza season to 44.2% (72.1% of those working in hospital settings) during the 2019–2020 season [44]. Another survey noted an increase of hospital-based HCP working under a mandatory vaccination requirement from 37.1% of respondents in 2013 to 61.4% in 2017 [45]. In addition, during the 2019–2020 influenza season, the HCP vaccination rate was 96% in clinical settings

where vaccination was required [44]. While some HCP have had their employment terminated due to vaccine refusal, the actual reported number of HCP dismissed has been very small compared with the thousands of HCP encompassed by these policies.

With the growing interest in HCP influenza immunization, the use of state regulation and legislation surrounding the topic has also increased. As of October 2017, 18 states had enacted laws that address influenza vaccination of certain categories of the HCP workforce. In most cases, the laws require healthcare facilities to develop and implement influenza programs, but more specific requirements for HCP to be immunized are rare. More than half of the laws require employers to "provide," "arrange for," "ensure," or "offer" influenza immunizations to HCP, while half of the state laws regulate only HCP in long-term care facilities.

The concept of requiring influenza immunization as a condition of HCP employment has now been endorsed by a growing list of professional societies and quality organizations, including every major US infectious diseases and infection prevention organization (Table 27.1) [40]. Those that explicitly endorse masking for unvaccinated HCP are noted in the table with[a]. Notably, in 2015, the American Nurses Association (ANA), a group that initially had not supported influenza immunization as a condition of employment, reversed their position and endorsed such a policy for the safety of HCP and their patients [46–48]. They also noted that "[i]ndividuals who are exempted from vaccination may be required to adopt measures or practices in the workplace to reduce the chance of disease transmission" which may include masking.

Table 27.1 Selected national organizations recommending HCP influenza immunization as a condition of employment ([a]specifically endorses masking of unvaccinated HCP)

American Academy of Family Physicians (AAFP)[a]
American Academy of Pediatrics (AAP)
American College of Physicians (ACP)[a]
American Hospital Association (AHA)[a]
American Medical Directors Association (AMDA)
American Nurses Association (ANA)
American Pharmacists Association
American Public Health Association (APHA)
Association for Professionals in Infection Control and Epidemiology (APIC)[a]
Infectious Diseases Society of America (IDSA)[a]
National Association of County and City Health Officials (NACCHO)
National Business Group on Health[a]
National Foundation for Infectious Diseases (NFID)
National Patient Safety Foundation (NPSF)[a]
Society for Healthcare Epidemiology of America (SHEA)
United States Department of Defense

Finally, HCP immunization data are used as part of formal assessments of healthcare facility quality (e.g., the U.S. News & World Report assessment of the Best Children's Hospitals in America utilizes HCP influenza immunization rates in its analysis [49]) and in accreditation standards. The Joint Commission requires healthcare facilities to "strive to increase compliance with influenza vaccinations and take action to improve vaccination rates," although they have retired a prior element of performance that specifically expected achievement of "the 90% rate established in the national influenza initiatives." [50] While not explicitly endorsing mandatory immunization, these programs have emphasized the importance of HCP immunization as a core safety intervention.

The use of such programs, while increasing across the USA, is not without some controversy. Internationally, the use of mandatory programs has also been met with resistance. In Ontario, two separate challenges to "vaccinate or mask" HCP influenza programs were successfully challenged by the Ontario Nurses Association in 2015 and 2018 [51, 52]. In contrast, a similar province-wide mandatory HCP influenza vaccination program in British Columbia was successfully upheld after similar court challenge [53]. In the following sections, we will address some of the espoused concerns regarding mandatory HCP influenza immunization.

"Healthcare-Associated Influenza Is Not a Problem"

The need for mandatory HCP influenza vaccination presupposes that healthcare-associated influenza, in both HCP and patients, has a considerable incidence. Unfortunately, comprehensive estimations of the burden of healthcare-associated influenza have been hindered by the lack of a standardized definition for this outcome, varying methods of surveillance, and lack of recognition of influenza as a cause of nosocomial respiratory failure by clinicians which leads to a lack of testing for the pathogen [1, 53]. There have been, however, a few studies that better define the burden of healthcare-associated influenza. A prospective laboratory-based surveillance program in Canada examined laboratory-confirmed influenza among hospitalized adults and found that 17.3% of all influenza cases were healthcare-associated [54]. Many outbreaks of healthcare-associated influenza are likely not reported in the literature, but several have been and are well reviewed by Voirin et al. [1]

Healthcare-associated influenza is also not an included target of most infection prevention surveillance programs, so data on disease incidence in key populations are not generally captured in a systematic manner outside of controlled studies. Additionally, in facilities where influenza antigen

testing is predominantly utilized, false negative results related to the lower sensitivity of these tests when compared to polymerase chain reaction (PCR) lead to missed cases of healthcare-associated infection [55]. So at the present time, the burden of healthcare-associated influenza has indeed not been well assessed; however, one should not conclude that these cases do not occur nor that these events do not result in substantial patient harm, as evidenced by the reports of nosocomial outbreaks of influenza cited earlier in this chapter.

Data do indicate that exposure to ill HCP and ill patients infected with influenza increases a hospitalized patient's risk of developing healthcare-associated influenza. Using the clinical endpoint of influenza-like illness (ILI, which will capture non-influenza infections as well), Vanhems et al. noted that the relative risk of developing healthcare-associated ILI (HA-ILI) was significantly increased based on exposure to HCP and patients with identified ILI. Specifically, for patients exposed to at least one contagious HCP compared with those with no documented exposure in the hospital, the relative risk (RR) of HA-ILI was 5.48 (95% confidence interval [CI], 2.09–14.37); for patients exposed to at least one contagious patient, the RR was 17.96 (95% CI, 10.07–32.03); and for patients exposed to at least one contagious patient and one contagious HCP, the RR was 34.75 (95% CI, 17.70–68.25) [56].

"Influenza Is Not a Major Problem Among HCP"

Data regarding the incidence of influenza specifically among HCP is also sparse. While one would expect the incidence to be at least as high as the general population during a given influenza season, there is reason to believe the rate could be higher due to added occupational exposures. There are several reasons why capturing this rate accurately is challenging. Issues surrounding sick day policies and the ability for employers to actively assess reasons for taking time off are significant. Specifically, due to restrictions on an employer's ability to request detailed specifications of illness (related to privacy and other appropriate employee protections), surveillance for employee influenza infections is often only based on passive reporting by the employee. In addition, many time-off policies bundle days off due to illness with days off for other reasons (e.g., an aggregate "paid time off" system where employees are given an allotted number of days to take off work for any reason, including vacation or illness), making accurate accounting of HCP influenza and days missed due to infection extremely challenging.

There have been some attempts to quantify the burden of HCP influenza infection. Often ILI is used as the surrogate for influenza infection with the recognition that other respiratory viruses can cause this syndrome and that actual laboratory-confirmed influenza infection may not present with the classic signs and symptoms of ILI. Henkle et al., however, utilized laboratory testing to confirm infections as part of a prospective surveillance study of 1834 HCP and noted that 15.7% developed an acute respiratory infection during that season with 3.1% due to influenza [57]. Other ecological studies have linked influenza vaccination with lower rates of absenteeism [58]. One study examined the risk factors for influenza acquisition among 133 nurses during flu season, and notably failure to receive the flu vaccine increased the risk of symptomatic influenza acquisition with an odds ratio of 4.82 ($p = 0.007$) [59].

"Mandatory Programs Have Never Been Shown to Impact Healthcare-Associated Influenza"

The impact of mandatory influenza immunization programs has repeatedly been shown to lead to high immunization rates [34–39, 60–62], and implementation of a mandatory program (in the setting of a multifaceted influenza infection control program and often with the use of masking for unvaccinated HCP) is arguably the most effective strategy to increase immunization rates above desired targets. Data on the impact of mandatory influenza vaccination and HCP absenteeism/sick days are also emerging [63]. In an analysis conducted as part of the multicenter RESPECT trial examining the use of medical masks vs. respirators on HCP acquisition of influenza, mandatory HCP influenza vaccination policies were associated with a significant increase in HCP influenza vaccination rates and a significant decrease in HCP absenteeism [64]. In an analysis of the province-wide vaccination with masking policy in British Columbia, researchers noted a significantly reduced rate of HCP absenteeism due to all-cause illness in vaccinated vs. unvaccinated HCP during the first season of the policy [58]. While this study is limited due to its observational nature and analysis of only a single year of the program, the initial difference in absenteeism with the new policy is informative.

Despite these important findings, some have advocated that the optimal evidence to support mandatory vaccination policies would demonstrate that vaccination of HCP leads to improved patient outcomes. Indeed, vaccination of HCP practicing in long-term care settings has been significantly associated with reductions in patient mortality in multiple large-scale clinical trials. Three cluster-randomized trials demonstrated that HCP vaccination was associated with a statistically significant decrease in mortality among nursing home patients [65–67]. One study, performed in 44 facilities and involving over 1700 HCP and 2600 residents, reported a significant decrease in patient mortality, influenza-like illness (ILI), ILI consultations with general practitioners, and

ILI hospitalizations during a moderate influenza season among residents of homes in the HCP vaccination arm compared with those residing in control facilities [67]. These reductions were noted even in the setting of high resident vaccination rates (78.2% in the intervention homes vs. 71.4% in the control facilities). A fourth study, conducted in France among 40 facilities that included nearly 3500 residents and 2000 HCP, noted a significant reduction in the risk of all-cause patient mortality between the 2 study arms even after adjustment for resident age, resident vaccination status, resident disability score, and Charlson comorbidity index (odds ratio = 0.80) [68].

These investigations do have some limitations, including concerns about outcome assessment in both study arms, vaccination ascertainment in both study arms, infrequent laboratory confirmation of influenza, and lack of a significant impact on laboratory-confirmed influenza. Nonetheless, this striking mortality benefit for patients in long-term care facilities from vaccination of their HCP is remarkably consistent across all four studies. In addition, after formalized assessment and consideration of this evidence base using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, Ahmed et al. noted that pooled risk ratios for all-cause mortality and ILI were 0.71 (95% CI 0.59–0.85) and 0.58 (95% CI, 0.46–0.73) with the use of HCP influenza vaccination [69].

Some have argued that the studies noted above do not provide evidence that vaccinating HCP against influenza protects patients in the acute care setting, calling for similar studies in each unique patient population. This stance, however, ignores several key points. First, performing a similar trial in the acute care setting would be exceedingly challenging and resource-intensive, given the increased number of HCP-patient interactions, the shorter length of stay, and the difficulty attributing influenza acquisition due to healthcare-associated exposure. Second and more importantly, the biological rationale for the vaccination of HCP to reduce influenza spread does not vary by practice setting. While in a long-term care facility, the interactions may be more prolonged and frequent in nature, in an acute care setting, the patient has interactions with many more unique HCP, each of whom could be shedding influenza at the time of contact.

Data from randomized controlled trials clearly show the impact of influenza vaccination on the risk of infection in HCP themselves. In a randomized controlled trial, vaccination was 88% effective in preventing laboratory-confirmed influenza in HCP [70]. In addition, studies have examined interventions to reduce healthcare-associated transmission of influenza, which is one of the major aspects of transmission to HCP. In a susceptible-exposed-infected-recovered (SEIR) model, vaccination of HCP was the second most effective strategy in preventing influenza transmission in the hospital by reducing number of cases 6–19% only behind handwashing with a 11–27% case reduction [71].

Data are emerging that illustrate an effect on patient outcomes as a result of vaccination of acute care HCP. One of the earliest studies on the effect of HCP influenza vaccination on patient outcomes came out of the University of Virginia. Salgado et al. noted a significant correlation between increasing HCP influenza vaccination rates and reduced healthcare-associated influenza among patients [72]. The study is limited by the ecologic study design but suggests an important impact. More recently, investigators at MD Anderson Cancer Center examined the impact of increasing HCP influenza immunization over the course of 8 years. Of note, the institution implemented a mandatory vaccine with masking policy during the study period. The proportion of influenza infections that were healthcare-associated among patients significantly decreased and was significantly associated with increased HCP vaccination rates [73]. A cluster-randomized trial in the Netherlands of HCP at six medical centers, where the intervention arms offered vaccination to HCP vs. no vaccination at control facilities, noted a significantly lower rate of healthcare-associated influenza among internal medicine patients (3.9% vs. 9.7%) at the facilities with the higher rates of HCP influenza vaccination [74].

In a study encompassing 7 influenza seasons and over 62,000 hospitalized patients, a significant association was noted between increasing influenza vaccine coverage among HCP and decreasing healthcare-associated ILI among patients at an Italian acute care hospital. Specifically, as vaccination coverage dropped from 13.2% to 3.1%, the frequency of healthcare-associated ILI in patients increased from 1.1 to 5.7% ($p < 0.001$) [75]. Finally, a nested case-control study in France noted a significant association between lower rates of laboratory-confirmed healthcare-associated influenza among patients and higher (≥ 35%) vaccination rates among HCP [76]. These data suggest that the immunization of HCP reduces mortality and ILI in the patients they care for and, furthermore, reduces influenza in the HCP themselves.

"The Influenza Vaccine Is Not Efficacious Enough to Warrant a Mandate"

The CDC notes that, on average, the influenza vaccine's effectiveness is 50%–60% [77], and some have argued that a lack of optimal efficacy suggests that such a vaccine should not be mandated. Many studies, particularly those performed prior to the past decade, utilized less specific outcomes (e.g., all-cause pneumonia and influenza based on administrative coding) or diagnostic testing (e.g., rapid antigen testing

which has poor sensitivity in some populations such as older adults) as markers for influenza infection. In addition, the selection of the control population is critical due to other unmeasured biases that can affect interpretation of the vaccine impact. For example, using a control population of all older adults that compares the effect of vaccination on medically attended visits for respiratory infection may be biased in that those persons who receive an annual influenza vaccine may be more likely to visit their physician when ill (healthy user bias). Those studies that use highly sensitive laboratory testing for influenza (e.g., PCR) and have a comparable control population (e.g., adults hospitalized for non-influenza respiratory illnesses) provide a far more accurate assessment of true influenza infection upon which to base vaccine effectiveness.

The most detailed summary of the vaccine effectiveness data was provided by Osterholm, where the effectiveness was estimated as 59% for the trivalent inactivated vaccine in adults aged 18–65 years [78]. Therefore, while not as effective as other vaccines such as the measles-mumps-rubella vaccine, the influenza vaccine has moderate benefit that may vary based upon the specific host and their ability to mount an immune response to the vaccine as well as the degree of antigen match of the vaccine to the circulating wild-type strains. Variation in individual vaccine response makes it even more imperative that vaccine rates are maximized to contribute to herd immunity and prevent transmission of the virus, especially in healthcare settings.

Some have taken this lack of optimal efficacy to also argue that the basics of infection prevention such as handwashing are substantially more important than vaccination and that mandatory vaccination should not be required until a more effective vaccine is produced [79, 80]. It is not known whether HCP feel that protection from the vaccine may make them more likely to undervalue basic infection prevention policies [81]. While influenza vaccine may provide some protection against influenza, it would indeed not protect against other respiratory viruses. Basic infection control practices remain important and may be synergistic with influenza vaccination. As in many areas of infection prevention, multiple overlapping safety mechanisms are vital, and reliance on one should not reduce compliance with the other.

"Influenza Vaccine Safety Is Still a Concern"

Healthcare organizations have both an ethical obligation and a regulatory obligation to ensure a safe workplace. In creating a mandatory vaccination policy, one must consider the safety of the employee, and as part of discussions regarding mandating influenza vaccination for HCP, the risk of harm to the HCP has often been appropriately considered. When compared to the risks of severe outcomes from influenza, the risk of receiving the influenza vaccine each year is far outweighed by the benefits. The vaccine can cause local side effects such as a sore arm or redness, but these symptoms are often very limited and can be easily mitigated with symptom-controlling medications and therapies. Rarely, as with any medication or therapeutic compound, a severe reaction may occur, such as allergy to a vaccine component. Some studies have found a possible small association of injectable influenza vaccine with Guillain-Barré syndrome (GBS). Overall, these studies estimated the risk for GBS after vaccination as fewer than one or two cases of GBS per one million people vaccinated. Other studies have not found any such association [82]. GBS also occurs after influenza infection. In fact, GBS is more common following influenza illness than following vaccination [83].

Concerns such as acquisition of influenza from the vaccine, exposure to toxicities related to compounds reportedly contained in the vaccine (such as formaldehyde or mercury), and confusion about how the vaccine is manufactured (e.g., utilizes aborted fetal cells) are unfounded when examining the scientific evidence. The fear that some individuals have regarding influenza vaccine is amplified by non-scientific and errant claims of adverse effects that are published in non-conventional sources, such as websites and alternative media. This can make implementing a HCP influenza program challenging and requires the program leaders to examine the scientific evidence when assessing claims about vaccine harm while also being respectful when educating HCP with such concerns.

"There's No Risk for Influenza Transmission from Asymptomatic HCP"

Even if HCP were perfectly adherent to staying home when ill, studies have shown that influenza virus is detectable in the upper airway and nasopharynx of influenza-infected persons up to several days prior to symptom onset. Much of this data comes from studies of household contacts of an influenza-infected index case with prospective viral surveillance and symptom capture to examine secondary transmission in the household. A study from Hong Kong from 2008 to 2014 followed a cohort of 824 households with an identified 224 cases of secondary influenza infection that developed in the household setting, examining the relationship between symptoms and viral shedding (as detected on nasal and throat swabs) [84]. Of note, only 35% of these cases reported a febrile illness that met the classic definition of an ILI, reinforcing the poor sensitivity of that entity as a surrogate for laboratory-confirmed influenza. Viral shedding without symptoms varied somewhat by influenza strain type. Shedding was detected before onset of respiratory symptoms in influenza A-infected persons but peaked on the first 2 days

of clinical illness, while influenza B shedding peaked up to 2 days prior to symptom onset. The authors noted that "[t]he start of viral shedding before symptom onset, albeit at low levels as demonstrated by both PCR and $TCID_{50}$, indicates the potential for influenza virus transmission in the presymptomatic phase of the illness before it becomes clinically apparent."

In addition to the potential spread of virus in the presymptomatic phase, up to 70% of cases may be asymptomatic [85]. A second study in Hong Kong detected viral shedding by PCR testing in the absence of any reported signs or symptoms in 14% of 59 subjects under prospective viral surveillance among household contacts of an index influenza-infected case [86]. A study in New York during the 2009 H1N1 influenza A pandemic noted that serologically confirmed infection occurred in 19% of household contacts [87]. Twenty-eight percent of those infected were asymptomatic during the surveillance period, but whether those individuals served as sources for additional cases was not known.

While influenza is clearly detectable in the nasopharynx of asymptomatic persons, there is some debate as to how important of a role this plays in transmission (i.e., are there shedding and spread outside of the nasopharynx if no symptoms are present). One nuance with this debate, however, is that even if an asymptomatic person does not result in transmission of virus to others, the development of symptoms, even mild ones, can facilitate spread. For example, the infected HCP initially without symptoms but detectable virus in their upper airway who starts to develop mild rhinorrhea may unknowingly start to spread the virus to others.

"Masking Unvaccinated HCP Is Punitive and Not Evidenced-Based"

Influenza is primarily spread through large droplets produced when infected individuals cough, sneeze, and even talk. These droplets can reach others up to approximately 6 feet away [88]. To reduce such transmission of influenza, many mandatory HCP influenza vaccination programs require unvaccinated HCP to wear a mask while in specific areas of the facility during periods when influenza is actively circulating in the community. Masking of HCPs has been shown to halt outbreaks of influenza in healthcare environments [13], and outbreaks of many respiratory diseases that spread similarly via droplets have been shown to abate with the introduction of masking of staff members. Even outside of the healthcare environment, masking has been shown to be effective in reducing influenza transmission among household members in settings with low influenza vaccination rates [89].

Masking of unvaccinated HCP is done for at least two reasons. First, masking may reduce the risk of primary infection of workers caring for patients with influenza. This, however, is not the primary reason for masking as HCP may become infected outside of the healthcare environment as influenza is often a community-acquired disease. The primary reason for masking is to reduce the transmission of influenza from an infected HCP to an uninfected patient (a.k.a. "source control"). Some argue that once symptoms develop, the HCP will just stay home or leave work, but in reality that often does not happen. Data consistently show that HCP, even with classic ILI with fever (a far more severe illness than mild upper respiratory symptoms), still come to work and work while ill for several days [59, 90–93]. To expect that a HCP who starts to have mild respiratory symptoms will always suddenly remove themselves from work is unrealistic and not the experience of most occupational and infection prevention programs.

Critics of masking programs have raised concerns that requiring some HCP to wear a mask could be interpreted as punitive or stigmatizing, especially to those who request personal belief exemptions. In addition, concerns have been raised that requiring a mask reveals details about the HCP's personal health history to others, which would violate their privacy. In contrast, in healthcare settings, there are often numerous reasons for HCP to wear a mask, including in HCP with non-febrile respiratory illnesses. In addition, the masking does not identify or target specifically why a person is unvaccinated (i.e., due to medical contraindications vs. religious/personal belief exemptions). Clearly, implementation and communication about a masking requirement must be done thoughtfully and fairly. A nice example is the Hospital Corporation of America (HCA) program, which uses stickers to denote visually those who require masking [39, 94]. As part of the program, they provided stickers to both vaccinated and unvaccinated HCP, and both carried the tag line "because I care," emphasizing that either intervention (vaccination or masking) is done with patient safety in mind.

Mandatory vaccination or mask policies should be part of multifaceted programs that include an array of infection prevention interventions such as use of hand hygiene, respiratory hygiene and cough etiquette, early (at initial point of facility contact) identification and isolation of patients suspected of having a contagious respiratory infection, restriction of ill visitors and HCP, and patient vaccination. In addition, potential exemptions to vaccination and masking should be reviewed in a multidisciplinary and thoughtful manner [95]. The goal of the vaccine or mask policy is to use and require strategies that will reduce and minimize viral shedding from infected HCP, including those who may not have symptoms. Both vaccination and masking will impede the shedding of respiratory viruses from the upper airway. The vaccine does this by reducing one's likelihood of becoming infected with the virus in the first place and may also result in less viral shedding in those that do become infected

as a result of the less severe illness that occurs. Masking also meets this goal by serving as a physical barrier to shedding from the upper airway. One key difference between the vaccine's effect and the effect of masking and the reason why vaccination is clearly preferred is that the vaccine's impact occurs wherever the HCP may contact influenza (i.e., either in the community or at work). A vaccinated individual has a lower risk of ever becoming infected to begin with. The mask will only serve its purpose when actually worn, so unless a HCP wears the mask all of the time, including when outside of the healthcare facility, influenza acquisition can still occur.

In the development of mandatory HCP influenza policies that use masking for unvaccinated HCP, however, facility leaders should attempt to ameliorate some of the potential issues surrounding such a policy. For example, accommodations for mask wearing in instances where the mask could impede the delivery of care to patients (e.g., in speech pathologists where visualization of the face and mouth is an important facet of therapy) should be made.

Conclusions

Healthcare-associated influenza infection is an understudied but important problem. While the true burden of disease is unknown, it is theoretically significant. Many healthcare professions take an oath to "first do no harm" to their patients. In this light, practices which can keep patients safe should be maximized to the greatest extent that is practical. Vaccination of HCP against influenza is a very low-risk practice which can protect the individual HCP from morbidity and lost work time due to a reduction in HCP infection. Likewise, masking of all symptomatic HCP (regardless of vaccine status) and universal masking for those without the modest benefit of vaccine protection have the potential to protect patients and colleagues from being exposed to infectious droplets, which can halt the chain of transmission. The data that are currently available support the practice of mandatory influenza vaccination for HCP, as best reflected by the decision in 2015 by the National Patient Safety Foundation (NPSF) Board to anoint the inaugural "must do's" for all HCP to ensure patient safety: handwashing and HCP influenza vaccination [96].

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Chlorhexidine Gluconate Bathing Outside the Intensive Care Unit

28

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Introduction

Chlorhexidine gluconate is a biguanide antiseptic with both bacteriostatic and bactericidal activity against gram-positive and gram-negative bacteria (both aerobes and anaerobes), fungi, and some enveloped viruses, but is not sporicidal [1]. One of the benefits is that it maintains residual activity for hours after it is applied [2, 3]. It has been employed with increased frequency in healthcare settings for infection control and prevention. Over the last decade, several studies have documented the success of daily chlorhexidine (CHG) bathing as a means of source control in intensive care unit settings. Daily CHG bathing in the medical intensive care unit (ICU) has been associated with a reduction in patient colonization with potential pathogens as well as a decrease in contamination of healthcare worker hands, thus reducing transmission of these potential pathogens to other patients (i.e., "source control") [4]. In addition, daily CHG bathing in various types of ICUs (medical, surgical, trauma) has led to reductions in healthcare-associated infections, including those due to multidrug resistant organisms such as vancomycin-resistant *Enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) [5]. As a result of the several studies demonstrating the effectiveness of CHG bathing in ICUs, several hospitals across the United States now use CHG for patient bathing in the ICU. This has prompted extension of the use of CHG from the ICU to hospital wards, ambulatory, institutional, and community populations. There may be a significant value of CHG bathing outside the ICU for both infection control and infection prevention. However, it is also essential to recognize the potential challenges of CHG bathing in more mobile and healthy patient populations.

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Hospitalized Patients

Hospital Wards

Individuals admitted to acute care hospitals in non-ICU settings still remain at risk for healthcare-associated infections [6]. Since bathing with CHG in the ICUs has been shown to be beneficial in reducing line-related bacteremia [7] as well as colonization with potential pathogens such as MRSA and VRE [5, 8], it begs the question as to whether daily CHG bathing would be effective in patients on general hospital wards. Patients on hospital wards may still have central lines in place (e.g., short-term femoral/internal jugular/subclavian CVCs, PICC lines, and dialysis access), which put them at continued risk for line-associated bloodstream infections. Huang and colleagues conducted a cluster-randomized multicenter trial to examine the use of CHG bathing in noncritical-care units (the ABATE Infection trial) and found that decolonization with universal CHG bathing and targeted mupirocin for individuals with MRSA carriage did not significantly reduce infection in the overall study population. However, results of the post-hoc analysis demonstrated a significant decrease in bacteremias as well as MRSA and VRE clinical cultures among patients with medical devices (e.g., central lines, midline catheters), suggesting benefit of CHG bathing in non-ICU settings among certain at-risk populations [9]. Hospitalized non-ICU patients may undergo invasive procedures such as cardiac catheterizations, paracenteses and thoracentesis as well as surgeries, and therefore, "source control" (i.e., reducing potential pathogens on patient skin and thus limiting the opportunity for contamination of healthcare worker hands and the surrounding environment) may be of value. Finally, unfortunately, healthcare workers' compliance with hand hygiene remains overall poor and thus

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_28

enhanced infection control interventions such as CHG bathing may be needed [10].

In a study by Climo et al., the impact of daily CHG bathing on acquisition of multidrug resistant organisms (MDROs, in this case VRE and MRSA) was examined along with incidence of hospital-acquired bloodstream infections in various ICUs (medical, coronary care, surgical, cardiac surgery) and bone marrow transplant units [5]. Daily CHG bathing was associated with a significant decline in the acquisition of MDROs and in hospital-acquired bloodstream infections. This finding was most notable for individuals with prolonged lengths of stay in the unit. Frequently, non-ICU level patients are hospitalized for extended periods of time as well, providing them more opportunity to develop nosocomial infections. In patients with prolonged hospitalizations, CHG bathing offers an attractive consideration for reducing healthcare-associated infections on hospital wards.

In a study by Kassakian et al., looking at general medicine wards, daily use of CHG bathing resulted in a reduction in the composite outcome of MRSA and VRE healthcare-associated infections in comparison to daily bathing with soap and water; no decrease in *Clostridium difficile* infections was observed [6]. In this before-after study, bathing for both study arms was performed by certified nursing assistants and there was no direct bathing compliance observations but rather an estimation of compliance by purchasing records. Nonetheless, the results suggest a possible role for CHG bathing on non-ICU units.

A before-after study by Bass et al., examined daily bathing with 2% CHG-impregnated cloths for patients on a hematology/oncology ward [11]. In this study, patients were given instructions on proper usage of the cloths and then were responsible for self-application. The authors noted a reduction in VRE colonization, but the association did not attain statistical significance. Compliance with cloths was not monitored in this study, making it unclear why a more significant decline in colonization was not observed. Further evaluation of CHG bathing on hospital wards that includes an assessment of patient compliance as well as reasons for noncompliance is needed.

A study by Wendt et al., enrolled MRSA carriers at the University Hospital of Heidelberg (inpatients as well as outpatients) and from surrounding nursing homes and randomized them to receive either 5 days of whole-body washing with 4% CHG solution or placebo (both study arms received nasal mupirocin and oral CHG) [12]. They observed only a reduction in inguinal MRSA colonization; colonization at multiple body sites was associated with eradication failure. Of note, bathing could be performed by a healthcare worker or by the patient (with instructions from study staff) and thus, compliance could be a factor in the apparent reduced effectiveness of CHG in this study. However, this study highlights potential patient populations (those with prolonged colonization with MRSA at multiple body sites) where optimal compliance with CHG may be essential for efficacy.

Long-Term Care Facilities

Long-term acute care hospitals (LTACHs) were created in the 1990s to transition stable but ill patients from acute care hospitals to a facility where high-level care and rehabilitation could continue to be provided [13]. More so than nursing homes, LTACHs frequently have ICU-equivalent patients (e.g., patients on ventilators, patients receiving tube feeds, hemodialysis, medications through central lines, specialized wound care), many of them with prolonged lengths of stay. These factors can lead to colonization and infection with MDROs including carbapenem-resistant *Enterobacteriaceae* (CRE), which can be a significant problem in this patient population [10]. LTACHs have been found to be critical components of regional outbreaks and spread of MDROs [14]; hence, optimization of infection control and prevention in this population is essential.

A study by Munoz-Price et al. used a quasiexperimental design to examine daily 2% CHG bathing in LTACH patients using a preintervention, intervention, and postintervention phase. They observed a significant reduction in CVC-associated bloodstream infections during the intervention period and an increase in infections in the postintervention period, supporting the efficacy of CHG in this population [13]. Another study by Hayden et al., utilized 2% CHG cloths for bathing of LTACH patients as a component of infection-prevention bundle (including admission and every other week screening for *Klebsiella pneumoniae* carbapenemase [KPC] rectal colonization, cohorting of colonized patients into specific geographic regions, and institution of a hand hygiene improvement campaign) [10]. This bundle was associated with a significant decline in the rate of KPC colonization at multiple body sites (inguinal region, upper back, antecubital fossa, axilla, neck), KPC bacteremia, all-cause bacteremia, and blood culture contamination [10, 15]. However, as this was a study utilizing an infection control bundle, we do not know the individual benefit of CHG bathing for the outcomes measured.

Preoperative Use

Surgical site infections have been identified as one of the most common causes of nosocomial infection, one of the most significant post-op complications, and reason for increased morbidity and cost to the patient [16]. CHG is not inactivated by blood or serum proteins and has persistent activity following application, making it an ideal agent to reduce bacterial burden preoperatively [3]. Although multi-

ple studies have been done looking at the actual risk reduction in surgical site infection and have failed to demonstrate a statistically significant decrease in the rates of SSI, bathing with CHG is still often used preoperatively [17]. The 2017 Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection recommends bathing with soap (antimicrobial or non-antimicrobial) or an antiseptic agent the night prior to surgery (1B recommendation), although it remains an unresolved issue of whether CHG soap or washcloth should preferentially be used for the prevention of surgical site infection [18].

Outpatients

While MRSA was once typically seen solely in healthcare facilities, over the past 15-plus years, colonization and infection with MRSA has been observed in community populations, many without prior healthcare exposures (so-called community-associated MRSA or CA-MRSA) [19]. By pulsed-field gel electrophoresis, USA300 has been identified as the most common strain of CA-MRSA [20]. With the emergence of CA-MRSA, several studies have examined the role of CHG outside the healthcare settings. Most infections due to CA-MRSA are skin and skin structure infections although more serious infections (e.g., bacteremia, necrotizing pneumonia, necrotizing fasciitis) have been reported. Outbreaks of CA-MRSA have been reported in distinct community populations (military recruits, inmates in correctional facilities, amateur, and professional athletes) with the common feature of these patient groups being close person-to-person contact, crowded living conditions, suboptimal hygiene, and increased opportunities for skin breakdown [21].

In the inpatient setting, colonization with MRSA has been associated with an increased risk of MRSA infection (up to four-fold overcolonization with MSSA in one meta-analysis [22]) and there has been reports of a strong correlation between *S. aureus* strains identified as colonizing the nares later being isolated from the bloodstream of those same patients, supporting endogenous flora as the source of infection [23]. Several outpatient studies have included decolonization as a component of an outpatient infection prevention strategy, particularly in cases where individuals have recurrent SSTIs. Miller et al. recently published data that in a subset of patients with *S. aureus* skin infection at the time of enrollment, not only did >60% have prior skin infection in the year prior to their enrollment, but 51% had reported recurrent, relapsed, or new skin infection at the 6-month follow-up visit [24].

The following sections will take a closer look at studies examining the use of CHG in nonhospital settings and highlight the potential complexities of CHG use in outpatients. However, as outlined in the IDSA MRSA treatment guidelines [25], reinforcement of infection control strategies (i.e., early identification of infection, good hand hygiene, adequate wound care, avoidance of shared personal items, washing clothes and towels at appropriate temperature, and avoiding contact sports until healed [21]) is a critical component of control and prevention and decolonization can be considered when the standard strategies are unsuccessful.

Outpatient Clinics

Chlorhexidine gluconate has been used among outpatients as part of a decolonization regimen for individuals with CA-MRSA infection, particularly recurrent SSTIs. Providers have also used intranasal mupirocin with or without CHG for decolonization, as a way to target nasal colonization with MRSA. There has been increasing evidence, though, that extranasal colonization with MRSA may be important and therefore inclusion of topical antiseptics that can target relevant extranasal sites may be needed. The IDSA clinical practice guidelines for the management of MRSA infections recommends considering a decolonization regimen only after standard infection control practices have been optimized and infection or ongoing transmission is still occurring. In this situation, the guidelines suggest decolonization utilizing intranasal mupirocin with or without topical body decolonization (chlorhexidine, bleach baths) [25]. Decolonization, though, can be transient and some of these individuals live or work in an environment where they may be at high risk of recolonization. In a study by Doebbeling et al., recurrence of nasal *S. aureus* colonization following 5 days of intranasal mupirocin occurred in 48% of individuals at 6 months and 53% at a year, with 36% of individuals being recolonized with a new strain and 34% with the same strain [26]. In addition, there is concern for the development of mupirocin resistance with widespread use [27, 28].

Military

In the military setting, chlorhexidine bathing may be a useful component of infection control as military personnel (especially recruits in the training phase of their careers) are required to live in close quarters, have higher potential for skin breakdown given rigorous training activities and outdoor exposure, and the potential for reduced access to optimal hygiene [2, 29]. All of these factors increase the risk for skin and soft tissue infections (SSTIs) including those due to *Staph aureus*. At one military training facility, it was estimated that one in ten recruits would develop an SSTI sometime during their training, with MRSA being the most common organism cultured [30]. In a study of soldiers, Ellis,

et al. observed that colonization with CA-MRSA significantly increased the chance of subsequent MRSA infection in comparison to methicillin-susceptible *Staphylococcus aureus* (MSSA) infection risk with prior MSSA colonization [31]. The goal of infection control should be focused not only on decreasing individual risk of development of SSTIs in this population, which depending on severity can contribute to significant loss of days and delay in training, but also reducing the person-to-person transmission that can potentially hamper the efficacy of the larger unit [29, 32]. Several studies have examined different strategies incorporating use of CHG-containing wipes or body washes into the military routine, mostly in conjunction with other interventions (e.g., instruction on hygiene, provision of personal soap and first aid kits, and ensuring adequate time for bathing [2, 29, 30, 32, 33].

Morisson et al. conducted a retrospective observational study to assess the rates of overall SSTIs and MRSA-SSTIs pre- and postimplementation of a facility-wide infection prevention intervention that included the use of 4% chlorhexidine gluconate body wash (upon arrival to the training site and then an additional six times over the 13 weeks of training) in addition to instruction on hand hygiene, provision of soap and first aid kits, and allotment of adequate time for showering [29]. Even though the study is limited by the lack of a control group, they did observe a significant decrease in the incidence of SSTIs and culture-proven MRSA-SSTIs with the intervention.

Whitman et al. conducted a cluster-randomized, double-blind, controlled trial of CHG bathing in military recruits to determine its effects on MRSA colonization and infection [2, 34]. Recruits were randomized into thrice weekly usage of 2% CHG-impregnated cloths versus thrice weekly control cloths. There was no significant difference in rates of SSTI between the two groups and the overall rates of nasal carriage of *S. aureus* increased from study initiation, although to a lesser extent in the CHG group. Incidence of colonization with MRSA in the CHG group was half that of the non-CHG group (2.6% vs. 6%, $p = 0.03$) [2]. Within the subset of those recruits who acquired MRSA, there was significantly less acquisition of USA300 strains in the CHG group in comparison to the control group, suggesting that CHG may have led to reduced USA300 MRSA transmission during the study [34]. One of the major limitations of this study was the relatively low levels of adherence reported by recruits, with less than 50% of recruits in the CHG group reporting ≥50% use of wipes by week six of the study. Poor adherence, in addition to factors such as inability to ensure proper application technique and impact of sweating and frequent showering on duration of antimicrobial effect of CHG wipes (even with optimal use), makes it difficult to assess the efficacy of the wipes themselves as well as ideal interval of use. Nevertheless, this study highlights a potential role for CHG in this population but demonstrates the many challenges with CHG bathing among outpatients [2, 33].

In a separate analysis, Ellis et al., examined rates of SSTI and MRSA-SSTI in US Army trainees randomized to standard hygiene education arm, enhanced standard hygiene education plus first aid kit arm, and once weekly CHG 4% body wash plus enhanced standard education arm [30] . The authors were unable to show a significant decrease in the rate of SSTI or culture-confirmed MRSA-SSTI between the study groups; however, CHG was used only weekly in this study, which may account for the observed lack of benefit.

If utilized in the military population, it remains unclear what the optimal frequency of bathing with CHG is, although as the studies highlight there are potentially logistical issues with daily CHG use. These studies also demonstrate that adherence with CHG bathing may be more challenging with a larger, healthier, and more mobile population.

Correctional Facilities

Detainees in correctional facilities are also at risk for CA-MRSA due to overcrowding, increased opportunity for skin abrasions, and reduced opportunity for optimal hygiene and infection control practices [35]. Several outbreaks in both jails (characterized by shorter-term stays and high turnover) and prisons (long-term stay) have been reported. Three of the largest documented outbreaks occurred in correctional facilities in Georgia (state detention center, prison, and county jail), California (county jail system), and Texas (Texas Department of Criminal Justice) [35]. During investigations of these outbreaks [35], lapses in basic infection prevention measures were identified including limited access to soap for handwashing and bathing, inappropriate laundry machine temperatures, and inadequate wound care. Included in the intervention during the outbreak at the Georgia detention center was daily CHG baths (body wash, percent CHG was not defined) for all inmates in conjunction with increased access to hand soap, education on skin and hand hygiene, provision of wound care supplies, and instruction on proper wound care [36]. Antibiotic treatment and 5 days of intranasal mupirocin were provided to inmates who had active infection (abscess or "MRSA skin infection"). No further MRSA infections were diagnosed in the subsequent postintervention period (a timeframe of 11-and-a-half weeks).

A randomized controlled trial by David et al. evaluated the impact of bathing with 2% CHG cloths on the rates of *S. aureus* carriage in the nares and hands of inmates in a jail in Dallas, Texas [37]. There were three study arms: (1) thrice weekly bathing with 2% CHG cloths, (2) thrice weekly bathing with water-containing cloths, and (3) no skin treatment. While the authors did observe a significant decrease in overall *S. aureus* carriage, there was no significant difference in

MRSA colonization when compared to the use of water-soaked, non-CHG wipes. Although this study reported relatively high adherence to the recommended intervention, there was no direct observation on how well the participants applied the wipes and it remains unclear if thrice weekly bathing in this study setting is enough. This study also highlights the significant challenges in studies done outside of the healthcare settings; some inmates changed locations during the study, which then assigned them to different study arms, and merging of certain jail units affected exposures. Nevertheless, given the overcrowding of correctional facilities and the reported association of incarceration exposure and MRSA, intervention such as done in this study warrants further investigation.

Athletes, Amateur, and Professional

In 2003, an outbreak of MRSA SSTI was reported in the St. Louis Rams professional football team [38]. The subsequent investigation revealed USA300 as the predominant strain in the outbreak. High contact sports such as football, rugby, wrestling, and fencing are identified as activities with increased risk for MRSA outbreaks among participants [39], and thus potential targets for enhanced infection control and prevention strategies. Sports such as these are associated with increased opportunity for skin breakdown as well as close person-to-person contact. Team sports can be associated with injuries (due to falls and equipment), as well as sharing of sporting equipment, towels, and whirlpools, all of which may also increase the risk for MRSA infection [40].

American football is the most studied of all of these sports, with outbreaks at the high school through the professional level reported. In one study of high school football players, incision and drainage was performed on 18 of 21 lesions and four of 13 players required hospitalization for IV antibiotics [41]. Outbreaks of MRSA at the collegiate level also demonstrated high numbers of affected athletes requiring incision and drainage and even hospital admission for further management [42, 43]. In these outbreaks, often, the most common cause of SSTI has been USA300 MRSA [38, 41–43].

In several of the outbreak investigations of athletic teams, MRSA was rarely isolated from nasal colonization surveillance swabs of individuals with infection [42, 43], making it unclear if extranasal MRSA colonization played a role in infection or if infections were due to a "hit and run" by virulent MRSA strains [44]. From outbreak investigations of football players, the following risk factors were associated with increased relative risk for infection: turf abrasions, body shaving, and playing certain positions (lineman or linebacker in the Rams outbreak, cornerback or wide receiver in the outbreak at a Connecticut university) [38, 42, 43]. During the outbreak investigation for the St. Louis Rams, they also found that members of opposing teams had developed abscesses with the same strain of MRSA (USA300 MRSA), suggesting person-to-person transmission during their matchup [38]. As seen with the other outbreaks mentioned in this chapter, lapses in team hygiene were noted; trainers lacked access to regular hand hygiene products, towels were shared among team members, there was lack of showering prior to whirlpool use, and infrequent cleansing of weight room and therapy equipment were also documented. Implementation of various hygiene processes (i.e., provided soap dispensers for routine handwashing, appropriate wound care, active surveillance for infection, requiring players to shower before whirlpool use and restricting case patients with active infection from play until wounds were healed) occurred in response to several of the reported outbreaks [38, 43]. It is unknown if CHG bathing could be utilized for infection prevention in some manner in high-risk sports settings.

Challenges

As evidenced by the studies discussed, there are many challenges to both studying and even implementing use of chlorhexidine in various non-ICU setting. Many reference adherence as one of the main limitations to their studies, while ability to perform the recommended procedures, access to necessary supplies, and concern for use of incompatible products are other identified areas where real-life implementation may be difficult.

Adherence and Technique

Studies have suggested that to gain maximal effect from CHG body cleansing products (i.e., skin concentrations high enough to kill significant pathogens), washing with the right amount of force for the right duration of time is likely required [45]. The LTACH study by Lin et al., demonstrated the small subset of patients who were bathed with proper technique had much higher CHG skin concentrations and better elimination of KPC from difficult-to-treat body sites [15].

One study by Vanhoozer and colleagues surveyed adult inpatients at an academic medical center about chlorhexidine bathing. They found that patients whom staff assisted with bathing had higher daily CHG bathing self-reported compliance, increased electronic medical record documentation of CHG baths, and lower use of nonhospital-approved personal care products in comparison to self-care patients. In addition, patients who were educated by staff had a better understanding of the correct method for CHG use. This study

emphasizes the importance of patient education and implementation of CHG protocols if used in settings where patients are responsible for their own hygiene [46].

On the outpatient side, some pre-op providers use instructional forms on how to use the product and allow patients to affix stickers documenting use [17]. Studies have also looked at the use of electronic alerts to remind patients to perform their preoperative bathing and found higher composite levels of CHG on the skin in patients who received alerts, which was suggestive of increased compliance in that group [47].

Avoidance of Incompatible Products

Many commercially available lotions and skincare products can cause reduced activity of chlorhexidine gluconate [48] and concomitant use of these products is discouraged. On hospital wards, staff can be encouraged to monitor patients' for use of these products and provide appropriate replacements. In nonhospital settings practitioners would need to educate patients on limiting the use of products that reduce CHG activity although compliance with this would be more challenging to measure.

Concerns with CHG Resistance and Other Potential Unintended Microbial Consequences

With increased use of CHG in ICUs, there has been concern about development of resistance. There is no defined CLSI breakpoint for CHG, making determination of resistance difficult. The *qac*A and *qac*B genes (encode for efflux pumps) found in *S. aureus* have been seen associated with higher CHG MICs and MBCs (minimum bactericidal concentration) and have been proposed as a cause of decolonization failure although this has not been widely demonstrated [49, 50]. Of greater concern is potential for decreased susceptibility to CHG in gram-negative organisms as they have inherently higher MICs to CHG than gram positives [50, 51]. CHG skin concentrations that have been measured on patients following appropriate application of CHG-containing products still greatly surpass the MICs for both gram-positive as well as gram-negative organisms, so the true significance of high MICs is not well defined [1, 49–51]. This depends on achieving adequate skin concentrations in the first place, which in turn may be related to type of product used (soap vs. impregnated cloths) as well as technique (i.e., time allotted for CHG to dwell) and body site [50]. In the REDUCE MRSA trial where isolates were analyzed, resistance to CHG as detected by *qac* A/B carriage and MIC was infrequent; out of over 3000 isolates, four isolates were found to contain either the *qac* A or B genes and only one isolate was nonsusceptible to CHG [52]. So far, it appears that resistance to CHG is relatively rare, but as usage continues to increase, it is essential that we continue to monitor for emergence of resistant organisms. Babiker and colleagues et al. discuss potential concerns such as antibiotic cross resistance, decolonization failure, and unhealthy alterations in health-associated skin microbiome to the list of potential unintended consequences of more widespread CHG usage and acknowledge that continued monitoring is warranted. However, the authors note that these potential concerns should not prevent CHG from being used in settings with documented benefit [50].

Conclusion

Several studies report the effectiveness of CHG in ICU populations. There may be at-risk groups of patients outside of the ICU—both in the hospital and in community settings—that benefit from CHG bathing. There are increased challenges in implementing CHG bathing in non-ICU populations, and it is unclear what the optimal frequency of use is when CHG is utilized in congregate living populations (i.e., individuals in correctional facilities or those in the military). As drug-resistant pathogens continue to be of increased significance not only in the hospital but also in community settings, enhanced infection control strategies such as CHG bathing may be of value. Resistance to CHG is thus far infrequent and CHG itself is largely well tolerated, making it an attractive option for infection prevention and control. Future studies should continue to investigate why compliance with CHG is often challenging in certain outpatient populations and failed to see the same beneficial effects with CHG use that have been seen in the ICU. In the meantime, though, simple infection control measures such as hand hygiene, proper wound care, and antibiotic stewardship remain of primary importance in both community and hospital settings.

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Airborne Precautions and Personal Protective Equipment: The Powered Air-Purifying Respirator-Only Approach

29

Pranavi V. Sreeramoju and Jose Cadena

Standard precautions including hand hygiene and proper use of personal protective equipment, as well as isolation precautions, are foundational strategies to prevent transmission of pathogens in hospitals and other healthcare settings. The common types of isolation precautions, based on known or suspected modes of transmission, are contact, droplet, and airborne isolation. Airborne isolation, in contrast to droplet isolation, is intended to break the chain of transmission of pathogens carried in aerosol particles less than 5 μ in size [1]. The term respiratory isolation is confusing as it may be used to mean droplet or airborne isolation, and we recommend against the use of this term. The pathogens transmitted via airborne route are tuberculosis (TB), varicella, measles, severe acute respiratory syndrome coronaviruses (SARS-CoV1 and SARS-CoV2), Middle East respiratory syndrome coronavirus (MERS-CoV), hemorrhagic fever viruses such as Ebola, and highly pathogenic avian influenza viruses such as H5N1 and H7N9 [2]. Airborne isolation is also employed for novel and emerging pathogens whose transmission is unknown. In contrast, droplet isolation is used for pathogens/diseases such as diphtheria, epiglottitis, or meningitis for the first 24 h of treatment, and pertussis and influenza [1].

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Airborne Isolation Precautions and Personal Protective Equipment

Airborne transmission can be classified into obligate (under natural conditions, transmission occurs only through the airborne route, e.g., *Mycobacterium tuberculosis*), preferential (multiple transmission routes are possible, but small particle inhalation is the most common route, e.g., influenza, MERS-CoV, SARS-CoV-1, SARS-CoV-2), and opportunistic (infection usually occurs through other routes but may occur through small particles under special circumstances, e.g., *Legionella*) [1].

The three major components of airborne isolation precautions as a strategy for reducing transmission of aerosol transmissible diseases are (1) physical space and engineering controls, (2) healthcare personnel respiratory protection and personal protective equipment, and (3) clinical protocols, policies, procedures, and regulatory considerations.

Physical Space and Engineering Controls

Because aerosol particles remain suspended in air, pathogens transmitted via airborne route can spread across hospital floors and across long distances. Therefore, physical space and engineering controls such as proper ventilation; air handling including air exchanges and air flow management, that is, negative pressure air flow; and high-efficiency particulate filtration are the cornerstone for preventing airborne transmission. Measures such as ultraviolet lights are also effective when used as an adjunct. Portable HEPA filters can also be used in certain situations. When combined with appropriate use of respiratory protection, airborne transmission can be

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_29

prevented effectively. Physical space controls gained particular importance in recent years as research into transmission of emerging pathogens such as coronaviruses (MERS and SARS) and influenza viruses (e.g., highly pathogenic avian influenza) identified potential for airborne transmission. To address hospital capacity surge and containment of infection transmission during the ongoing SARS-CoV2 pandemic, many health systems responded with carving out certain areas of the hospital as dedicated patient care units, and transforming open areas into drive-through testing sites and vaccination sites [2]. A complete discussion of physical space and engineering controls is beyond the scope of this chapter.

Healthcare Personnel Respiratory Protection

Respiratory protection against infectious airborne and droplet particles is an important part of the occupational safety of workers in healthcare settings. Some infections can be transmitted through the airborne route, where an infectious patient produces small particles, <5 μm, which are neutrally buoyant and can remain suspended in the air for prolonged periods of time, traveling relatively long distances, and are inhaled by a susceptible individual, reaching the alveolar tissue, and potentially leading to the transmission. This has been observed in Canada during the SARS epidemic (42% of cases were in HCW and resulted from transmission from patients), in New York during the surge of HIV-related TB transmission, and MERS-CoV in the Arabian Peninsula, all of which led to a significant infection rate of healthcare workers [3, 4].

Airborne Versus Droplet Transmission

Classically, the infection prevention literature and guidelines from the CDC and WHO have utilized airborne versus droplet transmission to guide the requirements of PPE and placement among patients with infection. The concepts of airborne versus droplet transmission may be misleading as they are more of a spectrum than a clear dichotomy (ranging from transmission of large particles that rapidly fall to the floor near the source patient, i.e., droplet transmission, to transmission through microscopic aerosols that can travel long distances and can remained suspended in the air for hours, i.e., airborne transmission). Furthermore, for respiratory viruses, more than one mechanism can contribute to spread, and some "droplets" may become "airborne" when aerosol-generating procedures such as bronchoscopy are performed [5]. This dichotomy became particularly controversial during the SARS-CoV2 pandemic, where respiratory protection recommendations were changed from preferential use of N95 respirators or higher, to a graded approach where surgical masks could be used based on availability during routine care, and the use of N95 was prioritized for use during aerosol generating procedures [6].

Why Facemasks Are Not Optimal for Airborne Respiratory Protection

Medical grade surgical masks are used for protection against large droplets and contain secretions of the wearer. Surgical masks are classified by the American Society of Testing Materials (ASTM) into levels 1–3 based on the filtration and fluid resistance characteristics of the mask. The protection they offer is limited by the lack of seal between face and mask and the potential of small particles (i.e., <0.20 μm) to enter the respiratory tract through the limited seal [6].

The use of surgical masks may still offer protection against viral respiratory infections (except for aerosol generating procedures), and a recent systematic review and meta-analysis comparing surgical masks to N95 to prevent respiratory viral infections, including six randomized controlled trials, with 9171 participants, found no difference in laboratory-confirmed influenza, confirmed viral respiratory infection or influenza-like illness between the use of both strategies. Additionally, several studies have shown no difference in protection for H1N1, or SARS-CoV1, transmission protection between N95 and surgical masks [6].

Cloth masks have been used frequently during the SARS-CoV-2 pandemic. They are not standardized and depending on the material and fitting, filtration and protection is variable. Several studies have shown that cloth masks are inferior to surgical masks given lack of standardization and materials and potential for inferior filtration. Cloth masks have a role for source control during COVID-19 pandemic, but they should not be used as personal protective equipment for patient care [6, 7].

Respirator Types and Classification

The most important piece of personal protective equipment to prevent infection from airborne pathogens is a respirator. In addition to prevention of airborne transmission of pathogens, these respirators are also used for protection against chemical, radiological, and nuclear materials [8]. The discussion in this chapter will be limited to respiratory protection against infectious pathogens.

Respirators have been shown to prevent transmission of airborne organisms such as tuberculosis. During previous studies, institution of a respiratory protection program

including use and fitting of N95 respirators has been shown to result in an absolute risk reduction of 0.4–11.5% of tuberculosis transmission in healthcare settings [9].

It is important to understand the different levels of protection offered by different types of equipment. Face masks are not considered respiratory protection as they are usually designed to protect from large particles and not smaller aerosol particles [8].

Respirators are classified based on specific factors as follows [10, 11]:

1. By air supply: Air-purifying respirators, which remove contaminants and pathogens from the air one breathes and air-supplying respirators, which provide clean air from an uncontaminated surface.
2. By whether they require a tight seal between respirator and the wearer's face and/or neck: Tight-fitting and loose-fitting. The tight-fitting respirators need a tight seal between the face and the respirator. Employers who require tight-fitting respirators to be worn in the workplace are required to have respirator fit testing programs in place.
3. By power requirement: Nonpowered or powered. All air-supplying respirators are powered, while air-purifying respirators may be powered or nonpowered.
4. By type of facepiece: Half-mask facepiece respirator that covers the nose and mouth or a full facepiece respirator that covers the nose, mouth, and eyes.
5. By reusability: Disposable or reusable (elastomeric – they have replaceable filters or cartridges, and the surface can be cleaned).
6. By splash protection: Surgical respirators, which have surgical mask material on the outside, to protect the wearer from splashes (e.g., surgical N95 respirators) versus medical respirators.
7. By pressure type: Negative pressure (commonest type), which is tight-fitting and generates negative pressure inside the facepiece relative to ambient air, or positive pressure respirator, which is used in an airplane to supply oxygen.

N95 Respirators

The commonly used N95 respirator (Fig. 29.1) is a negative pressure, nonpowered, air-purifying, particulate, tight-fitting, disposable respirator, which may be a medical or surgical (have surgical mask material on the outside to protect the wearer from splashes) respirator. It is also called the N95 mask or dust mask. It is useful to know that particulate respirators are classified as not resistant to oil, N; resistant to oil, R; or oil proof, P. Depending on percent filter efficiency of the air particles they filter, they are designated as 95, 99, or

Fig. 29.1 Picture of N95 respirator masks or respirators. This image depicts a still life composed of two N95-type face masks, or respirators, in the foreground, one turquoise (Lt), the other white, while in the background, you will note a third respirator, a N100-type mask. The N95 respirator works as an air-purifying respirator (APR), also known as a filtering face piece respirator, and is certified by the National Institute for Occupational Safety and Health (NIOSH). The N95 is designed to protect against particulate matter such as dust, fumes, mists, aerosols, and smoke, as well as biological particles, including pollen, mold spores, bacteria, viruses, animal dander, and allergens. It is also able to filter aerosolized droplets, in particular, smaller droplets, which evaporate to form droplet nuclei. Content providers(s): CDC/Debora Cartagena; this image is in the public domain and thus free of any copyright restrictions. (This image # 15482 accessed on 4/3/2021 at URL https://phil.cdc.gov/phil/home.asp)

100, thus resulting in nine classes of nonpowered air-purifying particulate filters. An air-purifying respirator can have an air-purifying filter, cartridge, or canister, and it can have a quarter mask facepiece, half mask facepiece, or a full mask facepiece. Powered air-purifying respirators (PAPRs) use a blower to force ambient air through air-purifying elements and then through tubing into a hood or helmet. Parts of a PAPR are a half or full facepiece, hood, or helmet, a breathing tube, a canister or cartridge with filter, and a blower. They may be able to provide additional protection compared to the usual N95 respirators if P100 filters are used, because they filter 99.7% of particles 0.3 μm in diameter and provide full face and neck protection including eyes and ears. Others such as supplied air respirators (as in airlines) or the self-contained breathing apparatus (SCBA) such as those used by divers are rarely necessary for a hospital respiratory protection program or pandemic preparedness. The reader is encouraged to look up resources from CDC, NIOSH, and OSHA [8, 10, 11] for a more detailed description of the different types of respirators. The respirator classes are given an assigned protection factor value, which is applicable when the respirators are properly selected and used in compliance with the OSHA Respiratory Protection standard (29 CFR 1910.134), with properly selected filters or canisters, as needed. A higher APF value is expected to provide greater respiratory protection to employees. For example, a common

N95 respirator has an APF of 5, a full facepiece PAPR has an APF of 1000, and a full facepiece SCBA has an APF of 10,000 [11].

The minimum respiratory protection required is an N95 respirator for routine patient care and aerosol-generating procedures in patients with diseases requiring airborne precautions, viral hemorrhagic fever, and possibly for emerging novel pathogens and pandemic influenza. This minimum respiratory protection is also required for aerosol-generating procedures in patients with seasonal influenza and similar infections requiring droplet precautions.

Powered Air-Purifying Respirator (PAPR)

PAPRs used by first responders need to be the most protective type of PAPR (Fig. 29.2) equipped with a filter and chemical cartridge. Surgical respirators (without exhalation valves) should be selected for use in environments where a sterile field is needed. The CDC isolation guidelines recommend the use of N95 masks (able to filter 95% or more of the particles <5 μm in size, as well as larger particles) or powered air-purifying respirator (PAPR) [1]. The World Health Organization has similar guidelines for protection of healthcare workers facing acute respiratory illnesses of concern such as SARS [12].

PAPRs are used not only in healthcare but in many other industries.

Pros and Cons of PAPRs

PAPRs do not require fit testing and are not affected by facial hair. They have a higher assigned protection factor and therefore useful in high-hazard situations. Patients can see the wearer's face, and they are easier for communication than an N95 respirator. Reusable respiratory protection equipment has advantages when dealing with pandemic events of potential airborne transmission (such as pandemic influenza or spread of coronavirus such as MERS). In the setting of a pandemic, it is likely that a very large volume of disposable N95 masks would be required to provide protection to every healthcare worker (including not only physicians and nurses but also any other individual, paid or not, who may share air space with individuals with potentially infections transmitted through the airborne route). In these situations, reusable equipment may be more advantageous. They have the disadvantages of being heavy to wear, interfering with stethoscope use, being noisy and sometimes making communication difficult, needing batteries or electricity, and potential for contamination with infectious material, thereby requiring decontamination and reprocessing between uses [13]. There

Fig. 29.2 Powered air-purifying respirator. This 1995 image depicts an anterior view of a laboratory technician wearing garments, usually worn by field techs, including a disposable white coverall, a disposable plastic apron, head covering, latex gloves, and foot coverings, and is equipped with what is known as a 3 M™ Breathe Easy™ Powered Air Purifying Respirator, PAPR. Though this 3 M™ PAPR can be equipped with either a biological rated filter cartridge, or a chemical rated filter cartridge, this outfit is rated only for a biologic interaction, and not chemical. (This image # 13161 accessed on 4/3/2021 at URL https://phil.cdc.gov/phil/home.asp)

are also theoretical concerns about how PAPRs may affect the wearer's performance. Some of this data comes from nonmedical use of respirators. Visual acuity may decrease, up to 75% in some reports, and visual range may be diminished. More concerning is the potential impact on steadiness and even cognitive impairment (although most studies have failed to prove this) during use due to thermal burden (when temperature rises over 85 °F, there is decreased reaction time, and this correlates with unsafe work behaviors) especially in hot environments [14–18]. A study performed by AlGhamri et al. [18] found no cognitive impairment in individuals using N95 or PAPRs while performing predeter-

mined tasks but found a negative effect on cognitive function when using negative pressure, full-face respirators. This study was limited by a small sample size and the lack of experience with respirator use by many of the studied subjects. A previous study showed that the use of a PAPR was associated with a potential decline in speech intelligibility, but this did not reach statistical significance when compared to other respiratory protection equipment or no respiratory protection at all. Even though full-face PAPRs do not require fit testing, they need to be properly size fitted. PAPRs are not exempt from limitations in their capacity to protect individuals when they are not properly size fitted. Gao et al. evaluated the level of protection provided by a PAPR in manikins, using different sizes of full-face masks. They found decreased protection when the manikins were not fitted with a properly sized full-face mask [17].

Baracco et al. developed a model to evaluate the cost of three options for respiratory protection requiring airborne isolation in the setting of a severe airborne pandemic event [19]. They compared the cost of stockpiling N95 masks, PAPRs, and reusable elastomeric half-face respirator. They took into account the storage space required, the half-life of the equipment, and the maintenance required, in the setting of a massive event requiring about six million contacts per one million population during the pandemic event. They based their model on assumptions derived from the 1918 influenza pandemic event. They found that the cost of stockpiling PAPRs is likely to be higher than the stockpiling of N95 masks, given the need not only of storage but also maintenance and battery care. Most batteries lose charging capacity over time and need to be replaced. Disposable batteries usually have a longer half-life, but only 10 h of battery life, and are more expensive. These batteries are usually made for the equipment, and regular batteries are not usually utilized. PAPRs need a larger storing area, need to be cleaned between uses, and the batteries expire, requiring battery recharging stations within reasonable access from the patient care areas. They are also more expensive, with each PAPR costing upward of $1000.

Pros and Cons of N95 Respirators

N95 masks work for most people and have the advantage of being disposable. The disadvantages are that they need respiratory fit testing annually in addition to the costs of storing. They are also not suitable for those with beards and those who have undergone facial surgery. The cost of mask fit testing is $18–20 per person using qualitative method. The cost of each mask is $0.73. For an organization that needs to fit test 5000 persons per year, the direct costs would be close to $100,000 per year. According to an occupational health professional, Susan Johnson, "The sheer number of staff who must be fitted (>8000 annually) is a challenge" [20, 21].

Advantages of the N95 mask include that they allow the use of stethoscopes, are easily available, are inexpensive, and allow for better communication. Disadvantages of N95 include the need for periodic fitting, risk of decreased protection with inappropriate fitting or facial hair, accumulation of moisture, exposure of the face and neck, need to purchase masks of different sizes, need for frequent replacement, and decreased tolerance due to resistance when breathing.

The cost of N95 masks was composed in 25–40% of long-term warehouse storage costs. In addition, many studies omit the costs of N95 issuing and training on their use. Table 29.1 highlights the key differences between N95 respirators and PAPRs.

Table 29.1 Considerations and controversies regarding the use of N95 respirators versus PAPRS for respiratory protection in healthcare settings

	N95 respirator	PAPR
Cost and preparedness	*Advantages*: Disposable Lower cost of stockpiling	*Advantages*: Does not need fit testing program
	Disadvantages: Needs fit testing program Need to purchase different sizes – cost of fitting Large volumes of disposable N95 masks may be required during pandemic Cost of storage given volume	*Disadvantages*: Needs power supply/battery chargers Units can be expensive (>$1000 per piece) Needs maintenance, which can be expensive Need to be properly size fitted, although no formal fitting program is required Need disinfection and cleaning between uses Chain of supply disruption of multiple parts/replacement during prolonged use
Training	Requires training	Needs special training
		Disadvantage: May increase body temperature
Contraindications for use	*Disadvantages*: Decreased protection with facial hair Decreased protection with increased moisture Not suitable for people with some facial surgeries	*Advantage*: Can be used with facial hair

(continued)

Table 29.1 (continued)

	N95 respirator	PAPR
Issues during use	*Advantages*: Does not interfere with stethoscope use Not heavy	*Advantages*: Faces are visible Reusable
	Disadvantages: Face may not be visible Can impair communication Appropriateness of fitting may change with weight changes and facial hair Exposure of the face and neck, with limited protection of mucous membranes Need for frequent replacement Decrease endurance of the wearer due to resistance when breathing	*Disadvantages*: Interferes with stethoscope use Heavy to wear Can impair communication Can affect performance of the wearer, decreasing visual acuity Additional protection, including coverage of mucous membranes available. Can be noisy Risk of exposure with battery or equipment failure Need for training for cleaning

Clinical Protocols, Policies, and Procedures

Robust clinical protocols, policies, and procedures are necessary to manage airborne infectious diseases in any healthcare facility. Clinical protocols need to be based on best available scientific evidence. While policies offer guiding principles, procedures offer step-by-step direction on what needs to be done. In addition to best available scientific evidence, regulatory considerations need to be factored in during the development of policies and procedures. The facility plan for managing highly communicable emerging infectious diseases needs to include an incident command structure, policies, screening and signage, triage and plan for inpatient care, staff training, availability supplies, storage, and maintenance. The plan must detail methods for controlling exposure to aerosol transmissible pathogens: airborne isolation to minimize the number of employees exposed, minimize the amount of infectious aerosol in the air through placement of mask on a patient and use of closed suctioning systems to minimize dispersion of aerosol, and protecting employees who must be exposed through vaccination if available, and use of personal protective equipment.

Experience with N95 Versus PAPRs During the COVID-19 Pandemic

During the COVID-19 pandemic, the world faced an unprecedent demand for respiratory protection equipment and availability of respirators was found to be insufficient. This was a worldwide problem that affected most nations, including the USA [22]. A modeling study calculated that a 400-bed hospital in the USA using a single use N95 for every positive SARS-CoV2 patient encounter could need about 6580 respirators if 30–60% of admissions were COVID-19 cases [23].

The N95 respirators were originally designed to be single use and disposable, but the unprecedented public health crisis led to the evaluation of multiple interventions to extend use or reuse the respirators. The CDC and several public health and scientific societies recommended prioritizing the use of respirators for aerosol-generating procedures, recommending the use of surgical masks as part of the PPE in lower-risk circumstances when N95 respirators are not available [6, 24].

Multiple interventions were studied and implemented to ensure availability of N95 respirators through the USA, including extended use of N95, reuse, disinfection with UV light, hydrogen peroxide or ethylene oxide sterilization, and use of expired respirators, among others [25, 26].

The FDA granted emergency use authorization to a list of respirators not produced in the USA that were not initially approved or evaluated but could potentially be used as PPE during severe shortages [27]. The National Institute for Occupational Safety and Health (NIOSH) evaluated some of these respirators in order to confirm the filtration efficiency of their material, and this information is available at their website [28].

The use of PAPRs during the COVID-19 pandemic was more common in US insititutions compared to the UK. The use of PAPRs for the care of COVID-19 patients was initially advocated by multiple scientific societies over the use of N95 and eye protection, in particular, during high-risk procedures. However, since then, there has been no evidence of superiority of PAPR over standard respirator with eye protection (N95/face shield or goggles) for the care of COVID-19 patients. The ability to use and clean the PAPRs for longer periods of time than the N95 could allow institutions to have appropriate respiratory protection. On the other side, as the pandemic persisted over time and the chain of supply was interrupted due to the pandemic, it was challenging for some institutions to obtain adequate parts to replace used or damaged PAPRs [29]. Over time evidence of proper protection with N95/eye protection during AGPs has been increasing [30].

It is possible that a combination of the N95 and PAPRs in the same facility may be required in order to optimize supply and ensure long-term sustainability of the respiratory protection program (i.e., use of PAPRs in areas where the healthcare workers must wear protection for many hours at the time, and use of N95 plus appropriate eye protection in instances where exposure is short-lived or when performing

AGPs in the outpatient setting). Further studies are required regarding the role of PAPRs during a global pandemic.

Regulatory Standards

Regulatory standards for respiratory protection are mostly set by the Occupational Safety and Health Administration (OSHA) [11, 21]. The OSHA standard 29 CFR 1910.134 requires that employers establish and maintain a respiratory protection program for workplaces in which workers may be exposed to respiratory hazards, and respiratory protection is used as an exposure control method. The OSHA recommends a hierarchy of controls – prevention or substitution, engineering controls, administrative controls and work practices, and, lastly, respiratory protection/personal protective equipment. One of the OSHA requirements is that the employer makes available respiratory protection gear in any workplace where respiratory protection may be required. This includes the presence of a program to select the type of respirators, ensure its proper maintenance, employee fitting if tight-fitting respirators are used, use during potential emergencies, cleaning/storage/maintenance of the respiratory protection equipment, training of employees on respirator use, risks of exposures, and evaluation of effectiveness of the program. It is required that respirators are fitted. The standard requires employees to be fit tested prior to the initial use of a respirator, annually, and whenever a different respirator facepiece (size, style, model, or make) is used. Furthermore, personal protective equipment must be provided at no cost to the employee.

Professionals in infection control and occupational health, as well as hospital administrators, need to be knowledgeable about and comply with regulations governing respiratory protection programs in their respective hospitals. While OSHA stipulates federal standards that are followed by the Centers for Medicare and Medicaid Services and most organizations, the Joint Commission requires that each healthcare facility clearly outlines elements of their respiratory protection program in their policies and procedures and demonstrates compliance [20]. Furthermore, there is considerable variation among states and organizations, especially those which are public, county-owned, or state-owned teaching institutions. The Centers for Disease Control and Prevention recommends that healthcare facilities follow their respective federal, state, or local regulations as it is not a regulatory agency [31]. It is important to know these nuances. Studies show that hospitals are experiencing challenges with the implementation of their respiratory protection programs. Twenty-four states have state-approved OSHA plans. These state-level plans incorporate regulations that are at least as strict as those set forth by OSHA at the federal level. In August 2009, during the peak of H1N1 pandemic, California enacted the nation's first occupational standard for aerosol transmissible diseases [32]. The standard requires, among other things, that hospitals care for patients with pandemic influenza using respiratory protection that includes an N95 respirator at a minimum. In addition to variation in state-level plans, recent studies in Minnesota, Illinois, and New York have demonstrated a wide variation in interpretation and implementation at the hospital level [33, 34].

During the COVID-19 pandemic, and due to the shortage of respirators, OSHA released discretionary enforcement guidance to the Compliance Safety and Health Officers regarding compliance with the respiratory protection standards, specially for institutions working under contingency or crisis modes. This discretionary enforcement does not release the institutions to maintain an appropriate respiratory protection program and requires the institutions to return to the standard practices as soon as the shortages resolve [35].

The FDA also allowed the use of nonhealthcare, NIOSH-approved respirators (including PAPRs, and other respirators with respiratory protection equivalent to that provided by N95 respirators or higher), expired or reprocessed single-use respirators in healthcare settings as another way to increase respiratory protection availability [36].

The CDC provided recommendations to optimize the use of respirators. They separated interventions in severe surge capacity, including conventional surge (following all standards, no shortages of respirators), contingency surge capacity (during periods where respirators are available and cover the needs of the facility, but there are expected N95 respirator shortages or uncertain supply), and crisis capacity (when the facility is unable to maintain the current future respirator use). During contingency capacity, expired N95 respirators may be used beyond expiration date for fit testing, and there can be extended use of N95 respirators. During crisis mode respirators can be used for clinical care beyond their expiration date, respirators approved by another country under similar standards than NIOSH approval may be used, respirators can be reused (limited to doffing 5 times or less), the period between uses should be >72 hours (time that the virus may persist on the surface), or they may need to be decontaminated. During crisis surge capacity, the use of respirators may be prioritized for aerosol-generating procedures. Healthcare facilities must return to conventional surge capacity standards as soon as supplies allow [37].

PAPR-Only Approach?

The most common approach in healthcare settings for respiratory protection is the use of N95 respirator masks along with employee fit-testing program, which could be expensive. An alternative approach used in some settings is the use of PAPRs only, which eliminate the need for employee fit

testing, if the PAPRs selected do not have a tight-fitting face piece.

Use of respirator masks versus PAPRs depends on the following variables in any given facility:

1. Ease of use
2. Training and competencies, for example, respirator fit testing annually
3. Cleaning between uses for PAPRs
4. Volume of patients and anticipated frequency of use
5. Storage/maintenance/repair and disposal
6. Annual costs
7. Regulatory standards
8. Level of protection needed
9. Intensity of contact and nature of healthcare personnel-patient interaction, including performance of any surgical procedures or aerosol-generating procedures (e.g., intubation, resuscitation, bronchoscopy, autopsy, aspiration of the respiratory tract)
10. Availability of engineering controls

Implementation Approaches in Different Hospitals and Health Systems

PAPRs are generally specified for high-hazard procedures, because they reduce risk more than the N95 respirators. The APF for loose-fitting PAPRs is 25 and for full facepiece tight-fitting PAPRs is 1000, which is more than the APF for a typical N95 respirator mask, which is 10. In a workshop conducted by the Institute of Medicine in 2015 [13], the participating experts noted that PAPR use is increasing in facilities across the nation. In a study (REACH II Public Health Practice Study – Respirator Evaluation in Acute Care Hospitals 2010–2012) that evaluated hospitals' respiratory protection programs and respirator usage in six states across the USA, CA, MI, MN, IL, NY, NC, more than 85% of the participating hospital managers and unit managers said their facilities had PAPRs available for use, while 30% of the healthcare personnel themselves were not aware of how to access a PAPR in their facility [13]. More than 40% of the healthcare personnel did not know what would happen if someone failed a fit test. A major finding of the study was that healthcare personnel were largely unaware of appropriate use of respiratory PPE and that the employer focus was on fit testing rather than training on proper use. PAPRs do not require fit testing, allow the patients to see their full face, and they accommodate facial hair. The disadvantage is they do not allow the use of a stethoscope. That being said, each PAPR costs about $1800, and there are costs associated with cleaning and disinfection between use and annual maintenance. Many experts are not convinced that there is a scientific basis for respirator fit testing annually as OSHA stipulates.

Before we decide on taking a PAPR-only approach in any health system, we need to recognize the unanswered questions in the area of healthcare worker respiratory protection. The key unanswered questions are:

PPE Choice and Safety

What PPE is required for aerosol-generating procedures?

What donning and doffing procedures are the safest and in what order? What is the clinical evidence on the safety of repeated donning and doffing of respiratory protection? Research is needed to strengthen the evidence of the effectiveness of PAPRs and of specific donning and doffing protocols.

What is the clinical evidence on the safety of different levels of wear compliance for respiratory protection?

How do we verify that improved filtration efficiency translates into enhanced healthcare worker safety?

What is the best way to use PAPRs in a sterile field?

How does an appropriate protection factor translate into adequate protection in actual clinical practice?

How does the respiratory physiology of a healthcare worker change during PAPR use?

Maintenance of PAPR

What are the appropriate procedures for the disinfection of PAPR components? Which components need to be disposable?

Indications for Use

What is the relative contribution of potential modes of transmission? Droplet, opportunistic airborne, or airborne transmission?

How strong is the evidence that respiratory worker safety translates to safer and healthier workers and patients?

Cost-Effectiveness for Routine Clinical Care and Pandemic Preparedness

What is the epidemiologic threshold at which the cost of N95 + annual fit testing outweighs use of PAPRs?

What should be the adequate size and composition of respiratory protective device stockpile?

PAPR Design

How can PAPRs be better designed so that they are more useful to healthcare?

How do we decrease noise, simplify cleaning and storage requirements, and improve battery life?

How do we improve products such as stethoscopes so that they are compatible with PAPRs?

When Would PAPR-Only Approach Work?

For ongoing respiratory protection to prevent transmission of TB and other airborne infections in the hospital, the expenses associated with annual respirator fit testing program may justify a PAPR-only approach. This is particularly true in healthcare facilities with a very low incidence of TB, and many such facilities are currently moving toward a PAPR-only approach for ongoing respiratory protection. This PAPR-only approach may not work in facilities with a high incidence of TB and a high volume of patients unless a seamless process for availability of PAPRs, cleaning and disinfection between uses, a maintenance plan, operational ownership plan, and training plan are fully established. In these facilities, a combination approach with N95 masks and PAPRs may be appropriate.

Pandemic situations present different challenges compared to ongoing prevention of infections potentially transmissible by the airborne route in facilities. Experts note that "given the high cost per unit, PAPR availability will always be a problem in the event of a major outbreak or act of bioterrorism. Healthcare facilities need to have dual systems for N95 respirators and PAPRs, and they need to train healthcare workers to use both" [13]. Studies have found that stockpiling Powered air-purifying respirators (PAPRs) was the most expensive strategy for a pandemic scenario. Furthermore, respirators do not eliminate the need for negatively pressured rooms or ultraviolet lights or the costs associated with triage and screening in pandemic situations. Therefore, for pandemic situations, a combination approach is probably better, and the proportion of N95 versus PAPR needs to be customized as per the local needs of the hospital.

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Donning and Doffing of Personal Protective Equipment (PPE): Is Training Necessary?

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Introduction

The use of personal protective equipment (PPE) to provide care to patients on "contact" isolation precautions is a standard infection prevention practice. This is despite the fact that limited data exists to show such practices are effective in preventing transmission of organisms from patient to patient [1–3]. Yet contamination of healthcare providers after interaction with the patient care environment has been well documented in the ICU setting, where multidrug-resistant organisms similar to those colonizing patients can be found on the gloves and gowns of healthcare workers after providing care [4, 5]. Several human factors presumably limit effectiveness of contact precautions as they are currently practiced, including poor adherence [6]. In addition, technique in PPE donning and doffing is increasingly recognized as a widespread opportunity for improvement among healthcare providers [7].

Self-Contamination

Self-contamination risk when doffing PPE was highlighted during the Ebola virus outbreak of 2014 [8]. Yet well before this crisis, Casanova et al. observed high rates of self-contamination using gowns, gloves, goggles, and masks in PPE donning and doffing simulations [9]. They contaminated PPE with both a non-pathogenic RNA virus and a fluorescent tracer and found the virus was transferred to the volunteers' skin or clothing 100% of the time while using the current standard method [10] for donning and doffing PPE advised by the Centers for Disease Control and Prevention. Transfer of the synthetic tracer occurred less frequently, but exact concentrations and technique of application are not discussed in detail in this report [9]. While the CDC method for doffing PPE is clearly not 100% effective in preventing potential pathogen transfer, it has been shown to be better than most provider-driven doffing procedures [11, 12]. Healthcare providers doffing PPE contaminated with a liquid fluorescent marker performed a series of PPE doffing simulations using various gown materials and either their own doffing method or the CDC-recommended method. The CDC method was found to be superior in preventing small stains to the front of underlying clothing, while it was ineffective in preventing larger area stains to the back [11]. The CDC method was further evaluated in a study by Tomas et al. in a series of 435 doffing observations in which the contamination rates, which is defined as the transfer of fluorescent lotion to the skin or clothing, occurred over twice as frequently in those using a doffing procedure other than the CDC-recommended method (70% versus 30% self-contamination rates) [12]. The CDC's doffing method "Example 2" which begins with gown and glove removal in a single first step [13] may further prevent self-contamination when compared to the traditional "Example 1" doffing procedures [14].

Self-contamination when doffing PPE has implications for patient and provider safety. Interventions to improve PPE removal technique are widely employed in the context of care for hemorrhagic fevers such as extensive provider training, paired and observed donning and doffing procedures, and ongoing practice to ensure skills are maintained [15]. However, training for PPE use in general inpatient healthcare settings is expected to be met with more skepticism. Contact precautions requiring gowns and gloves for the provision of patient care are controversial in their own right; to require training for these procedures pushes the debate even further. The central question relates to the effectiveness of contact precautions for preventing acquisitions of healthcare-acquired infectious agents; these questions have not been definitely answered in the scientific literature. Thus any benefit from a training program will be difficult to assess in terms of hard outcomes. There may be decreased self-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_30

contamination, but proving that this reduced bioburden is clinically meaningful will be more difficult. Nevertheless, high rates of self-contamination while using PPE arguably defeats the purpose of the intervention and may be implicated in the difficulty in showing benefit to PPE use in general, in terms of decreasing disease transmission. Finally, self-contamination is a problem that is distinct from general adherence issues, since providers who are faithfully following infection prevention policies could be inadvertently be putting themselves and patients at risk, rather than intentionally neglecting recommendations.

Types of Training and PPE

Training to improve the use of PPE has taken a variety of forms. The simplest examples are educational campaigns, similar to those traditionally used to promote adherence. Training can also take the form of hands-on practice of the procedures involved in donning and doffing PPE. Finally, enhanced training with the use of technology and/or feedback has been employed to strengthen experiential learning. Results are mixed and likely highly dependent on the type of intervention and the quality of the implementation. The Cochrane Group conducted a systematic review of training interventions for respiratory PPE use in the workplace that included occupational health and industry literature as well as healthcare settings. They found very low-quality evidence that training in the form of either education or physical practice was able to improve the correct use of respiratory PPE [16]. However, as the complexity of PPE increases, so do the potential benefits of training interventions. For practical reasons, centers involved in the care of patients with known or suspected Ebola developed intensive, protocolized training procedures for donning and doffing complex PPE. A recent study designed to validate CDC recommendations [15] for PPE use in the care of patients with Ebola hemorrhagic fever concluded that the strategies including detailed step-by-step instructions, trained observers, doffing assistants, and frequent hand hygiene were effective in preventing self-contamination with bacteriophage MS2 [17]. However, some virus was found on gloves, hands, and scrubs of several participants after doffing [17]. Similar to PPE for Ebola, Hazmat-type PPE for the first responders is complex and requires step-by-step instruction for appropriate use. Paramedic students were recently found to have a 0% error rate after completing training for Level C PPE when assessed by direct observation by trained evaluators [18]. On the other hand, doffing of Ebola-type PPE after a 40-min training session among otherwise untrained medical staff was shown to result in high rates of infection control breaches by trained observers [19].

Training for Reduction of Self-Contamination in the Acute-Care Hospital

In contrast to PPE for the care of patients with in public health emergency settings, PPE for use isolation precautions in acute-care hospitals is relatively simple at first glance. Many providers may not even be aware that specific procedures exist for donning and doffing [20]. However, observations of PPE use on medical units suggest that there is a need for increased education and training regarding the choice of PPE [21] and avoidance of contact with the outer surface of PPE during patient care or doffing [20, 22, 23]. Additional observations of simulated isolation care using PPE have identified improper PPE technique even when volunteers were well aware that they were being observed [23]. In defense of healthcare providers, there appears to be a lack of emphasis on proper PPE use; many providers have never had PPE training of any kind [8, 24], and those who have had training report a focus on the choice of PPE for various clinical situations over technique in using PPE [24]. Even in the era of the COVID-19 pandemic, a survey of infection control professionals from Australian and New Zealand hospitals revealed variability in frequency and type of PPE training, with simulations or healthcare provider practice in donning/doffing encompassing a small minority of strategies employed [25].

Training that emphasizes recommended PPE procedures has been effective in improving PPE technique and/or decreasing contamination rates in several studies [12, 26, 28, 29]. Hung et al. developed and trialed a computer simulation program in which participants led an animated figure through donning and doffing 5 part PPE for a respiratory isolation scenario [26]. The simulation program also asked the participants knowledge questions throughout the drag-and-click simulation. Participants using the computer simulation training were compared against a control group without access to the simulation; both groups attended a standard demonstration of donning/doffing procedures. Participants' donning and doffing techniques were evaluated before and after all training interventions. The study found that adding computer simulation training to conventional demonstration significantly improved PPE evaluation scores, albeit in a small, single-center study [26]. Unfortunately, it is not entirely clear how the participants were scored in their evaluations [26]. Some training studies focus on an outcome of proper PPE selection for the clinical situation and proper order of application [27]. While these are important considerations, they do not address the issue of technique for avoidance of self-contamination.

A series of quasi-experimental studies that use hands-on experiential learning have shown promising effects on participants [12, 28]. An educational program consisting of a 10-min instructional video, followed by a practice session in which participants donned and doffed PPE that was contami-

nated with fluorescent lotion, was evaluated with pre- and post-intervention doffing evaluations [12]. The investigators found that the training program reduced healthcare worker self-contamination rates by 68%. Furthermore, this result appears to be durable, with sustained rates at 1 and 3 months reported despite no additional provision of training [12]. Using the same training program, another study evaluated self-contamination rates after participants provided simulated patient care to a mannequin that was "contaminated" with fluorescent dye and bacteriophage MS2 [28]. There was an equal amount of spread of the surrogate contamination throughout the room and onto PPE of providers; however, the training program effectively decreased transfer of both markers to the skin and clothing of providers after doffing [28]. Of note, in both studies, while self-contamination rates using fluorescent lotion fell from 60% to 19% [12] and from 30% to 3% [28], respectively, there is clearly some residual transfer. Complete, consistent avoidance of self-contamination when using PPE may not be attainable.

At the start of the COVID-19 pandemic, many centers began urgent PPE training in efforts to protect healthcare workers from infection as a result of patient care activities. Tan et al. describe a three-part emergency training that included (1) in-class lecture, (2) simulation practice in the presence of trained staff, and (3) evaluation in which healthcare workers needed to demonstrate competency in donning and doffing [29]. Performance in the correct use of PPE significantly improved as a result of the program, with all participants passing the evaluation [29]. Similarly, Pokrajac et al. describe an additional educational intervention for healthcare providers scoring low on PPE skills assessment during the COVID-19 pandemic [30]. These individuals completed a simulated donning and doffing exercise using contact and airborne precautions on entry and exit to a model isolation room. Scores in the evaluations increased 26.9%, and all participants passed the assessment after the intervention [30].

Training simulations that include real-world experiences mimicking actual patient care are increasingly recognized as important to provider confidence in PPE to protect them while providing care to a patient with a known transmissible pathogen. In addition to the previously noted study using contaminated mannequins to simulate infected patients [28], Poller et al. developed a mannequin which actively secretes surrogate contamination via remote-controlled output of UV-fluorescently tagged fluids as sweat, cough, diarrhea, or vomit [31]. Study participants found it helpful to observe the extent and distribution of self-contamination after simulated patient care episodes with the mannequin; the authors envision the mannequin assisting in PPE training programs for hemorrhagic fevers [31]. Finally, a group in Singapore conducted PPE training in teams using simulated protracted cardiopulmonary resuscitations [32]. The goal was to identify unforeseen issues that could potentially expose healthcare vworkers as they provide critical care for individuals infected with COVID-19. Multiple issues were noted including poorly applied N95 masks, lapses in hand hygiene, and inappropriate decontamination of Powered Air-Purifying Respirator (PAPRs). Team competencies in both resuscitation activities and infection prevention improved from 40% to 60–70% with repeat simulated practice. Workflow interventions were also enacted based on the observations to limit team movements and opportunities for cross-contamination of team members and the environment [32].

Limitations of the Available Data

A meta-analysis of PPE that included studies on PPE removal, training, and use concluded that the body of literature to date offered very low evidence to support training for PPE. The analysis was only able to include a handful of studies as most reports on the topic were observational, lacking control groups, or lacking details about the interventions or outcomes [33]. Another issue is the use of various surrogate markers for potentially infectious organisms. It is unclear if simulation results would correspond to real self-contamination with infectious agents in the hospital and patient environment. Furthermore, it is unclear if fluorescent dye contamination correlates with contamination with actual organisms. Some studies that have used both the dye and bacteriophages found good correlation in transfer rates between the two [12], while others have demonstrated that the virus is transferred much more readily to provider skin/clothing than the fluorescent dye [9]. Some of this discrepancy might be explained by different methods of application of the fluorescing substance, as well as different quantities and formulations: spray, gel, lotion, and powder. Lastly, multiple studies report the site of most frequent self-contamination is the provider hands [12, 20, 34]; it is unclear to what extent this contamination remains a clinical concern after appropriate hand hygiene.

Conclusion

As our world becomes increasingly interconnected and the patients in our hospitals become ever more complex, effective infection prevention practices are critical for public and patient safety. When it comes to the use of personal protective equipment, we have opportunities for improvement. There is an urgent need for rigorous assessment of the existing PPE with a focus on application and technique considerations. In the meantime, healthcare centers must re-examine the existing PPE programs to ensure that they meet the educational needs of healthcare workers to provide care that is safe for themselves and safe for others.

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Rapid Diagnostics in Infection Prevention

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Introduction

There are several relevant pathogens in today's healthcare environment that can result in severe infection and death. Many of these pathogens can be rapidly spread to susceptible hosts, leading to outbreak situations [1]. Bacterial pathogens often harbor antibiotic resistance, resulting in limited treatment options, which may also have significant toxicity [1–3]. Because of this, preventing transmission and subsequent infection is ideal. Employment of rapid diagnostics to swiftly identify patients infected with these pathogens may have a significant impact on an individual's health as well as the health of the public.

Significant advancements have been realized over the past few years in the expanding field of rapid diagnostics. Compared to traditional laboratory methods where final culture and susceptibility results are typically obtained within 48–72 h, rapid tests are able to provide identification within hours of organism growth or, in some cases, sample collection [4]. A paradigm shift in organism and susceptibility identification, rapid diagnostics allow for earlier initiation of targeted antimicrobial therapy in infected patients, resulting in decreased mortality, hospital length of stay, broad-spectrum antimicrobial use, and health system costs [4–8].

Rapid diagnostics may also be employed for infection prevention and control purposes, in addition to treatment of infections. Rapid identification of colonizing or infecting pathogens, as well as certain resistance patterns, results in prompt implementation of procedures to prevent subsequent development of infection within a colonized patient or transmission of infection to others [9]. Upon pathogen identification, infection prevention bundles that may include implementation of isolation procedures, hand hygiene reinforcement, patient cohorting, decolonization regimens, and utilization of proper environmental cleaning may be employed in order to minimize risk of infection or transmission. Utilization of rapid diagnostic tests may also be employed during outbreak situations in a similar manner to mitigate further spread, and in some cases determine clonality.

Rapid Diagnostic Testing

There are various types of rapid diagnostic tests that can be employed in practice. It is important to understand the functionality, benefits, and limitations of each in order to implement the test and interpret results. Antigen-based tests and molecular tests are some of the most common rapid diagnostics employed in healthcare settings. Generally, molecular-based tests (e.g., polymerase chain reaction [PCR]) have a higher sensitivity and specificity compared to antigen-based tests [10]. Thus, molecular tests are often associated with a higher negative predictive value than antigen-based tests. Tests with lower sensitivity could result in false negatives, which could result in further transmission of infection, especially if prevention methods are not employed [11]. This high sensitivity assists with the identification of colonization in addition to infection; however, these tests may still detect genetic material after the infection has been cleared by antibiotics, which complicates treatment and infection prevention decisions [12].

Rapid diagnostic tests are also more costly than traditional culture and susceptibility methods. Institutions will have to decide if the prevalence of the infection identified by the rapid diagnostic test is high enough to justify the excess cost [13]. Additionally, molecular tests such as polymerase chain reaction (PCR) often require specialized training, personnel, and equipment to employ, which can further increase

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_31

cost associated with these tests [14]. Because of the need for specialized training and equipment, testing may be completed in batches, which may delay results [15]. However, point-of-care PCR tests that do not require specialized personnel are also becoming available on the market.

The expansion of rapid diagnostics has also unearthed challenges with the reporting of healthcare-associated infections. Matrix-assisted laser desorption ionization – time of flight (MALDI-TOF), another molecular test, has enabled identification of multiple organisms down to the species level. Some of these organisms may be inappropriately identified as a pathogen when they are truly a colonizing organism, which can impact reporting of relevant healthcare-associated infections, such as central line-associated bloodstream infections [11]. Recently, multiplex rapid diagnostic tests for respiratory infections have entered the market, resulting in rapid test results that may be completed on-demand in certain laboratories [11]. These tests are generally associated with high sensitivity, particularly when compared to traditional culture methods. Additionally, these tests are classified as semiquantitative and may detect colonization or normal respiratory flora, complicating the use of these tests for diagnosis. However, the identification of bacteria by these tests could contribute to the diagnosis of possible ventilator-associated pneumonia (VAP), a condition tracked by infection prevention departments in the United States under the direction of the National Health and Safety Network (NHSN), and potentially increase VAP rates for health systems.

In addition to general considerations with rapid diagnostics, this chapter also discusses the utility of rapid diagnostic testing for the following relevant pathogens: carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus spp*. (VRE), *Clostridioides difficile*, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza, and *Candida auris*.

Carbapenem-Resistant *Enterobacteriaceae*

Carbapenem-resistant *Enterobacteriaceae* (CRE) are an emerging global health concern due to rapid interpersonal transmission, the ability to transmit resistance determinants to other bacteria, and the dearth of antimicrobial agents demonstrating activity [1, 3, 16]. First described in the 1980s, CRE have become endemic in certain areas of the world [17]. Colonization with CRE is a significant risk factor for subsequent infection as well as transmission [18]. Infections due to these organisms are associated with a mortality rate between 24% and 70% [3]. CRE infections pose a major threat to individual and public health and require rapid identification to ensure initiation of strategies to prevent progression of infection within a colonized patient, transmission to uncolonized patients, and initiation of appropriate antibiotic therapy to minimize morbidity and mortality [11, 19].

Detection of CRE poses several challenges for microbiology laboratories. Identification of CRE using traditional phenotypic methods can take up to 4–6 days after culture collection, which can result in significant delays in initiation of appropriate infection control strategies and antibiotic therapy, subsequently increasing the risk of infection transmission [20, 21]. While some phenotypic tests themselves can result quickly, these tests are often only employed once carbapenem resistance has been demonstrated via traditional culture and susceptibility methods. The most concerning mechanism of resistance in these organisms is enzymatic degradation via carbapenemases, as these resistance genes are typically located on mobile elements within the organism allowing for easy transfer to other bacteria [19]. Carbapenemase-producing organisms are responsible for the majority of CRE outbreaks throughout the world [3, 17]. Phenotypic methods generally do not distinguish between type of carbapenemase present, which can complicate treatment decisions [22]. Phenotypic methods are also required to identify resistance due to porin mutations or efflux pumps, since molecular-based tests identify enzyme-mediated resistance only [21]. Molecular-based rapid diagnostic tests may be employed upon identification of carbapenem resistance, but also may be used to detect carbapenemases 24–48 h earlier than culture-based methods [13]. Several single and multiplex PCR-based molecular tests have been developed to detect enzyme-mediated carbapenem resistance in *Enterobacteriaceae* from clinical specimens or rectal swabs, but the multiplex tests are unlikely to identify the entire library of carbapenemase enzymes [21, 22]. These tests are costly, and may not be employed in settings with low carbapenemase prevalence [13].

The Centers for Disease Control and Prevention (CDC) has developed a CRE Toolkit that outlines recommended components of a bundle that should be initiated upon identification [19]. Institutions may elect to utilize components of the bundle that apply to their specific setting. Bundle components include active screening of contacts of the index patient, surveillance of high-risk patients, timely notification upon laboratory identification, education of staff about CRE, reinforcing hand hygiene and environmental cleaning practices, initiation of contact precautions, cohorting of patients and staff, utilizing 2% chlorhexidine gluconate (CHG) for patient bathing, minimizing utilization of invasive devices, communication of CRE status upon transfer, and antimicrobial stewardship.

Active surveillance utilizing rapid diagnostic tests for CRE has largely been utilized as part of an infection control bundle to prevent or contain outbreaks within institutions [9, 23–26]. Sample collection has been described at varying

time points: upon hospital or intensive care unit (ICU) admission, weekly, or on demand based on identification of a colonized or infected patient. Once a patient is identified as infected or a carrier, further infection control measures may be employed. Infection control bundles incorporating active screening upon admission and weekly thereafter, contact isolation, patient cohorting, CHG bathing, caregiver education, and adherence monitoring at four long-term acute-care hospitals found that bundle implementation significantly decreased rates of CRE colonization, CRE infection including bloodstream infection, and blood culture contamination [25].

While utilizing surveillance for the prevention of horizontal spread has shown some promise, there is still uncertainty of the impact of surveillance on the vertical spread of CRE. Studies evaluating use of rectal swabs for identifying CRE demonstrated low positive predictive values for true infection [27–29]. This brings into question the utility of CRE surveillance with rapid diagnostics in areas with low endemicity in the absence of an outbreak [13].

Methicillin-Resistant *Staphylococcus aureus*

Staphylococcus aureus is the most frequent pathogen associated with healthcare-acquired infections and is also highly prevalent within the community [30, 31]. Antibiotic resistance is common, and infections caused by MRSA place a large burden on health systems. In 2017, the CDC estimated over 10,000 deaths attributable to MRSA infection [1]. Patients with hospital-acquired MRSA (HA-MRSA) infections are not only at an increased risk of mortality but also a prolonged hospital stay and increased healthcare costs [32]. Fortunately, since 2013, active infections caused by MRSA in the United States have decreased by 21% [1].

The highest MRSA colonization and infection rates within a hospital are found in intensive care unit (ICU) settings, occurring in up to 21.9% of patients within an ICU, compared to 3.4% in hospitalized patients overall [33]. MRSA colonization has been associated with acquisition of MRSA infections in the acute care setting, with colonized patients demonstrating over a tenfold greater risk of MRSA infection compared to those who are not colonized [34–36]. It has been estimated that 218,000 MRSA infections would occur annually within the ICU setting if no infection prevention activities are employed [37]. Therefore, preventing the spread of this infection within patients and healthcare settings is vital.

Multiple rapid diagnostic tests exist that can be utilized to identify MRSA, with PCR being the most utilized [4, 38]. PCR test results demonstrate a turn-around time of only 1–2 h [39]. MRSA screening can be performed at multiple anatomical sites including the nares, axillae, groin, perineum, and throat. However, the nares are most commonly utilized, because they provide an optimal environment to facilitate *S. aureus* survival and have been shown to be the most sensitive site of detection for MRSA colonization [40, 41].

For infection prevention purposes, rapid diagnostics have typically been employed for active surveillance in high-risk patient populations to quickly identify colonized patients and subsequently implement further measures to mitigate transmission. Additional prevention strategies to reduce MRSA transmission have been defined by the CDC and the Society for Healthcare Epidemiology of America (SHEA) and include the following: conducting an institutional MRSA risk assessment, rapid reporting of MRSA results, assessment of hand hygiene, implementation of contact precautions, adequate environmental disinfection, identification of patients previously colonized with MRSA (passive surveillance), education of healthcare providers, patients and families, and reporting MRSA data to key stakeholders within the institution [42, 43].

Several studies have evaluated the utilization of active surveillance and its impact on MRSA infection and transmission. While a majority of the published studies demonstrate a positive association with use of active surveillance, there are some studies that question its overall utility [43]. Because most studies utilizing active surveillance also implemented concurrent infection control interventions, it is difficult to draw conclusions about the benefit of active surveillance alone. For these reasons, the employment of active surveillance testing is not currently recommended as a core strategy for MRSA infection prevention or transmission, although some states do have legislation requiring its use [43, 44].

Molecular tests may also be used to prevent vertical transmission of MRSA by identifying the presence of MRSA colonization prior to surgery in select patient populations [45]. Once MRSA is identified, decolonization strategies can be employed to minimize risk of subsequent postoperative infection. However, the utility of a screening-based preoperative decolonization strategy may be similar to that of universal decolonization for all patients [46].

Vancomycin-Resistant *Enterococcus spp.*

Enterococci are considered to be normal flora of the gastrointestinal tract of humans that generally display low levels of virulence but are intrinsically resistant to several antibiotics [2]. In hospitalized patients, especially those that are immunosuppressed or critically ill, enterococci can disseminate and proliferate, causing significant infections such as bloodstream infections and infective endocarditis [47]. In particular, infections caused by vancomycin-resistant enterococci are a significant cause of morbidity and mortality globally, especially in high-risk patient populations including ICU,

hematology/oncology, and solid organ transplant [2]. The CDC reported 5400 deaths attributable to VRE in 2017 [1]. Treatment options for VRE infections in particular are limited, and several of these antimicrobials are associated with substantial toxicities [48]. Luckily, the incidence of VRE infection has decreased over time [1].

PCR tests are available that detect the presence of *vanA* and *vanB* genes within enterococci, the genetic elements responsible for vancomycin resistance [2, 49]. These tests demonstrate poor specificity for *vanB*, which is thought to be due to the presence of that gene in several other anaerobic bacterial isolates that can be harbored in the gastrointestinal tract. Since stool samples and rectal swabs are submitted for VRE surveillance, it is possible that the PCR may detect *vanB* from another organism colonizing the gastrointestinal tract. PCR tests also do not detect other *van* genes responsible for vancomycin resistance, although *vanA* and *vanB* are known to be the most common.

Strategies utilizing rapid diagnostic tests aimed at identifying high-risk patients colonized with VRE may help prevent spread and progression of infection [50–53]. An active surveillance strategy is useful for initiating contact precautions or patient and staff cohorting to contain the spread of VRE to other patients, and is commonly used in outbreak settings. Active surveillance can be done at hospital admission combined with subsequent periodic screenings or when certain criteria are met (e.g., onset of neutropenia). Several studies employ weekly screening while inpatient; however, the optimal frequency of conducting surveillance is not well defined. Based on a mathematical model, utilizing active surveillance in a 10-bed ICU prevents an average of 46 new cases of VRE colonization in a year, whereas passive surveillance prevents only 5 cases per year [53]. Immediate isolation of all patients admitted to an ICU with removal only if surveillance cultures were negative may prevent up to 77 cases per year; however, the feasibility of this strategy is limited.

Clostridioides difficile

C. difficile infection (CDI) is increasing in prevalence across the world and is associated with significant morbidity, mortality, and excess healthcare costs [54]. As *C. difficile* spores persist on surfaces for prolonged periods of time and can subsequently infect other patients, rapid diagnosis may reduce further transmission as it will allow for rapid initiation of infection prevention strategies, such as isolation, hand hygiene, and the appropriate use of sporicidal cleaning products. While the CDC suggests implementation of isolation procedures immediately upon suspicion of infection, this may not be routinely employed in all settings. Active surveillance for *C. difficile* is not routinely performed nor currently recommended, and there is no evidence outlining what infection prevention activities should be implemented upon positive active surveillance result.

There are several rapid diagnostic tests that may be used to identify the presence of *C. difficile*. Enzyme immunoassays (EIAs) detect toxin produced by *C. difficile* and provide rapid results, but are fraught with poor sensitivity, leading to false negatives [11]. Patients with false-negative test results may not have appropriate infection prevention strategies employed, which may increase transmissibility. Tests that identify glutamate dehydrogenase (GDH) have demonstrated higher sensitivity than toxin-based tests, but often are used as part of a 2-step testing process as GDH could be indicative of colonization or active infection as it is unable to distinguish if the *C. difficile* detected is producing toxin [55]. PCR tests to detect *C. difficile* result within 1 h, and demonstrate improved sensitivity compared to EIA, when used with or without initial glutamate dehydrogenase screening [56]. With short turn-around time and high sensitivity, it may be possible to delay isolation until result. However, these highly sensitive tests also identify those who are simply colonized with *C. difficile*, and not actively infected, complicating treatment strategies for the clinician [11]. It is important to know what test is available within health systems as well as the utility and challenges of each so that infection prevention and treatment decisions can be made appropriately.

Active surveillance for *C. difficile* is not routinely performed nor currently recommended, and there is no evidence outlining what infection prevention activities should be implemented upon positive active surveillance result [57].

Severe Acute Respiratory Syndrome Coronavirus 2

The rapid emergence and worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) highlighted the need for methods to quickly identify patients infected with the virus in order to mitigate spread. The coronavirus disease 2019 (COVID-19) pandemic continues to cause significant morbidity and mortality for patients, and with minimal treatment options available, rapid diagnosis and isolation of positive patients is needed to minimize transmission [58]. Multiple rapid tests for SARS-CoV-2 are available, and primarily consist of antigen- and molecular-based (PCR) tests [10].

Antigen tests may be desirable for diagnosing COVID-19 infection, as they are easy to employ and do not require specialized laboratory personnel or technology for use [14]. Due to this, and the availability of results in 15–20 min, antigen tests may commonly be employed in various healthcare settings. However, a recent Cochrane review found significant variation in sensitivity among antigen-based tests, with an

average sensitivity of 54% (range of 0–94%) [10]. Negative predictive value for these tests ranged from 90% to 98%, which decreased with increasing prevalence of SARS-CoV-2 in the community. The best time to perform antigen tests is during symptomatic infection when the viral load is at its highest to minimize the risk of obtaining a false-negative result [14]. A false-negative result can increase risk of transmission as the patient will no longer be isolating.

Rapid molecular tests have demonstrated increased sensitivity (average: 95.2%, range of 68–100%) and a negative predictive value of 99% [10]. The results of molecular testing for SARS-CoV-2 can be influenced by viral load, time since symptom onset, collection technique, and sample location (nares, nasopharyngeal, oropharyngeal), but generally are more reliable than antigen-based tests [58]. PCR-based tests are the preferred molecular tests by the World Health Organization and the Food and Drug Administration [14]. Rapid PCR-based tests can provide results within 30 min to 18 h, depending on the test. Loop-mediated isothermal amplification (LAMP) is also an emerging molecular test that may be employed in some areas. LAMP does generate rapid results, within minutes up to 2 h. Depending on the manufacturer, it may demonstrate higher sensitivity than PCR-based tests as more primers are used to amplify the target DNA. LAMP technology also requires less expertise to run than PCR-based methods; however, there have been challenges with developing primers and optimizing the limit of detection.

Influenza

Influenza is a respiratory virus that occurs seasonally, and respiratory symptoms may be caused by either influenza type A or type B [59]. It is associated with significant morbidity and mortality with annual hospitalizations ranging from 140,000 to 710,000 and deaths from 12,000 to 52,000 [60]. It is easily transmitted from person to person; therefore, early identification of infection is important to prevent further spread.

Like SARS-CoV-2 detection, both rapid antigen- and PCR-based molecular tests are commonly used for the diagnosis of influenza. In addition, rapid digital immunoassays (DIAs) may also be employed [15]. Point-of-care antigen tests are commonly utilized for influenza diagnosis due to their ease of use and rapid time to result. Antigen tests typically provide results within 30 min of sample collection, which is comparable to DIA and PCR testing. The use of antigen-based tests is limited by their poor sensitivity, reported to be 54.4% for influenza A and 53.2% for influenza B. DIAs demonstrate improved sensitivity with 80.0% and 76.8% for influenza A and B, respectively. PCR-based tests show the highest sensitivity with 91.6% for influenza A and 95.4% for influenza B. Specificities were similar among all three testing modalities. PCR-based tests, while highly sensitive, may be difficult to employ in many settings, as these test results are often batched at specialized laboratories despite the availability of rapid PCR point-of-care tests for influenza.

Active surveillance for influenza is not routinely employed in healthcare; however, it may be utilized in long-term care facilities to mitigate spread. In Winnipeg, Canada, influenza-like infection outbreaks at long-term care facilities must be reported to public health departments [61]. From 2003 to 2011, 80 of 154 outbreaks in Winnipeg were caused by influenza. Influenza screening was completed by rapid antigen test, viral culture, or PCR. Identification of the outbreak within 3 days of onset was associated with lower infection and mortality rates in residents, demonstrating the benefit of rapid results and quick implementation of infection prevention strategies.

Candida auris

An emerging pathogen of concern, *Candida auris*, was first identified in Asia in 2009 and has been identified in over 30 different countries [1, 62]. First isolated in the United States in 2015, it was added to the CDC's Urgent Threat list in 2019 [1]. *C. auris* is a multidrug-resistant fungal pathogen that may demonstrate resistance to all existing classes of antifungal agents, with associated mortality rates of over 50%. It can form biofilms and live on surfaces within healthcare facilities, and thus is commonly isolated in patients with severe health conditions who have recently had invasive procedures or an indwelling prosthetic device who are cared for in long-term care facilities or hospitals [62, 63]. Because of its high mortality, resistance pattern, and ability to easily spread, it is important to identify this pathogen in colonized patients so that infection prevention strategies can be put into place.

Identification of *C. auris* is challenging, as other *Candida* spp. contain similar phenotypic characteristics, which may lead to misidentification [62]. Because of this, molecular identification through PCR-based tests or MALDI-TOF is preferred. Facilities can test for *C. auris* in-house, but samples may also be sent to the CDC, where identification can take several weeks even when molecular-based tests are used [64, 65].

The CDC recommends screening all patients at high risk for *C. auris*, including close healthcare contacts of those found to be infected or colonized and patients who were hospitalized overnight in another country within the past year [66]. In 2019, *C. auris* was isolated from a patient in a long-term care facility in Orange County, California [64]. Subsequently, point prevalence surveys using PCR identified

patients at three separate facilities who had received transferred patients from the index long-term care facility. This resulted in the California Department of Public Health implementing screening requirements for all long-term care facilities and ventilator-capable skilled nursing facilities within Orange County. If any cases were identified in these facilities, isolation precautions were initiated and screening continued every 2 weeks. Patients transferred out of facilities with cases were screened upon admission to the new facility and placed in isolation. Point prevalence testing identified a total of 182 patients at nine facilities who were infected or colonized with *C. auris*; however, the outbreak was contained to two facilities by October 2019, demonstrating the importance of rapid identification of cases.

Conclusion

The use of rapid diagnostic tests for infection prevention purposes will continue to be an area of research as the burden of antimicrobial resistance continues to expand. As these tests will continue to be used for earlier identification of relevant pathogens to help optimize treatment and mitigate infection spread, it is important to understand the benefits and limitations of the rapid test so that the test can be implemented and results can be interpreted appropriately.

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Diagnostic Stewardship

32

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Background

Diagnostic stewardship refers to "modifying the process of ordering, performing, and reporting diagnostic tests to improve the treatment of infections and other conditions" [1]. As an idea with growing attention, the meaning has evolved over time. Although not named as such, the goals of diagnostic stewardship have existed since at least 1974, when Dr. Raymond C. Bartlett noted:

> Our technical capabilities are exceeding our ability to apply them effectively and economically to human problems" and the microbiology laboratory is "faced with a superabundance of academic information and pressure to perform exhaustive, expensive, clinically irrelevant" testing which can "mislead physicians into erroneous diagnosis and inappropriate therapy" and requires a "more practical, economical, clinically meaningful approach. [2, 3]

Modern use of the term diagnostic stewardship emerged in 2017 [1, 2]. The term diagnostic stewardship primarily relates to infectious disease and microbiology, but it is also a philosophy and a process that can be used to improve the use of all diagnostic tests to improve infectious and noninfectious patient outcomes. The Centers for Disease Control and Prevention (CDC) is currently completing a White paper to endorse the approach of diagnostic stewardship.

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Definitions

Although diagnostic stewardship has been used to describe processes to improve quality and speed of sample processing, we use the broader definition of "modifying the process of ordering, performing, and reporting diagnostic tests to improve the treatment of infections and other conditions" [1, 4]. We also support a modified version of the antimicrobial stewardship definition of Messacar et al., the "*right test* for the *right patient*" prompting the right *action* (rather than the "right time") [2]. While some have questioned whether the term diagnostic stewardship is too broad or is in fact encompassed by antimicrobial stewardship, we believe the broader term is intuitive, acceptable, and important to improve patient care. Likewise, there is overlap between the clinical and laboratory definitions of ordering, processing, and reporting tests that parallel the laboratory terminology: preanalytic, analytic, and postanalytic. See Table 32.1 for definitions.

General Techniques for Diagnostic Stewardship

While patient- or clinician-focused diagnostic stewardship relies primarily on education to achieve a change in behavior, system-based diagnostic stewardship is centered on behavior change in real time while providing some education in the process. System-based diagnostic stewardship interventions are grounded in two general approaches—the "paternalistic libertarianism" of behavioral economics and more didactic rules and processes [5].

All interventions should be focused on improving patient outcomes through optimizing care and avoiding unnecessary treatments or additional diagnostics [1]. Behavioral economics is based on Choice Architecture and primarily relies on nudges or framing to produce desired outcomes [5, 6]. Nudges are interventions intended to alter "behavior in a predictable way without forbidding any options." Framing is

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_32

presenting choices in a way that "highlights positive or negative aspects of a decision, leading to changes in their relative attractiveness" [7].

Table 32.1 Key chapter definitions

Diagnostic stewardship	Modifying the process of ordering, performing, and reporting diagnostic tests to improve patient outcomes.
Nudges	Behavioral interventions to guide decision making through choice architecture while maintaining prescriber autonomy.
Framing	Presenting choices in a way that highlights positive or negative aspects of a decision, leading to changes in their relative attractiveness.
Reflex testing	Strategy wherein tests are only performed after prespecified criteria are met. For example, urine cultures are only performed if an antecedent urinalysis indicates the presence inflammation (i.e., pyuria).
Results suppression	Strategies of reporting only some (or none) of the available result information. For example, not releasing organism identification if multiple organisms are present in a urine culture.
Selective reporting	Strategy of only reporting organism identification or antibiotic susceptibility results when specific criteria are met.
Cascade reporting	Strategy of reporting antibiotic susceptibility in a stepwise fashion when specific criteria are met (e.g., organism resistant to first-line antibiotic agents).
Preanalytic	The step of ordering tests and collecting samples that occurs before processing in the microbiology laboratory.
Analytic	Work or interventions within the laboratory. Analogous to processing.
Postanalytic	The reporting of results and other steps that occur after processing in the microbiology laboratory.

More proscriptive rules include defining situations when a test *cannot* be ordered. For example, not allowing *Clostridioides difficile* tests on a patient taking laxatives, or not reporting urine culture results if more than two species are identified. These are often referred to as "hard stop" interventions in contrast to the "soft stops" of nudges [8]. However, even these more authoritarian rules generally have an option whereby clinicians can still request the desired test with additional outreach or explanation. The points at which different diagnostic stewardship strategies are implemented are displayed in Fig. 32.1.

Relationship Between Diagnostic Stewardship and Infection Control

Many diagnostic stewardship efforts have been led by Infection Control due to the relationship between testing and healthcare-associated infection (HAI) reporting. Given *C. difficile* infection (CDI), central line-associated bloodstream infection (CLABSI), and catheter-associated urinary tract infection (CAUTI) are defined by laboratory reporting, part of the impetus for Infection Control involvement has often been the desire to optimize hospital metrics. Although Infection Control has led many beneficial efforts to reduce unnecessary or inappropriate testing practices, there can be a tension between minimizing HAI rates and assuring appropriate patient care. Sometimes known as "gaming the system," the desire to improve HAI rates should not interfere with appropriate clinical diagnostics and treatment. While foregoing all testing would result in HAI rates of zero, the negative impact on patients is obvious. The institutional importance placed on HAI metrics is driven by performance

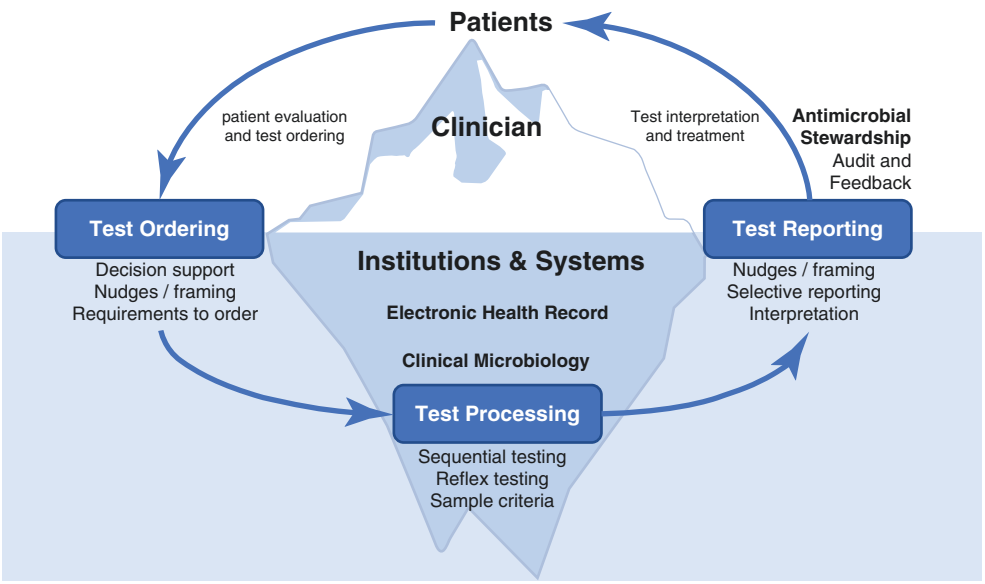

Fig. 32.1 The diagnostic stewardship iceberg representing patients, clinicians, and healthcare systems at the core of diagnostic stewardship. Arrows demonstrate the movement of samples and information. Members of the diagnostic stewardship team are involved in multiple steps to optimize the impact on patient care

incentives, and the Hospital Epidemiologist or Infection Preventionist must balance the drive to minimize HAI rates while ensuring appropriate patient care. For some HAIs such as *C. difficile* and CAUTI, there is a large component of overdiagnosis and rates can be significantly reduced by diagnostic stewardship efforts while also benefiting patients by avoiding unnecessary treatment.

Relationship Between Diagnostic Stewardship and Antimicrobial Stewardship

Antimicrobial Stewardship (AMS) programs are interprofessional programs that facilitate the use of antimicrobials to optimize patient care [9]. AMS programs utilize interventions to meet these aims, including prospective audit and feedback, prior authorization, and tracking and reporting. Additionally, although these programs are commonly led by Infectious Diseases–trained physicians and pharmacists, AMS has strong collaborations with the Clinical Microbiology laboratory [2, 10, 11]. AMS has led initiatives with diagnostic stewardship components, such as cascade or selective reporting of antimicrobials and nudges to avoid certain antimicrobials. Additionally, AMS programs are often integral in the clinical success of implementing novel molecular diagnostics through active clinical review and feedback to providers.

Importance of the Clinical Microbiology Laboratory

The microbiology laboratory is where many steps in diagnostic stewardship occur. Before the subject was termed diagnostic stewardship, the responsibility of performing the right test, on the right patient, for the right indication was the responsibility of the laboratory. Clinical laboratorians ensure that tests, which are implemented for clinical use, must meet quality, safety, and efficiency standards before they are put into use. The microbiology lab must perform rigorous validation, verification, and quality control testing to demonstrate these standards on all equipment, testing platforms, and individual tests.

Clinicians who order tests, hospital epidemiologists and AMS members who follow the system-wide downstream effects of this testing, all must work closely with microbiology for diagnostic stewardship. Aspects of clinical microbiology include testing criteria applied to the quality of the specimen and the timing of collection or reporting of results. Specimen quality control helps to increase the pretest probability influencing the posttest positive or negative predictive values. Reporting may directly or indirectly influence interpretation of results to better guide the clinician toward appropriate management. While diagnostic stewardship cannot be performed without the input and cooperation of the microbiology laboratory, stewardship is much stronger when the lab, clinicians, those maintaining the electronic medical record and the institution as a whole work together to create a robust feedback loop that promotes appropriate testing and decreases inappropriate testing and subsequent actions.

Diagnostic Stewardship for Clinicians Versus Institutions

Diagnostic stewardship has been used to refer to clinician decision-making as well as hospital laboratory, electronic medical record, and AMS processes. Front-line clinicians and patients clearly have a role in diagnostic stewardship that should be explored further. However, this chapter will focus on the system of test ordering, test processing, and test reporting as the cycle on which diagnostic stewardship intervenes.

Education

The most effective diagnostic stewardship interventions are those that serve to educate clinicians about future decisions while impacting their immediate choices and actions. However, the goal of diagnostic stewardship interventions is primarily to modify patient care decisions in real time. The most effective educational interventions will train clinicians such that they no longer need nudges or framing to change their behavior in the future.

Methods to affect behavior change through education have not been well defined. Electronic medical record tools that explain the evidence behind nudges and framing educate clinicians while motivating appropriate behavior in real time may be an effective approach to education. Reporting interventions may include links or references as further evidence to explain changes in processes.

Diagnostic Stewardship in Specific Disease States

Urinary Tract Infections

Urinary tract infections (UTIs) are among the most common bacterial infections encountered in healthcare [12–16]. Despite being relatively common, diagnosis remains a clinical challenge, with a heavy dependence on laboratory results [17, 18]. Additionally, the incidence of asymptomatic bacteriuria (ASB), defined by presence of bacteria in the urine in absence of localized symptoms, can be as high as 50–100%

among elderly or catheterized patients [19–21]. Urine cultures are frequently ordered in response to nonspecific findings and absence of a clear indication [22, 23]. As such, ASB is frequently mistaken for UTI and is a major driver of unnecessary antimicrobial prescribing [24–26]. AMS programs use methods that focus on changing prescribing after a diagnosis has been made [9, 27]. Diagnostic stewardship can work synergistically, upstream of, AMS in order to improve diagnosis of UTIs.

Ordering

Often, urine cultures are ordered without a compelling indication, leading to false-positive results. Numerous policies and interventions have focused on reducing unnecessary urine culture ordering. Directed educational initiatives, employed in conjunction with changes to internal guidelines, decrease inappropriate treatment of ASB [28–31]. The "Kicking CA-UTI" campaign included educational initiatives, treatment algorithms, and peer-to-peer feedback resulting in a 43% decrease in ordering urine cultures and a 75% decrease in treatment of ASB [31].

Numerous studies have also leveraged the EMR to decrease unnecessary urine culture ordering [32–34]. Through a built-in electronic nudge recommending against urine culturing in the absence of symptoms, paired with orders for urinalysis, urine culture, and certain antibiotics, researchers saw a small reduction in urine culture and antimicrobial orders [33]. Changes in the design of order-sets that remove urine cultures when not explicitly necessary, or change them to reflex urine cultures, have also been shown to decrease inappropriate testing [35].

Processing

Cancelling urine cultures in low-risk patients can decrease unnecessary testing by over 30% [36]. Implementation of a two-step algorithm wherein urinalysis was performed, but urine cultures were withheld until provider requested additional testing, has also demonstrated the ability to significantly reduce the number of unnecessary cultures performed [37, 38].

Reflex urine culturing is an approach to reduce unnecessary testing wherein urine cultures are only performed based on predefined criteria on urinalysis [39, 40]. A study of five intensive care units where urine cultures were only performed if there were >10 WBC/ high power field (hpf) on UA found a significant decrease in urine culture volume and diagnosis of CA-UTI [41]. In a follow-up study, the investigators also examined the impact of reflex testing on antibiotic use [42]. Again, they found a >30% decrease in urine cultures processed, but overall antimicrobial days of therapy did not significantly change. In a subset of patients, however, the proportion of antimicrobial courses with an order indication specific for UTI decreased by 18%. Reflex testing has demonstrated the ability to decrease the number of urine cultures ordered in several additional publications; [43–47] however, the impact on antibiotic use remains questionable [48].

Although data support the use of reflex to urine culture, the specific UA criteria are poorly defined. An early retrospective review of over 1500 UAs with paired cultures determined that positive leukocyte esterase, nitrite, and presence of >10 WBC/hpf were highly predictive of urine culture positivity [49]. Two recent studies, however, have supported divergent cutoff values. In a prospective study combined criteria of >5 WBC/hpf with nitrite or leukocyte esterase positivity were recommended [50]. In contrast, a urology practice reported >50 WBC/hpf had the highest negative predictive value [51]. Two surveys have attempted to aggregate criteria commonly employed by medical centers [52, 53]. In academic medical centers across the United States, criteria used to reflex to urine cultures varied considerably [52]. In a group of community hospitals, only 55% used reflex urine culture practices [53]. Criteria from UA that were employed varied considerably. Almost all (86%) used more than one criterion; 75% incorporated a WBC cutoff, 75% used leukocyte esterase positivity, and 79% used nitrite status.

Reporting

Altering reporting practices may reduce inappropriate initiation of antibiotics or use of unnecessarily broad-spectrum therapy. Diagnostic stewardship interventions related to reporting can largely be thought of as falling into one of three main categories: providing comments or "nudges" with culture results, restricting culture results based on predefined criteria, or cascade reporting of antibiotic susceptibility data.

Evidence related to the use of "nudges" has been documented for the management of other types of infections discussed in this chapter. There is less data specific to the management of UTIs. In a quasiexperimental study implementing an EMR memorandum for patients receiving systemic antibiotics with a positive urine culture, antibiotic utilization was lowered by 65% [54]. Complete restriction of culture results with comments to contact the clinical microbiology laboratory can been considered a more severe version of framing [6]. Not reporting urine culture results in noncatheterized patients, instead instructing to call the microbiology laboratory to release results if there was strong suspicion of true infection resulted in a significant decrease in antibiotic therapy for ASB (48% to 12%) [55]. A randomized controlled trial with a similar intervention also demonstrated that the proportion of inappropriately treated ABS was lower in the modified reporting arm, 80% versus 52.7% without harms [56].

Selective reporting antimicrobial susceptibilities can have a direct impact on choice of antibiotic prescribed for UTIs and help guide clinicians to appropriate agents [57, 58].

Selective or cascade reporting can reduce antibiotic prescribing for ASB [59–61]. Hall and colleagues recently implemented cascade reporting to suppress broad-spectrum agents such as piperacillin/tazobactam among non–extended-spectrum β-lactamase-producing *E. coli* and *Klebsiella* without change in antibiotic use [62].

Clostridioides difficile Infection

Clostridioides difficile (*C. difficile*) is the most common cause of healthcare-associated diarrhea in the United States. *C. difficile* causes over 450,000 infections annually [63–65]. The clinical definition of *C. difficile*-associated diarrhea requires the presence of diarrhea (>3 watery bowel movements in a 24-h period), recent antibiotic use or contact with the healthcare system, other supportive symptoms (fever, abdominal pain), and a diagnostic test. Polymerase chain reaction (PCR) has emerged as the primary diagnostic tool to identify *C. difficile* infection. Its speed, ease of use, and sensitivity speak to the appeal of this modality along with the ability to combine multiple PCRs into syndromic diagnostic panels, which can simultaneously test for an array of gastrointestinal pathogens. However, poor clinical sensitivity can lead to overdiagnosis, erroneous diagnosis, and overtreatment given *C. difficile* may colonize the gastrointestinal tract without causing symptoms in up to 26% of adult inpatients and 5–7% of long-term care patients [66, 67]. Overdiagnosis after adoption of PCR has contributed to a surge in lab-identified events reported. Adaptation of the adjusted standardized infection rate, in part, accounts for the 18% decrease in hospital-onset *C. difficile* infections between 2018 and 2019 [68]. Inappropriate testing can result in the incorrect diagnosis and unnecessary treatment of *C. difficile* infection, increased cost, falsely elevated healthcare facility-associated rates, and decreased Medicare/Medicaid reimbursement [69].

Ordering

Testing for *C. difficile* may be initiated for a variety of reasons including clinical suspicion for acute *C. difficile* disease, asymptomatic screening, test of cure, surveillance, and unintentional inclusion in multiplex array testing. A highly sensitive PCR to detect chromosomal genes encoding toxin B (*tcdB*) or toxin regulator (*tcdC*) is as likely to detect colonization as true disease when the pretest probability is low. As such, ordering interventions have focused on clinician education, testing algorithms, electronic medical record physician support tools to reduce the ordering of *C. difficile* PCR when the pretest probability or clinical suspicion for disease is low. In a single-center quasiexperimental retrospective cohort study, Madden et al. found that 67% of lab-identified hospital-onset *C. difficile* infections potentially lacked an indication for testing. Using a best practice alert to discourage ordering of duplicate *C. difficile* tests within 28-days, in the absence of clinical diarrhea, other systemic symptoms or increased risk factors for infection, they reduced rates of overall tests performed by 41% [70]. Incorporation of a test-ordering algorithm into the electronic medical record, outlining patient criteria for ordering a PCR only in the absence of recent laxative or enteral tube feeding was shown to profoundly reduce total hospital days, *C. difficile* related costs, and total *C. difficile* treatment costs without an increase in severe disease outcomes [69].

Processing

Laboratory services can also help to maximize the utility of *C. difficile* testing by setting parameters under which processing of the tests cannot occur. For instance, many labs will cancel *C. difficile* orders on formed stool specimens. Liquid stool must pass the "stick test" in order to be processed; a specimen in which a wooden applicator stick will not remain upright. Automated policies include canceling tests ordered within a certain timeframe of a recent test (e.g., repeat tests ordered within 7-days or not received within 24 h of order placement). Such lab-based interventions have been shown to decrease the number of *C. difficile* tests ordered by nearly half and decrease a hospital's standardized infection ratio of *C. difficile* attributed to hospital onset by over 60% [71]. Given the incentives tied to lower rates of hospital associated infections, drug costs associated with inappropriate treatment and laboratory costs of over-ordering, lab-based interventions are simple, low cost and effective at decreasing inappropriate testing. The positive predictive value of a *C. difficile* PCR may be enhanced by adding a toxin-specific enzyme immunoassay, which may be done as a "reflex" order following a positive *C. difficile* PCR, for example.

Reporting

Reporting on *C. difficile* test results has both clinical and infection control implications. How results are reported can affect decisions on *C. difficile* treatment, room placement, isolation, precautions and personal protective equipment as well as scheduling of procedures. Diagnostic stewardship can impact the interpretation of *C. difficile* results reporting through a variety of means: result comments, nudges to consult Infectious Disease or the Antimicrobial Stewardship program, or suppression of reporting (e.g., *C. difficile* results on multiplex molecular panels for gastrointestinal infections). Data on this postanalytic form of diagnostic stewardship is scant but has the potential benefit of being the most clinically appropriate form of stewardship. With the above interventions, strict adherence to guidelines may be "gaming the system" or achieving monetary or hospital goals, which are not patient-centered. Interpretation of results with the aid of subject matter experts adds a counterbalance of the third

principle of diagnostic stewardship: the right test, for the right patient, and the right *action*. Relevant posttest probability results, expert analysis, and counseling of the clinical provider may help to add the appropriate nuance in the final phase of decision-making [72].

Gastrointestinal Infections

Gastrointestinal tract infections are a common medical complaint. Worldwide, there are over 2 billion cases of diarrheal disease every year, and diarrheal diseases are the second leading cause of death among children, resulting in about 800,000 deaths annually [73]. In the United States, over 25,000 cases are caused by known bacterial pathogens including *Campylobacter*, *Salmonella*, *Cyclospora*, *Listeria,* Shiga-toxin-producing *Escherichia coli* (STEC), *Shigella*, *Vibrio*, and *Yersinia* as reported to the CDC in 2019 [74]. However, the predominant identified etiology of diarrheal disease is viral, and of these, norovirus is the most frequently identified cause of disease.

The clinical presentation of disease is similar regardless of etiology. Diarrhea is defined as >3 loose stools within a 24-h period. The diagnostic assessment may include a stool culture for bacterial pathogens, enzyme immunoassays for targeted organisms, and microscopic exam of ova and parasites, when applicable. Given the time requirements of traditional culture and microscopy, many laboratories have turned to culture-independent techniques to evaluate gastroenteritides. Culture independent techniques typically consist of molecular tests like PCR. These tests are often rapid, highly sensitive, and may be combined into multiplex arrays to test for multiple pathogens simultaneously. Unfortunately, multiplex panels may be associated with an overall *increase* in antibiotic prescription, and their speed and ease of use can lead to overuse [75, 76]. To maximize the benefit of these tests, diagnostic stewardship should be employed to establish criteria for acceptable specimens, target common pathogens before rare ones, selectively report only organisms of clinical significance, and directly involve the antimicrobial stewardship team in treatment decisions [77].

Ordering

Inappropriate ordering reduces diagnostic yield and may occur in several settings. Repeat testing, testing within 4 weeks of a previous test is unlikely to change the results or be informative [78]. Additionally, stool samples ordered >72 h after hospital admission may be low yield for non-hospital associated diarrheal disease (such as *Clostridioides difficile* which is discussed elsewhere). Hitchcock et al. looked at results of multiplex array testing performed >72 h after hospital admission and found that only 5% of such encounters were positive and of these, only half of those were clinically relevant [79]. Thus, interventions, which target provider ordering practices, could reduce the volume of multiplex array testing and improve the diagnostic yield. Borrowing from lessons learned from diagnostic stewardship of *C. difficile* testing, clinician education, testing algorithms, electronic medical record physician support tools can all help to decrease clinician ordering in the setting of prolonged hospitalization (which increases the likelihood of nosocomial etiologies but decreases the likelihood of community etiologies of diarrhea), recent/duplicate testing, or laxative use within 48 h preceding the test. There have not been many studies to assess the downstream effects of these diagnostic stewardship interventions, but further research would be easy to pursue in conjunction with similar interventions targeting *C. difficile* testing, as discussed elsewhere in this chapter.

Processing

According to O'Neal et al. in their evaluation of the appropriateness of multiplex PCR gastrointestinal testing, most of the inappropriate testing had a negative panel result and correlated with a lack of documented diarrhea [80]. This means that inappropriate testing may be greatly reduced by enforcing preanalytic decision making through ordering prompts to document the frequency and consistency of stool. This may be further bolstered through guidance from the lab rejecting any samples, which are not Bristol Stool Scale 5 or greater, unless there is additional clinical input provided. As noted above, repeat testing is also unlikely to result in different outcomes or change management; thus, a lab-mediated "hard stop" for repeat tests ordered in <7 days and a "soft stop" (requiring additional clinical rationale) for ordering community acquired pathogens testing >72 h after admission may also assist in decreasing inappropriate ordering practices.

Reporting

Many of the multiplex stool pathogen arrays concomitantly test for *C. difficile* in addition to foodborne diseases and viral pathogens. As discussed in this chapter's review of diagnostic stewardship of *C. difficile*, this organism alone has multiple needs for stewardship. Adding *C. difficile* to a panel increases the risk for misattribution of a community acquired infection as a hospital acquired infection, identification of colonization as pathogen, persistent shedding of bacterial DNA in the absence of ongoing infection, among others. To improve accuracy of reporting and decrease duplicate ordering, clinical laboratories should consider censoring *C. difficile* reporting on the panel. Additionally, patients with a positive *C. difficile* within the preceding 7 days should have their results suppressed or test rejected. Because these multiplex panels may report over 20 pathogens and organisms may exist in pathogenic or commensal states, the interpretation of these tests must be considered carefully. Institutions

may choose to suppress results with the option to release them following additional clinical input [77]. Laboratories may also opt to suppress panel results for pathogens for which other standalone tests are available. A tiered approach to diagnostic test use; ordering separately tests for pathogens of highest clinical concern and cascading to rarer diseases, increase the pretest probability and therefore the positive predictive value of the results.

Bloodstream Infections

Bloodstream infections (BSI) are a leading cause of healthcare-associated morbidity and mortality [81]. There are over 30,000 CLABSI reported annually in the United States [82]. *Staphylococcus aureus* is a leading cause of BSI and there has been increased incidence of ESBL-producing gram-negatives and carbapenem-resistant infections [83]. Reducing time to active antimicrobial therapy is important to improve patient outcomes [84–89]. Numerous studies have reported AMS interventions using molecular rapid diagnostic testing to decrease time to appropriate therapy in BSI (Fig. 32.2). These tests can assist in identification of key organisms and genetic markers of resistance hours to days sooner than traditional testing methods [90–93]. Based on published literature, multiplex PCRs used with active AMS intervention can be cost-effective [94, 95]. The benefits of incorporating molecular testing into AMS activities and routine clinical practice have been established; however, diagnostic stewardship interventions related to blood culturing have not been thoroughly investigated.

Ordering

The decision to order blood cultures in septic patients has not undergone extensive evaluation, especially in adult patient populations [96, 97]. A review of implementing automatic blood cultures upon ICU admission increased rates of BSI and contamination that could lead to unnecessary antimicrobial administration (risk ratio = 4.3) [97]. A quasiexperimental study of implementing blood culture orders that were preferentially drawn from venipuncture as opposed to central lines was able to significantly decrease contamination rates [98]. After staff education and policy implementation, the proportion of blood cultures that were determined to be contaminated decreased from 1.6% to 0.5%. In the pediatric setting, researchers have demonstrated the beneficial impact of decreasing the overall number of blood cultures ordered [99]. With the implementation of a blood culture decision algorithm, there was a 46% drop in the rate of blood cultures ordered without a negative impact on mortality or hospital length of stay. Lastly, there has been considerable discussion regarding the need for follow-up blood cultures in gram-negative BSI [100–103]. As opposed to gram-positive BSI, numerous studies have determined that follow-up blood cultures are largely unnecessary and, when drawn, often lead to prolonged treatment or hospitalizations.

Processing

Following the expansion of available molecular tests for BSI, recent investigations have sought to compare the potential clinical impact of choice of test at the institutional level [104]. Taking into consideration local Infectious Diseases epidemiology and prescribing practices, the Clinical Microbiology laboratory in collaboration with AMS and ID providers can make a more informed decision on which test to bring in-house [105, 106].

Most data regarding diagnostic stewardship relates to the incorporation of molecular testing into routine clinical practice for the reporting and management of BSIs [107–110]. This is often accompanied by active AMS prospective audit and feedback. Without active AMS intervention, these tests have limited impact. In a study of multiplex PCR for gram-positive BSI, investigators evaluated outcomes without AMS intervention, followed by implementation and then subsequent removal of AMS. With the introduction of active AMS interventions, which included prospective audit and feedback, treatment guidelines, educational initiatives, and time to effective and optimal antimicrobials decreased.

Among gram-negative BSI, integration of molecular testing into routine clinical practice, with concurrent AMS inter-

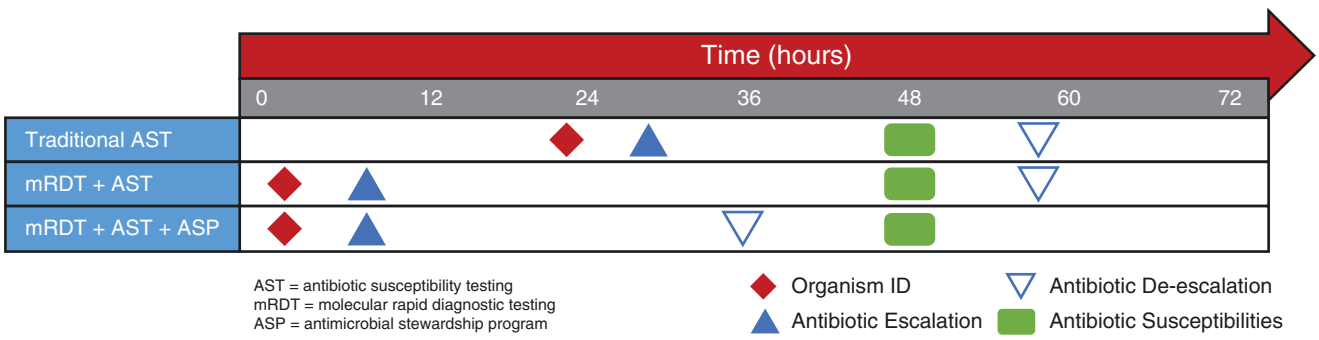

Fig. 32.2 Incorporation of rapid molecular testing, particularly with AMS intervention, significantly decreases time to antibiotic changes in BSI

vention, can also decrease time to appropriate therapy [107, 111–113]. In a study implementing molecular testing without AMS resulted in decreased time to optimal therapy by 47 h, which was driven by antimicrobial escalation [114]. With the introduction of AMS interventions, time to optimal therapy among those requiring antimicrobial de-escalation improved, as did overall proportion of patients placed on appropriate therapy (66.5% vs. 78.9% vs. 83.2%, $p < 0.0001$). Changes in clinical outcomes, such as in-hospital mortality or length of stay, however, tend not to be impacted.

Reporting

Reporting of blood culture results has the potential to be an important diagnostic stewardship intervention. For instance, blood culture contamination rates increase healthcare costs and exposure to unnecessary antimicrobial therapy [115]. Insertion of a comment or "framing" for likely contaminants can decrease the negative clinical impact. Common contaminants include coagulase negative *Staphylococcus* species, which may prompt the initiation of empiric therapy with potentially toxic antimicrobials such as vancomycin. When present in only one bottle and in the absence of a mechanical heart-valve, most patients may be spared the risk of renal toxicity or other adverse drug reactions if clinicians are prompted to consider skin contamination as opposed to pathogenic bloodstream infection.

Selective, or cascade, reporting is a strategy wherein antimicrobial susceptibility results are only reported when certain criteria are met [6]. A study of infections caused by *Escherichia* and *Klebsiella*, where broad-spectrum agents were not reported unless resistance was present to narrower agents, demonstrated significant decrease in use of cefepime with no negative impact on clinical outcomes [116].

Reporting of molecular test results has had a mixed impact. Among providers that do not specialize in ID, misinterpretation of results occurs upward of 50% of the time [117]. Additionally, only 60% of providers reported adjusting antimicrobials based on molecular test results. A randomized trial evaluated patients randomized to standard blood culture processing versus multiplex PCR with templated report comments on optimal therapy, or multiplex PCR with report comments and active AMS review [118]. Compared to standard of care or multiplex PCR with templated comments, AMS resulted in significant decreased time to antimicrobial de-escalation (34 vs 38 vs 21 h) and escalation (24 vs 6 vs. 5 h). Involvement of AMS appears necessary to achieve improved outcomes.

Lower Respiratory Tract Infections

Diagnostic uncertainty remains a challenge for the appropriate management of lower respiratory tract infections (LRTIs). LRTIs can have both viral and bacterial etiologies and can be difficult to differentiate clinically [119, 120]. Timely diagnosis of viral LRTI results in early addition of antiviral treatments, patient isolation, and early discontinuation of unnecessary antimicrobials [121]. Despite viral etiology accounting for half of all LRTIs, patients commonly receive broad-spectrum antimicrobials, putting them at an increased risk of developing a multidrug-resistant organisms or prolonged hospital length of stay [122].

Rapid detection of viral pathogens with tests specific for influenza or COVID-19, as well as multiplex PCR respiratory viral panels are thought to be effective stewardship tools with sensitivity greater than 90% and turnaround times of less than 1 h. Recent advances in molecular diagnostics have allowed for the development of various multiplex respiratory viral panels that are able to detect a wide range of viral and bacterial pathogens [123]. Like many other types of infections, opportunities for diagnostic stewardship are present, but to date have been poorly implemented or adopted [124]. Similar to BSI, the majority of studies evaluating the implementation of these tools do so with concurrent AMS interventions, though success of these interventions has been mixed.

Ordering

There are several key considerations to ordering the appropriate diagnostic test for LRTI, including the range of tools available, their detection abilities, and their turnaround times [125, 126]. While there are specific guidelines to assist providers in ordering of tests for influenza, appropriate use of multiplex respiratory viral panels, with or without procalcitonin (PCT), is less clear [127]. The availability of these testing modalities, each with specific strengths and limitations, can pose challenges to ordering providers when they are not familiar with these tools. Through implementation of stepwise testing (respiratory viral panels only after negative influenza test) and modified clinical decision support tools, unnecessary ordering of multiplex respiratory viral panels can be decreased [128]. Educational initiatives concurrent with implementation of multiplex respiratory viral panels have also decreased antimicrobial total duration, although initial antimicrobial use did not change [129].

Processing

There has been an increase in the number of molecular tests that detect viral and bacterial pathogens [126, 127]. Rapid molecular testing for influenza is associated with decreased antimicrobial prescribing, antiviral prescribing, and decreased ED or inpatient admission times [130]. Studies of multiplex respiratory viral panels found providers regularly responded to results of influenza virus through antimicrobial discontinuation, but rarely made interventions for

other viruses that were on panels [131, 132]. Antimicrobial use, however, remains high, even among those patients with laboratory-confirmed influenza virus respiratory infections [133].

The use of multiplex respiratory viral panels in combination with the inflammatory marker procalcitonin (PCT) may be more impactful in changing antimicrobial-prescribing practices. A Cochrane review of 32 randomized clinical trials employing PCT cited a 2.4-day reduction in antimicrobial exposure and lower risk of antimicrobial-related adverse events (16.3% vs 22.1%) [134]. Investigators evaluated testing algorithms that incorporate results of respiratory viral panels with or without PCT. In one randomized study of viral PCR plus PCT, overall algorithm adherence was 64% [135]. Notably, algorithm adherence was higher when PCT values were elevated and supported antimicrobial continuation and lower when PCT values supported antimicrobial discontinuation.

As seen with BSI, implementation of multiplex respiratory viral panels (with or without PCT) is often accompanied by concurrent AMS interventions. This makes the evaluation of the clinical impact of these tools without AMS difficult [136]. A study evaluated a pharmacist-led ICU bundle of multiplex respiratory viral panels, PCT, and pharmacist collaborative practice agreements that allowed pharmacists to order diagnostic tests alter antimicrobial therapy [137]. When compared to the standard of care, the intervention group had more frequent pathogen identification and antimicrobial de-escalation twice as much antimicrobial de-escalation. The only variable determined to be independently associated with these outcomes was pharmacist involvement through the collaborative practice agreement.

There are many examples in the literature highlighting the ability of multiplex respiratory viral panels with PCT algorithms and active AMS interventions to improve patient outcomes [138–141]. There are also studies, however, that failed to demonstrate a benefit with these tools, calling into question whether publication bias may contribute to our current understanding of their efficacy [120, 130, 142]. Hesitation often surrounds de-escalation based on respiratory viral panels due to the concern for a superimposed bacterial infection, suggesting further interventions are needed to determine how common secondary bacterial infections are and how best to diagnose them.

Reporting

Once these tests have been completed and results posted into patient charts, there remains opportunity to impact provider behavior. Use of nudges or framing in the results of the culture report has been shown to decrease treatment of normal respiratory flora. Additionally, in a quasiexperimental study, investigators added a comment specifically calling attention to the absence MRSA or *Pseudomonas aeruginosa* in culture. Through use of this nudge, they were able to significantly decrease the use of anti-MRSA and anti-pseudomonal antimicrobials [6, 143, 144]. Additionally, in a multisite quasiexperimental study, investigators were able to demonstrate the positive impact of an automated EMR memo that alerted providers of low PCT and negative respiratory viral panels [145]. Antimicrobial days of therapy were reduced by a mean of 2.2 days and discharge antimicrobial prescriptions significantly decreased by over 25%.

Controversies

Controversy	Pros	Cons
Does diagnostic stewardship decrease antimicrobial use?	Intuitively, reducing unnecessary tests decreases antimicrobials.	Limited evidence exists to show decrease in antimicrobials.
How proscriptive should diagnostic stewardship be? (e.g., suppress urine culture results vs. provide interpretation)	More proscriptive interventions should have a stronger impact.	More proscriptive interventions could limit clinician input and lead to missed diagnoses.
Does diagnostic stewardship result in patient harms through missed/delayed diagnoses?	There is no evidence of harms from diagnostic stewardship and abundant overdiagnosis.	Limiting testing likely limits diagnosis. Some of these diagnoses may be real.

The purpose of diagnostic stewardship is to achieve optimal test use while maintaining patient safety and improving downstream patient outcomes [72]. Controversy surrounds the methods of diagnostic stewardship when they impinge on a clinician's freedom. Hard-stops and analytic interventions in the lab may be the most contentious where a clinical workflow is directly altered, or when interventions may not be readily apparent to the provider. However, recent data has shown that clinicians may benefit from structured interventions to counterbalance an inherit bias toward risk overestimation and therefore inappropriate interpretation of test results [146]. Such systematic interventions should incorporate input from impacted clinical services and be subject to review and feedback from the end users to achieve optimal results.

The aims of diagnostic stewardship may also be questioned when they align too closely with system metrics as opposed to patient-centered objectives. Absolute reduction in test use will decrease rates of hospital-associated infections (there can be no hospital-attributable MRSA infection without MRSA culture or PCR), but test underuse, forgoing testing when clinically indicated, and risks missing diagnoses could lead to patient-harms and worse outcomes. Prospective study to capture patient-harms associated with

diagnostic stewardship is necessary to calibrate the quality and caliber of stewardship interventions.

Conclusion

Diagnostic stewardship strives to improve patient outcomes by promoting the right test, for the right patient, prompting the right action. These aims, with the patient at the center, motivate appropriate decision-making, test interpretation, and decrease downstream use of inappropriate therapies and procedures. With these goals, patient care advances and improved system metrics are the fortuitous side effects.

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Innovations in Ambulatory Stewardship

33

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Introduction

The goal of antimicrobial stewardship in any setting is to implement coordinated interventions to increase appropriate use of antimicrobial agents and systematically measure the impact of these interventions to optimize clinical outcomes while minimizing adverse consequences, such as antimicrobial resistance, *Clostridioides difficile* infections, and drug toxicities [1]. Unfortunately, at least 30% of outpatient antibiotic prescriptions in the United States are unnecessary, amounting to approximately 47 million prescriptions per year and up to 60% of total antibiotic expenditures between 2010 and 2015 [2, 3]. Antibiotic prescriptions are provided to patients in up to 46% of urgent care visits, even when not required; 50% of encounters for acute respiratory infections at a large urgent care network in Utah resulted in antibiotic prescriptions [4]. Collectively, infections of the respiratory tract, skin and skin structure, and urinary tract are the most frequent diagnoses for which antibiotics are prescribed and are high priority stewardship targets [2]. Given the scale of outpatient antibiotic consumption, ambulatory stewardship program implementation and maintenance is required as a condition of participation by the Centers for Medicare and Medicaid Services and is a Joint Commission accreditation standard for hospitals and their associated outpatient facilities [5, 6].

While stewardship is now required across the healthcare spectrum [5], implementation by busy frontline ambulatory-care providers in high-volume settings remains a challenge. A Pew-American Medical Association survey study of 1550 primary care physicians revealed that the majority supported the need for outpatient stewardship but would require significant assistance with implementation, tracking, and reporting of antibiotic use. Unfortunately, respondents also ranked antimicrobial resistance lowest among public health priorities, below smoking, obesity, diabetes, and opioid misuse [7].

Likewise, antibiotics are heavily prescribed in primary care settings across low- and middle-income countries (LMICs) and have increased over the past 2 decades [8]. Much of this use occurs without antibiotic prescriptions from healthcare providers [9]. Antibiotic resistance and stewardship are major priorities of the World Health Organization, which has developed implementation toolkits for LMICs like the CDC Core Elements of Outpatient Antibiotic Stewardship [2, 10].

The Core Elements include (1) commitment, (2) action for policy and practice, (3) tracking and reporting, and (4) education and expertise [2]. Similarly, the Joint Commission established Elements of Performance, which include (1) identifying an antimicrobial stewardship leader, (2) establishing an annual stewardship goal, (3) implementing evidence-based practice guidelines related to the stewardship goal, (4) educating clinical staff on the use of resources and guidelines to meet the goal, and (5) analyzing, collecting, and reporting data to stakeholders [6]. While these standards serve as the framework for this review, authors recognize that implementation, tracking, and reporting of antibiotic use and clinical outcome data represent the most resource-intense aspects of ambulatory stewardship. Therefore, we suggest that programs identify high impact stewardship targets and settings (e.g., antibiotic prescribing for respiratory viral infections in pediatrics and urgent care centers) can help programs prioritize effort and resource allocation.

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_33

Core Elements

1. *Commitment*: The CDC Core Elements define "commitment" as dedication to and accountability for optimizing antibiotic prescribing and patient safety [2]. A dedicated leadership team should direct stewardship activities, define stewardship-related responsibilities, and ensure that communication is provided to all team members to help set expectations regarding antimicrobial prescribing practices [11, 12]. An outpatient team that is collectively invested in antimicrobial stewardship helps ensure that expectations for patient outcomes remain consistent. Entrances, waiting rooms, and exam rooms displaying statements in support of antimicrobial stewardship are important visual reminders for patients and providers and help to nudge guideline-concordant prescribing [13]. Assigning team accountability for optimal antimicrobial prescribing reinforces that patient safety is everyone's responsibility.
2. *Action for policy and practice*: The Core Elements recommend that policies and practices are implemented to improve antimicrobial prescribing and evaluated regularly and modified as needed [2]. These actions should target high priority conditions vulnerable to inappropriate prescribing, such as viral upper respiratory infections. Stewardship interventions can be implemented electronically, or via trained personnel, such as antimicrobial stewardship pharmacists. Examples of successful stewardship actions include delayed antibiotic prescriptions with watchful waiting, justification notes in the electronic medical record for guideline nonconcordant prescribing, and use of call centers, nurse hotlines, or pharmacist consultations as triage systems to prevent inappropriate prescribing [14–16].
   (a) *Electronic tools:*
   Computerized decision support tools and smartphone applications can be used to disseminate the latest professional society guidelines and help providers align clinical decisions with best practices. For example, the guidelines for the treatment of sexually transmitted infections (STIs) were updated in 2021 with changes to preferred regimens and doses for commonly encountered STIs such as gonorrhea and chlamydia [17]. Using a regularly updated computerized decision support tool with the preferred regimens and doses for STIs can help prevent treatment failures and/or treatment emergent resistance. Electronic order sets designed to guide ambulatory provider prescribing behaviors can successfully augment stewardship. An order set requiring providers to select an indication for urine studies resulted in decreased urine testing, decreased antibiotic days of therapy, and significant overall cost savings [18].
   (b) *Pharmacist-driven stewardship actions:*
   Limited diagnostic information is a commonly identified barrier to effective antimicrobial stewardship. Roy and colleagues showed that 41% of patients had pending laboratory results at the time of discharge, 9.4% of which were actionable. Since physicians were often unaware of actionable results, these were not reviewed to reassess therapy [19]. Culture susceptibilities resulting after discharge may impact the choice of prescribed agent and, ultimately, patient outcomes. Studies indicate that pharmacists' management of postdischarge culture results has favorable outcomes. If patients are noted to be on inappropriate or suboptimal therapy, emergency department staff may contact patients, adjust therapy, and provide counseling. However, physicians have multiple clinical responsibilities limiting their ability to dedicate appropriate time to culture follow-up. As such, Jones and colleagues assessed pharmacy-driven management of patients discharged on antimicrobial therapy with pending culture results and found that therapy modifications increased 40% compared to a preimplementation cohort [20]. Davis and colleagues found that pharmacist-driven models of culture follow-up outperformed nursing-driven models in terms of number of interventions for inappropriate therapy [21]. Additionally, compared to physician-led culture review activities, those led by pharmacists lead to faster time to modification of inadequate antibiotic therapy [22, 23] Recently, ASP-trained ID pharmacists have participated in a collaborative culture review and call-back approach with ED nurse practitioners, independent of physician review improving the efficiency and success of postdischarge stewardship interventions [24].
3. *Tracking and Reporting*: Tracking and reporting involves monitoring of prescribing practices and providing regular feedback to clinicians or prompting clinicians to assess their own prescribing practices as part of overall process improvement initiatives. There are unique considerations for monitoring antibiotics in the outpatient setting. Unlike the inpatient setting, where antibiotic administration is measured in days of therapy, outpatient antibiotic use is often abstracted from prescription data for select diagnostic codes such as acute bronchitis, urinary tract infection, or cellulitis, and can be measured at the provider, clinic, or system level. The proportion of visits in which antibiotics are prescribed can be aggregated for individual physicians, clinics, or health systems, and be stratified by visit type based on diagnosis. However, limiting monitoring to certain diagnoses can create incentives for clinicians to manipulate diagnostic coding to justify antibiotic prescribing (e.g., selecting "bacterial sinusitis" instead of

"acute bronchitis" [25]. This practice, referred to as "diagnosis shifting," can be mitigated by monitoring the percentage of all visits for which antibiotics are prescribed. The authors' stewardship program worked with institutional ambulatory practice leadership to analyze EHR data on the percentage of all visits and those for upper-respiratory infections resulting in antibiotic prescriptions. These reports were created for the entire ambulatory network, for individual sites (including teaching and nonteaching practices), and were shared with leadership to track progress and identify areas for improvement.

Assessing appropriateness of antibiotic prescribing may require manual chart audit and feedback to individual providers [26, 27]. These data can be included in provider-specific antibiotic-use reports and combined with peer-to-peer comparisons. Studies demonstrate that overall antibiotic use can decrease by disseminating monthly provider reports with peer-comparison data [28].

Tracking and Reporting Antibiotic Prescription Data During COVID-19

Recent studies demonstrate the importance of tracking ambulatory antibiotic use during the novel coronavirus disease 2019 (COVID-19) pandemic. Using data from a national prescription database (IQVIA), Buehrle and colleagues found significant reductions in prescriptions of the 10 most prescribed antibiotics early in the pandemic (April – July 2020) [29]. Similarly, Vaduganathan and colleagues found that while prescriptions of hydroxychloroquine and azithromycin increased, use of most other commonly prescribed antibiotics declined in the first few months of the pandemic [30]. Finally, Dilworth and colleagues found a reduction in ambulatory visits, urgent care visits, and emergency department visits for acute, uncomplicated viral bronchitis during the COVID-19 pandemic [31]. Several studies have demonstrated a low incidence of bacterial coinfection in patients with COVID-19, which may explain downtrends in ambulatory prescribing during the pandemic [32, 33].

Although not yet published at the time of this review, the CDC is conducting a large study to characterize national trends in inpatient and ambulatory antibiotic use and resistance throughout the COVID-19 pandemic.

At a local level, our stewardship program conducted an analysis of prescribing patterns within our ambulatory practices in 2019, 2020, and 2021 to understand the impact of the pandemic. We evaluated the percentage of visits with an antibiotic prescribed for all-visits and COVID-19-specific diagnoses (Table 33.1). Although we observed a slight increase in all-visit antibiotic prescribing during the first COVID-19 surge in New York City (March through June 2020), antibiotic prescribing decreased during the second COVID-19 surge (November 2020–June 2021), likely due to an improved understanding of COVID-19 pathophysiology and management.

Table 33.1 Antibiotics prescribed at ambulatory visits, all-visit, and COVID-19

Time period	Total visits *N*	Total visits with antibiotics prescribed *N* (%)	COVID-19 diagnosis visits *N*	COVID-19 diagnosis visits with antibiotics prescribed *N* (%)
Pre-COVID (2019 Mar–Jun)	152,713	12,018 (8%)	–	–
COVID Surge 1 (2020 Mar–June)	103,776	10,145 (10%)	5260	658 (13%)
COVID Surge 2 (2020 Nov–2021 Mar)	141,303	9746 (7%)	5769	525 (9%)

4. *Education and Expertise*

Providing education and access to expertise helps to reinforce antimicrobial stewardship best practices. Twice a week academic detailing to providers caring for solid organ transplant patients helped to improve appropriate antimicrobial use without increases in adverse events [34] Using an electronic system to implement weekly audit and feedback resulted in improvements in appropriate antimicrobial use, and documentation of indication and a duration [35]. Westerhof and colleagues demonstrated the success of a pharmacist-led audit-and-feedback intervention at a family medicine resident clinic involving (1) positive reinforcement of appropriate prescribing, (2) constructive recommendations for optimized management, or (3) general academic detailing [36]. Their approach resulted in improvement in guideline-concordant prescribing based on indication, dose, and duration of antimicrobial therapy.

As stated previously, skin and skin structure infections are considered a high-priority stewardship target [2]. Skin and skin structure infections result in over two million visits to the emergency room annually [37]. Long-acting injectable glycopeptides are available for the treatment of acute bacterial skin and skin structure infections. Provider education can result in increased uptake of long-acting injectable glycopeptide regimens, which ultimately leads to deferred hospital admission, early discharge, utilization of infusion centers or home health programs, and avoidance of potential line-associated complications from prolonged intravenous therapies. Examples of patients who may benefit from long-

acting glycopeptide therapy include those with very high body mass index, known history of poor adherence to oral therapy, or persons who inject drugs.

Urinary and respiratory tract infections are additional high-priority stewardship targets, given the propensity of clinicians to overdiagnose and overtreat these syndromes [2]. Antibiograms allow clinicians to select the best and most narrow-spectrum initial empiric therapy for infections using local susceptibility data. When bundled with other stewardship interventions such as education on signs and symptoms of infection and appropriate use of diagnostic testing, antibiograms can optimize patient care. The New York City Department of Health has collaborated with stewardship programs and microbiology laboratories throughout the city to publish borough-specific and citywide antibiograms for urinary tract infections, and invasive *Streptococcus pneumoniae*. Both are readily available online and via smartphone application, which can be downloaded for free [38]. Successful collaborations between hospital-based stewardship programs and local health departments are essential to combat rising multidrug resistance in the community [39].

Novel Uses of Ambulatory Stewardship During the COVID-19 Pandemic

During the COVID-19 pandemic, specific therapies such as remdesivir, corticosteroids, and immunomodulators have become a mainstay of national guidelines but target hospitalized patients with advanced disease [40]. Several treatment options for ambulatory COVID-19 patients with mild-to-moderate illness, now, exist.

Since November 2020, monoclonal antibody regimens administered as monotherapy or combination therapy (bamlanivimab, casirivimab/imdevimab, bamlanivimab/etesevimab, and most recently, sotrovimab) have received Food and Drug Administration (FDA) Emergency Use Authorization (EUA) to treat ambulatory adult and pediatric patients (12 years of age or older weighing at least 40 kilograms) with early, mild-to-moderate COVID-19, who have risk factors for progression to severe disease. These agents, administered by intravenous or subcutaneous route, act by attaching to the ACE-2 receptor–binding domain of the spike protein of SARS-CoV-2, blocking viral entry into host cells [41–44]. Combination therapies (bamlanivimab/etesevimab, and casirivimab/imdevimab) and sotrovimab demonstrate retained efficacy against SARS-CoV-2 variants [43–45]. When administered during the active viral replication phase of SARS-CoV-2, monoclonal antibody therapies have reduced the risk of hospitalization, death, and decreased symptom duration as well as viral loads [45–49]. Clinical trial findings have been supported by numerous real-world studies demonstrating the success of monoclonal antibodies [50–54].

The availability of these agents compelled stewardship programs to rapidly establish the necessary infrastructure to provide treatment to eligible patients [55]. Shortly after EUAs were issued, ASPs across the United States developed system-wide outpatient treatment pathways for patients meeting monoclonal antibody EUA criteria, enabling the treatment of thousands of patients, preventing admissions, and offloading critically stretched acute care hospitals [56, 57].

ASP oversight of monoclonal antibody programs aligns with the CDC Core Elements and The Joint Commission accreditation standards [2, 6]. The intended stakeholders and champions of the outpatient CDC Core Elements include primary care clinics, emergency departments, urgent care clinics, outpatient specialty/subspeciality clinics, and health systems. Throughout the pandemic, COVID-19 patients have sought care at each of these locations. Ambulatory ASPs can serve as a unifying link for each point-of-care to ensure the appropriate delivery of COVID-19 treatments to high-risk patients.

Molnupiravir (Merck) is the first oral antiviral agent seeking FDA emergency authorization for the treatment of mild-to-moderate COVID-19. Clinical trial data demonstrated that compared to placebo, molnupiravir reduced the risk of hospitalization or death by approximately 50% (7.3% vs. 14.1%, $p = 0.0012$) [58]. Although molnupiravir and monoclonal antibodies have similar indications, molnupiravir offers significant advantages in terms of route of administration and convenience. Ambulatory ASPs can spearhead the development of local treatment criteria and identify a role for each agent once sufficient clinical data are available.

Another crucial pandemic stewardship intervention is audit-and-feedback to providers prescribing unproven treatments such as ivermectin, which can contribute to significant patient harm [59]. ASPs both in developed nations and LMICs can promote evidence-based COVID-19 outpatient management via guideline dissemination and electronic decision support tools [60]. There are numerous benefits to ASP-led outpatient COVID-19 treatment programs. ASPs are often overseen by physician leaders with specific training in infectious diseases and coled by infectious diseases trained pharmacists. The physician lead can ensure support from institutional leadership to secure necessary human, financial, and informational technology resources. Pharmacists can communicate medical information to patients; maintain stock of the product; coordinate compounding, storage, and delivery of medications; and develop guidance for shortage mitigation. The ASP "command center" established by our hospital for outpatient COVID-19 management is shown in Fig. 33.1.

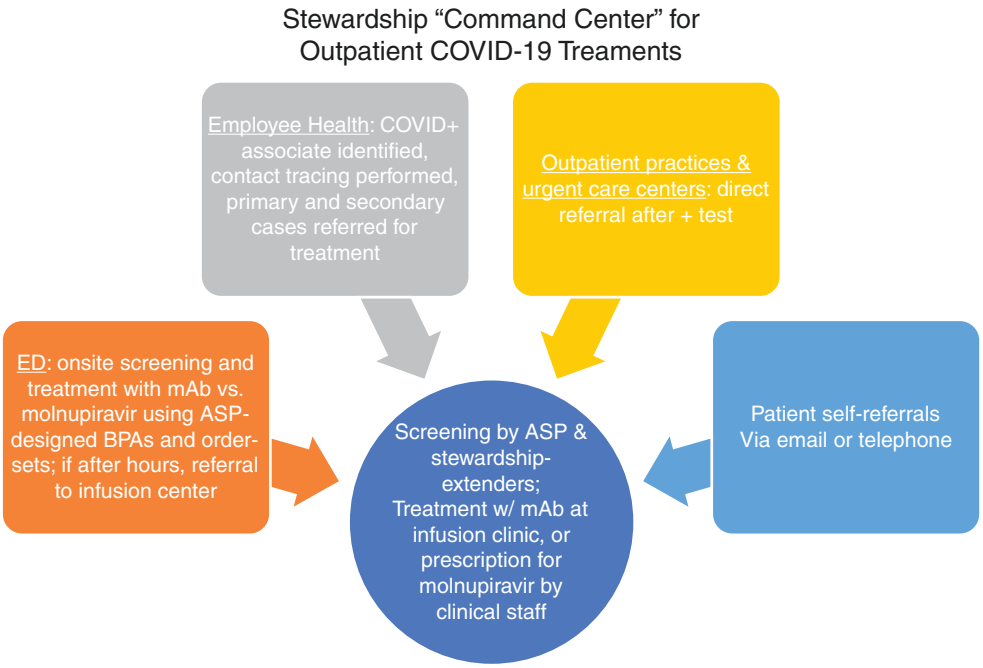

Fig. 33.1 Ambulatory ASP COVID-19 Command Center. Abbreviations: ASP antimicrobial stewardship program, mAB monoclonal antibody, BPA best practice alert

Ambulatory Stewardship in Low- and Middle-Income Countries

Antibiotics are highly prescribed in primary care settings across low- and middle-income countries (LMICs) [8]. Data from the Global Antimicrobial Resistance and Use Surveillance System (GLASS) emphasize the urgency of addressing antimicrobial resistance in LMICs. Of the 424 and 576 reported *Escherichia coli* blood specimens from 2019 to 2020, ceftriaxone resistance was demonstrated in approximately 75% and 70% of isolates from India and Indonesia, respectively. Rates of ceftriaxone-resistant *Klebsiella pneumoniae* reach as high as 96% of 290 blood specimens from Egypt [61].

Efforts to mitigate drug resistance through ambulatory antimicrobial stewardship in LMICs confront unique challenges. Sanitation and limited access to clean water can increase infection rates overall and drive antimicrobial prescribing. Antimicrobial overuse is compounded by limited governmental regulation on the sale and dispensation of antimicrobials by only licensed healthcare professionals. Auta and colleagues found that antibiotics such as fluoroquinolones and penicillins are frequently dispensed without a prescription in LMICs, especially for urinary tract and upper respiratory tract infections [9]. Institutions also face a lack of microbiology laboratory resources, insufficient staffing or expertise, provider unawareness of antimicrobial stewardship principles, and poor access to quality-assured antimicrobials [62, 63].

In 2015, the World Health Organization (WHO) recognized antimicrobial resistance as a worldwide threat and developed a global action plan in response. Objectives of the global action plan encompass increasing the awareness, surveillance, and knowledge surrounding antimicrobial resistance, as well as advocating for greater investment of resources into infection prevention measures, optimization of current antimicrobials, and new diagnostics, vaccines, and therapies. To supplement these objectives, the WHO released a practical tool kit in 2019 for LMICs to provide both national and healthcare facility-specific core elements. Among the national core elements are recommendations addressing challenges unique to LMICs, such as government regulation of prescription-only antibiotic sales or dispensations and quality assurance of antibiotic products [10].

Antibiotic overuse in LMICs was potentially exacerbated during COVID-19. Sulis and colleagues reviewed antibiotic sales data from India and noted an initial decline during early lockdowns, followed by a steady rebound, which ultimately exceeded previous expenditures for certain agents. Authors estimated that COVID-19 contributed to approximately 216 million excess doses of total antibiotics (95% CI: 68.0 to 364.8 million; $p = 0.008$) and 38.0 million excess doses of azithromycin (95% CI: 26.4 to 49.2 million; $p < 0.001$) between June and September 2020 [64]. Of note, this study did not account for the 2021 Delta variant surge in India during which antibiotic and antiparasitic use was widespread.

Conclusion

Implementation of ambulatory stewardship can seem dauntingly large in scope and heterogenous compared with acute care or long-term care stewardship. There are many practice settings and provider stakeholders to integrate into ambulatory stewardship programs. However, focusing on certain high-yield locations or syndromes (e.g., acute respiratory tract infections, skin and soft tissue, and urinary tract infections) with well-proven, evidence-based interventions can be impactful. Interventions demonstrating a commitment to improving patient outcomes and minimizing patient harm have proven successful across a variety of settings. Use of electronic decision support tools and smart phone applications can assist with dissemination of stewardship best practices on a large scale. Tracking and reporting of ambulatory prescribing trends is resource-intense and requires leadership commitment as well as data analytic support. However, provider feedback and peer comparison reports can be particularly motivating for reducing unnecessary antibiotic prescriptions. The CDC Core Elements of Outpatient Stewardship can provide a framework for programs invested in initial implementation or expansion of stewardship activities. However, these were written prior to the COVID-19 pandemic and do not address numerous recent challenges encountered by ambulatory stewardship programs during this time. At present, there is little published guidance for stewardship programs exploring expansion into ambulatory management of COVID-19 through monoclonal antibodies or oral antiviral agents. As such, we hope this review provides guidance on pandemic stewardship for the ambulatory setting, including incorporating new treatments into the stewardship paradigm, and preventing use of unproven and potentially harmful treatments.

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34 Clinical Controversies in Outpatient Parenteral Antimicrobial Therapy (OPAT)

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Outpatient parenteral antimicrobial therapy (OPAT) is an increasingly common therapy that allows otherwise stable patients requiring long-term parenteral therapy to receive these treatments outside of acute-care hospitals, in the home with or without support from home care services, in outpatient infusion centers, in hemodialysis facilities, and in skilled nursing facilities (SNFs) [1, 2]. Benefits of OPAT are myriad, including decreased costs and increased satisfaction [3–7]. However, patients on OPAT do require close management including early follow-up, close laboratory monitoring, and management of catheter complications [1, 8–13]. There are variations across the United States in OPAT delivery practices, and we present here examples of relevant clinical controversies in OPAT provision [2, 8, 14].

Where Can OPAT Be Safely Provided and Initiated?

OPAT can be administered safely and effectively in a variety of settings. SNFs, home with home infusion and nursing, home with self-administered infusion, infusion center administration, and hemodialysis center administration are all viable options for patients discharging from an acute care facility on parenteral antimicrobials [15]. Location determination is multifactorial and can be based on patient and/or caregiver ability, additional patient care needs (e.g., wound care), insurance coverage, and patient preference.

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Currently, in the United States, a majority of OPAT patients receive their care in the home with assistance of home health or home infusion agencies [9, 14, 16]. This is a favorable option for many patients, because it allows them to be in the comfort of their own home and avoid potential risks of SNFs, such as increased infection risk. However, for patients to safely administer home OPAT therapy, several characteristics are required. The patient or caregiver must be mentally and physically able to learn and provide sterile practices while properly administering antimicrobials and caring for the parenteral catheter. The patient must also have a safe and stable home environment. Finally, the patient must have adequate storage for the prescribed antimicrobial, which often necessitates refrigeration [8].

Typically, home-based OPAT is initiated with an instructional visit either prior to the patient's hospital discharge or when arriving home post discharge. A home health nurse demonstrates proper antimicrobial administration and catheter maintenance directly with the patient and caregiver. Previously published literatures have demonstrated similar clinical outcomes as well as adverse event rates when comparing home-based OPAT to OPAT in other care locations [6, 7, 10–14, 16, 17]. Some home infusion companies provide both medication and nursing care, whereas others will provide medication only and contract with nursing companies for home visits. Most OPAT patients receive a minimum weekly nursing visit in the home. Although less common, in an innovative home-based OPAT model, no home nursing is provided, but the patient visits an infectious diseases (ID) clinic weekly for catheter care, laboratory monitoring, clinical assessment, and supply needs [10]. In addition to providing weekly line care and replenishing supplies, most OPAT patients require weekly labs to safely monitor for infection resolution, adverse events, and therapeutic drug monitoring throughout the course of antimicro-

G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_34

bials. Labs may be done by home nursing or through a clinic or laboratory [2, 8, 18].

OPAT delivery at SNFs is the second most common OPAT model within the United States. SNFs provide care for those unable to administer antimicrobials in the home, and also may provide additional services such as physical therapy and wound care. In addition, some insurers will cover OPAT in SNFs and not in the home regardless of patient ability or preference [19, 20]. However, SNF-based OPAT requires a patient to spend the duration of the OPAT course away from the comfort of their home at an increased cost to the healthcare system. In addition, SNFs often have more restrictive formularies and may not be able to acquire certain antimicrobials. The competencies at SNFs may vary; some facilities may be better able to provide OPAT than others [21]. SNFs may also place patients at risk for development of infection with nosocomial pathogens or disease outbreaks [8, 22]. However, SNFs provide an effective option for patients unable to utilize home care and prevent hospital admission for the duration of OPAT.

Infusion center administration can provide a safe and effective alternative to home administration for patients wishing to remain at home throughout the course of therapy [15]. Advantages of this model are the convenience of remaining home and avoiding SNF admission, as well as not relying on patient ability to self-administer antimicrobials. However, the infusion center OPAT model requires the patient to have easy and frequent transportation to the infusion center [19]. In addition, as many antimicrobials require multiple daily doses, patients requiring a frequently dosed agent would have to spend a large portion of their day at the infusion center. Frequently dosed antimicrobials may be inconvenient for the patient, take up space in the clinic, and even require after-hours dosing. Finally, many infusion centers are closed on weekends and holidays, requiring additional strategies to ensure access to antimicrobials when centers are closed. This model of OPAT would be most beneficial for patients receiving once-daily antimicrobials in a healthcare system with access to an infusion center open 7 days a week [2, 8].

The final model for OPAT is antimicrobial administration via hemodialysis center. This model allows patients already receiving intermittent hemodialysis to administer OPAT therapy with hemodialysis sessions, avoiding additional nursing costs and preventing infection risk by avoiding additional central line placement. Downsides of this model are the inability of hemodialysis facilities to provide all needed antimicrobials due to cost, and the inability of many antimicrobials to be dosed with hemodialysis [4]. In addition, while hemodialysis centers are able to draw laboratory tests for monitoring therapy, some hemodialysis centers are not able to run certain tests due to capitated payments (e.g., erythrocyte sedimentation rate, C-reactive protein, therapeutic drug monitoring, etc.).

OPAT initiation most often occurs in an acute care setting; however, outpatient initiation in clinically stable patients is often ideal, allowing patients to avoid admissions simply for the start of an antimicrobial course [8, 15, 23, 24]. Healthcare systems may offer several options for outpatient line placement, such as in radiology facilities, clinics, infusion centers, or even the home via outpatient teams who are able to provide sterile venous catheter placement [24]. While these options may not be available to all patients, healthcare systems across the country will likely increase resources such as those targeted at preventing unnecessary hospital admissions. There is also a safety concern for patients administering the first dose of an antimicrobial in a home setting. Several studies have demonstrated a potential risk of anaphylaxis during first dose administration, although most allergic reactions occur later in the course of therapy [6, 23, 25, 26]. Based on more recent literature and evidence in practice, the Infectious Diseases Society of America (IDSA) revised this recommendation with the release of the 2018 OPAT guidelines and now supports the recommendation of first time dosing in the patient home provided this is done in the presence of a competent healthcare worker [8].

In summary, there are multiple models, which can provide safe and effective OPAT administration for patients, including skilled nursing facilities, home with home infusion and nursing, home with self-administered infusion, infusion center administration, and hemodialysis center administration. Despite previous concerns of administering first lifetime dosing of medications in the home and outpatient initiation of OPAT, literature has demonstrated safety in select clinically stable patients.

OPAT Versus Highly Bioavailable Equivalents

Accessibility to OPAT has improved patient quality of life as well as decreased hospital stays and costs. While OPAT is an effective option for many patients, there are also benefits to avoiding OPAT and prolonged parenteral therapy in cases where an oral antimicrobial would provide effective treatment. Studies evaluating the benefits of ID consultation and antibiotic stewardship (AS) assessment prior to discharge have demonstrated improved clinical outcomes, decreased adverse drug reactions, and OPAT avoidance with a transition to oral therapy in select patients [2, 27–33]. One study found 16% of OPAT consults could be transitioned to alternative oral therapy [31].Oral therapy can also decrease healthcare costs and prevent catheter-associated complications when utilized appropriately [29].

When determining whether OPAT or oral antimicrobial therapy is the right option for a patient, several factors must be considered. These include the indication for treatment and the potential oral antimicrobials that can provide reliable bioavailability, site penetration, spectrum of activity, and drug stability against present resistance mechanisms [2, 28–33].

Properties of oral antimicrobials affecting form of administration include bioavailability, molecule size, hydrophilicity/lipophilicity, and penetration of infection site [2, 8, 34–36]. Fluoroquinolones, tetracyclines, oxazolidanones, trimethoprim-sulfamethoxazole, and rifampin all possess high bioavailability, low molecular size, and high lipophilicity. This lends these drugs to be favorable oral options for select clinical scenarios, even allowing for distribution and penetration to difficult sites like cerebrospinal fluid and bone [2, 34]. Oral beta-lactams generally have low bioavailability, decreasing their utility when compared to OPAT for some indications [2, 34].

Infections traditionally treated solely with parenteral therapy now have literature supporting oral therapy as step-down from parenteral treatment after patient stabilization. Multiple studies have described completing treatment courses for uncomplicated gram-negative bacteremia with an oral antimicrobial [37–39]. Bone and joint infections also have supporting evidence for either partially oral or entirely oral treatment options [34, 35, 40]. Most recently, a study demonstrated noninferior clinical outcomes for patients treated for bone and joint infections with oral therapy started within the first 7 days of therapy compared to those who remained on parenteral treatment for the entire 6-week course [35].

A randomized controlled trial evaluating oral step-down therapy for infective endocarditis in European patients was published in 2019. Outcomes were noninferior for patients transitioned to oral therapy for the last 2–3 weeks of the treatment course. This study provides evidence for utilization of oral step-down therapy in a select patient population with infective endocarditis; however, ID consultation is recommended in these scenarios [36].

Finally, oral therapies can provide potential treatment alternatives for organisms with particular resistance mechanisms. For example, patients with certain infections caused by an extended-spectrum beta-lactamase (ESBL)-producing *E. coli* may be able to utilize an oral fluoroquinolone or trimethoprim-sulfamethoxazole provided sensitivities have been tested [41].

In summary, select patients may be able to avoid OPAT and risks associated with central line placement by completing treatment courses with oral antimicrobials when appropriate. Oral therapy allows resumption of normal daily activities, decreases healthcare costs, and avoids complications of long-term indwelling lines. Drug bioavailability, treatment indication, site penetration, and spectrum of activity all play a role in this determination.

Convenience Versus Stewardship

Recent expansion in OPAT has occurred in parallel with an increased global focus on AS [42, 43]. AS is a multidisciplinary approach toward improving antibiotic use for the purpose of optimizing clinical outcomes while minimizing toxicities, healthcare-acquired infections, and antimicrobial resistance [44]. Unfortunately, regimens following AS principles may not be the most convenient for use in OPAT. In OPAT, once-daily dosed regimens, and regimens that lack therapeutic drug monitoring (TDM) are preferred for convenience as well as to improve compliance and potentially patient safety [8, 13, 45]. However, once-daily agents such as ceftriaxone, daptomycin, and ertapenem may be overly broad for many indications [46]. Therefore, despite tremendous growth in both OPAT and AS efforts, the aligning of the two has remained difficult. Designing an OPAT regimen that is both convenient for patients and compatible with AS standards continues to be challenging for many providers [19]. The challenge has come to be known as the "stewardship/OPAT dilemma" [46].

The "stewardship/OPAT dilemma" and concerns regarding conducting stewardship in the OPAT setting have been acknowledged by many [46–51]. A primary concern is that OPAT may contribute to the development of resistance and adverse events by compromising AS in favor of convenience [28, 46, 47, 52]. For example, carbapenems and third-generation cephalosporins have been shown to increase the risk of *Clostridiodies difficile* infections (CDI), but remain likely to be used in OPAT [52–54]. In a review by Duncan et al., ceftriaxone was described as being the most commonly used agent in OPAT for a number of indications [55]. Additionally, in a retrospective review by Britt et al., OPAT patients readmitted on broad-spectrum "ease of administration" regimens (e.g., daptomycin, ertapenem) were identified for de-escalation in 28% of the cases when the ID or AS teams intervened during these readmissions [56]. Furthermore, in a recent antimicrobial prescribing survey audit, 11% of OPAT prescriptions were assessed as inappropriate with unnecessarily broad-spectrum antibiotics used in 9% of prescriptions [56]. These studies identify that opportunities exist for improving AS interventions for OPAT, particularly when it comes to the overuse of broad-spectrum antimicrobials [50, 56].

Broad-spectrum, once-daily dosed antimicrobials continue to be preferred by many OPAT prescribers given barriers to provision of narrower, more frequently dosed regimens in the outpatient setting [8] such as lack of once-daily dosed narrow-spectrum antimicrobials, lack of or delayed IV to

oral switching, patient-specific factors, and insurance coverage [8, 44, 56–60]. In addition, the availability of OPAT itself may reduce the incentive for providers to switch to oral antimicrobials for more severe infections [60]. Moreover, health insurance can also play a significant role in preventing providers from being able to select outpatient regimens more closely following AS goals [46]. For OPAT, insurance plans can limit which antimicrobials patients are able to receive as well as the locations where they can receive them [8, 19]. For example, patients receiving Medicare who do not have coverage for home-based OPAT may end up either receiving once-daily antimicrobials to accommodate outpatient infusion centers, or spend more for frequently dosed narrower-spectrum alternatives [2, 19, 20]. Patient-specific factors, such as the ability to self-administer or patient preference, may prevent the use of narrower-spectrum therapies if those regimens have the potential to prevent patient compliance [49, 60].

Narrower-spectrum antibiotics such as cefazolin, nafcillin, oxacillin, and penicillin can be viewed as inconvenient. This is due to the perception that the patient will need to be attached to an IV pole frequently due to the need for frequent administration. In actuality, these agents can be administered via an ambulatory pump via either continuous infusion or intermittent infusion while allowing patients the freedom of mobility [49]. This convenient method allows patients to receive narrower-spectrum antimicrobials while minimizing both interruptions to daily activities and the need to access the parenteral catheter. Additionally, many avoid antimicrobials with shorter stability in OPAT. Ampicillin, for example, has limited stability and may require the use of cold packs when being administered via intermittent dosing pump programming or continuous infusion [2, 61–63]. However, ampicillin remains the preferred treatment option for *Enterococcus* spp. infections, and it should continue to be preferred as long as more than once-weekly drug deliveries can be accommodated [2].

Despite these barriers, it has been suggested that antibiotic selection should be conducted according to proper AS principles regardless of the setting in which the antibiotic is being administered [64]. Recent guidance from the Centers for Disease Control and Prevention, the Centers for Medicare and Medicaid Services, The Joint Commission, and other organizations has made AS in acute, long-term care, and ambulatory settings (such as where OPAT is typically delivered) a priority [44, 51, 65–67]. In 2019, the United Kingdom's updated OPAT guidelines highlighted the importance of AS in all 5 sections of their recommendations [25]. The growing pressure to optimize antimicrobial use within OPAT has now become even greater with the increased focus on AS in the ambulatory setting [49, 51, 66].

Focusing on AS within OPAT must balance patient-specific needs with AS needs. It has been suggested that AS in the OPAT setting should focus on standards such as (1) elimination of unnecessary antimicrobials, (2) avoidance of line placement, (3) reduction in durations of therapy, and (4) transitions to oral antimicrobials as soon as appropriate [49]. It has also been suggested that OPAT programs operate in conjunction with AS programs [49, 50]. OPAT antimicrobial-use protocols and AS checklists have been proposed as a way to ensure that programs are meeting their AS goals [50]. In addition, ID expert review of OPAT prior to discharge and after the posthospital transition is an essential step in ensuring AS [50]. The 2018 IDSA OPAT guidelines highlight a body of evidence demonstrating reduced antimicrobial misuse with ID expert review resulting in the limitation of antimicrobial use, improvement in clinical care, substantial cost savings, and reduction in readmissions [8, 28, 29, 32, 50, 68].

AS needs to be adapted and incorporated into the OPAT setting [46]. OPAT programs will need to integrate AS principals within the confines of patient-specific and infusion-model limitations [46]. This will allow antimicrobial regimen optimization from both a convenience and stewardship standpoint. Further research on antimicrobial-use outcomes and resistance within OPAT programs will be needed in order to support stewardship efforts moving forward [46].

OPAT in Injection Drug Use

The opioid crisis of the last decade has led to an increase in numbers of persons who inject drugs (PWID). A consequence of the opioid crisis and increases in PWID has been an increase in blood-borne infections, including bacterial and fungal infections, as well as skin and soft tissue infections resulting in increased hospitalizations [69–71]. Increases in bloodstream infections, endocarditis, osteomyelitis, epidural abscesses, skin and soft tissue infections, and other infections have been attributed in part to the increases in PWID [71–74]. The costs associated with the increased number of admissions related to injection drug use (IDU)-associated infective endocarditis increased 18-fold between 2010 and 2015 [75].

Many of these IDU-associated infections can be treated with OPAT. However, historically, there has been a reluctance to treat PWID requiring OPAT in a home-based setting. Instead many of these patients have been admitted to SNFs to receive OPAT, or remained in acute care hospitals for the duration of their therapies. Underlying this reluctance are theoretical concerns including patients misusing their vascular access, struggles to adhere to a treatment plan, and the potential for accidental drug overdose [8, 76]. However, alternatives to home-based OPAT (having the patient go to an SNF for OPAT where illicit drug administration may continue to be of concern, or an outpatient infusion center with new

peripheral access placed for each infusion) may not necessarily provide significant improvements [8]. Meanwhile, PWID may experience other challenges (e.g., inadequate housing, inadequate insurance, psychiatric disorders, etc.) that may further complicate OPAT delivery. Data for the use of home-based OPAT in PWID has been limited; so in recent IDSA OPAT Guidelines, no recommendation could be made for or against treatment of PWID with home-based OPAT [8].

For select acute bacterial skin and skin structure infections and select gram-positive infections in PWID, some have used weekly long-acting injectable glycopeptides in outpatient infusion centers (e.g., dalbavancin, oritavancin) with success [77, 78]. However, for those requiring OPAT for other conditions, it is unclear whether PWID receiving OPAT at home are at a higher risk of complications than PWID receiving OPAT in other settings. In a retrospective case-control study of patients receiving OPAT at a large healthcare center comparing patients on OPAT with current history of IDU with matched controls, no differences were seen between the two groups in treatment outcomes. It should be noted that in this population, 82% of patients with current IDU were discharged to SNFs [76]. Meanwhile, in another study, PWID with and without housing each were less likely to achieve clinical success than OPAT in patients without IDU who had housing [79]. However, in this study, patients without housing often went to a respite facility, and many patients went to SNFs. In a larger cohort of 1461 patients, 16 of which were PWID, IDU was found to be a risk factor for vascular access complications [14].

Innovative approaches have been used to allow PWID to receive OPAT outside of SNFs. A study in Singapore showed success among 29 PWID who were discharged with indwelling vascular access devices with a tamper-evident seal and returned to an infusion center daily for antibiotic infusions [80]. Care management programs combining close monitoring of OPAT with substance abuse treatment programs have been piloted. For example, patients hospitalized for severe injection-related infections requiring OPAT and opioid use disorder were discharged to the home with weekly ID follow-up and close follow-up in a buprenorphine treatment clinic and achieved success [81]. In another study, PWID managed in a hospital outpatient unit by day were sent to an off-site supervised residential shelter at night with substance abuse treatment program capabilities [82].

However, uptake in these programs may be low, and only select PWID may be interested and eligible. In a small mixed methods study of 27 PWID requiring OPAT, patients were offered the option to integrate OPAT into residential treatment for substance use. Only 7 enrolled in the program, and only 3 completed their OPAT course [83]. Barriers to combined treatment included the high demands of residential treatment, restrictive practices due to the parenteral catheters, and the feeling of "standing out" among other participants in the residential treatment program. Meanwhile, in another program, a multidisciplinary team including ID, OPAT leadership, addiction psychiatry, care coordination, and risk management offered discharge to the home with OPAT for selected PWID. Eligible patients had to have safe housing without others with substance abuse disorders in the home, be engaged in addiction treatment, not engaging in substance abuse or violent behavior during the hospitalization, and agreement to return to substance abuse and OPAT clinics. Only 20 patients of 68 PWID were enrolled; of these, all completed the recommended OPAT course, no overdoses occurred, and no parenteral access complications were observed [84].

Carefully planned multidisciplinary pilot programs involving selected PWID who wish to engage in home-based OPAT and treatment for substance abuse disorder may be possible, but larger studies (likely including mixed methods) are required to understand best practices for and the impact of these programs.

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Construction and Remodeling in the Healthcare Environment: The Critical Role of the Healthcare Epidemiologist

Jessica Fullerton and Susy Hota

Introduction

Healthcare-associated infections as a result of construction, renovation, and maintenance activities are well documented in the literature [1, 2]. Dust or water particles contaminated with fungi and bacteria can be disrupted and dispersed during construction and maintenance activities. Changes in ventilation and airflow in construction zones may also enhance transmission of airborne pathogens in adjacent areas if not properly contained.

In this chapter, we review the common sources of healthcare-associated infection from healthcare facility infrastructure and outline the role of the healthcare epidemiologist in the planning, construction, and maintenance of construction and renovation projects.

Healthcare Infrastructure and Construction-Related Sources of Infection

Waterborne Sources of Healthcare-Associated Infections

Healthcare-associated bacterial infections featuring the genus of Gammaproteobacteria (e.g., *Legionella*, *Pseudomonas*, *Klebsiella*, *Serratia*, *Enterobacter*) have been linked to inappropriately designed and maintained water systems. These waterborne pathogens can cause significant morbidity and mortality among immunosuppressed patient populations, including solid organ or stem cell transplant recipients, and those receiving immunosuppressive therapy [3]. Evolving resistance among Gammaproteobacteria, including extended-spectrum β-lactamase (ESBL) and carbapenemase-producing organisms, amplifies the morbidity and mortality concerns of these pathogens, and highlights the importance of preventing healthcare acquisition and transmission events. Reservoirs in healthcare facilities include cooling towers, evaporative condensers, hot- and cold-water storage tanks, humidifiers, ice machines, decorative fountains, dead leg plumbing or parts of the system temporarily out of use, and drainage systems [3, 4].

Legionella species colonization of hospital water systems is a significant healthcare concern. A single case of healthcare-acquired Legionnaire's disease should prompt immediate investigation into potential environmental sources. *Legionella* is typically transmitted via contaminated aerosols and droplets emanating from contaminated water sources. Sources described in outbreaks include aerating faucets and shower heads, humidifiers, respiratory devices, ice machines, aspiration of contaminated water, decorative fountains, whirlpool spas, and HVAC systems [4–6]. *Legionella pneumophilia* serogroup 1 is responsible for the majority of documented Legionella outbreaks [3]. Identification of other serogroups is hindered by the specificity of the urine antigen test for serogroup 1 along with difficulties in culturing the bacteria, potentially delaying diagnosis and initiation of effective treatment [3]. Incidence rate of laboratory confirmed cases averages 1–2 cases per 100,000; however, the true incidence is likely underestimated, and many countries have observed marked increases in sporadic Legionella incidence in recent years [7–10]. Case fatality of Legionellosis is as high as 40–80% in untreated immunosuppressed patients [11].

Outbreaks of waterborne pathogens are commonly associated with facilities that have large, complex water systems and areas of low-flow water pressure, particularly involving the hot water system, presenting a risk for stagnation and biofilm formation. Changes in the building water supply that

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_35

disrupt flow or cause turbulence can increase the risk of contamination. Facility shutdowns for construction or maintenance, followed by repressurization of piping when the water is turned back on, can result in descalement inside the pipes, disruption of biofilm, and release of contaminants into the supply water.

A comprehensive water management plan is crucial for identification of building-specific risks. Appropriate monitoring, control limits, and interventions should be established with a focus on preventive measures to decrease the reservoir of organisms within water systems [4–6]. Systemic disinfection through hyperchlorination, superheating, ultraviolet light, and/or silver-copper ionization may also be considered, but care should be taken to perform a risk assessment of the existing system prior to undertaking any additional disinfection processes, as disinfection may harm the integrity of the system, leading to greater problems [5, 12, 13]. Distal, point-of-use filtration, involving a clear maintenance plan, has proven effective for short-term outbreak mitigation [14, 15]. Several studies have demonstrated colonization of wastewater drainage systems with Gammaproteobacteria resulting in nosocomial outbreaks [16, 17]. Careful design and routine maintenance of drainage systems is important to prevent exposure of resident organisms in waste plumbing.

Fungal Sources of Healthcare-Associated Infections

The most common microorganism transmitted through the air during construction, renovation, and maintenance activities is fungi. Healthcare-associated fungal infections are frequently caused by species of *Aspergillus*, although invasive fungal infections caused by other classes and genera including *Zygomyetes, Fusarium,* and *Scedosporium* have also been observed [1, 2]. *Aspergillus* infections can be life-threatening and often fatal for severely immunocompromised patients. In hematopoietic stem cell transplant recipients and neutropenic patients with hematologic malignancies, invasive aspergillosis remains a significant cause of infection-related mortality [18]. Immunocompromised patients at a lower risk for invasive disease include solid organ transplant recipients, patients with AIDS, and those with Chronic Granulomatous Disease [19]. The population of high-risk patients has increased significantly in recent years due to developments in aggressive immunosuppressive therapy, as well as, new chemotherapeutic and immunomodulatory agents [20].

The true burden of invasive fungal infection is likely underestimated due to the complexity of clinical presentation and diagnosis, the challenges associated with timely and sensitive diagnostics, and lack of national public health surveillance for most fungal diseases [2, 21]. The emergence of new or resistant pathogens further hampers diagnosis and effective treatment. Available data suggests an incidence rate of 2.2 per 100,000 population and 2 per 10,000 hospital discharges for invasive aspergillosis in the United States of America [20]. The average length of stay for a hospitalization related to *Aspergillus* infection is 17 days, with a median cost of $82,427 [21, 22]. The overall estimated national total cost is $1.2 billion, making up 17% of the total fungal disease costs [22]. Mortality rates vary depending on severity of disease and underlying risk factors; however, overall case-fatality rates of 50–60% have been demonstrated [23], with critically ill patients with confirmed invasive disease and bone marrow transplant recipients demonstrating higher mortality rates (79% and 86.7%, respectively) [23, 24]. Determination of a case of invasive aspergillosis as healthcare-acquired is often difficult due to the lack of a clearly defined incubation period and the timeline of exposure within the hospital and subsequent infection [25]. Sources of fungal exposure in healthcare facilities include soil excavation, dust above false ceilings, contaminated building materials including drywall, insulating material, ceiling tiles, and carpeting, and inappropriately maintained heating, ventilation, and air-conditioning (HVAC) systems [1, 2].

Source containment with environmental controls during construction, renovation, and maintenance activities is crucial to prevent exposure of vulnerable patient populations to these construction-related infections. An effective surveillance system must be in place to monitor for these construction-related infections and allow for timely intervention. Surveillance should take into account that fungal outbreaks originating from the healthcare environment may be polymicrobial. Appropriate design of architectural and mechanical systems, including building material selections, is very important in the prevention of nosocomial infections related to the built environment. Different classes of healthcare facilities will have different needs and specific infection prevention and control requirements.

Stages of a Construction or Renovation Project

Healthcare construction/renovation projects should follow the typical project management process outlined in Table 35.1.

Involvement in the earliest planning stages provides the best opportunity for intervention to support IPAC efforts. It is important for IPAC programs to be involved in organizational master planning discussions so that they may be apprised of upcoming projects and table critical IPAC requirements as early as possible. It also allows IPAC teams to assess the human resources, knowledge, and education

Table 35.1 Stages of Project Management Process

Stage	Description
Master planning	A long-range plan for developing or improving a building. This process includes feasibility studies that assess the strengths and weaknesses of a proposed project
Functional planning	Overall goals of a project, highlighting the functional and operational requirements
Schematic design	General overview of how the project will look, including description of building systems
Detailed design	Development and refinement of the general overview to produce specific room layouts
Procurement	Sourcing and acquiring of materials and services
Project execution (Construction)	Activities that disturb or modify facility structure or systems
Project monitoring	Performed concurrently within Construction, Project Monitoring involves the monitoring of project-related metrics such as budget, schedule, milestones, potential problems, etc.
Commissioning	Systemic verification, documentation, and training process to ensure the building/area is functioning as designed
Project closure (close-out)	Completion of all project activities including financial close-out in order to transfer the project back to the owner

needs within the program to ensure adequate project support is provided. A clear process for functional planning, schematic design, and detailed design activities with timelines and human resource implications must be established, with a documented process for sign-off from stakeholders at various milestones. The commissioning requirements must also be determined early in the planning process to ensure adequate time and resources are accounted for.

Planning a Construction or Renovation Project

Early establishment of a planning and design multidisciplinary team (MDT) with commitment by all members to proactive risk mitigation is critical to the outcome of a safe, successful project. An important objective of the team is to assess risk and provide guidance on mitigation strategies related to IPAC concerns. This team should consider representation from the following stakeholders, where available: Planners, Architects/Design Consultants, Engineers, IPAC Professionals, Administration, Facility Operations and Maintenance, Environmental Services, Occupational Health and Safety, as well as Physician, Nursing and Allied Health groups as appropriate. For expertise not available in-house, the MDT should determine early in the planning stages what additional project support/expertise may be required for the project (e.g., external experts in IPAC or Environmental/Industrial Hygiene) as this may have funding/budgetary implications.

An Infection Control Risk Assessment (ICRA) is recommended for any project of significant size and/or impact [26–29]. This document should be initiated during the planning stage to identify IPAC risk factors associated with the planning, design, construction, and commissioning phases, and allow for strategic, proactive prevention of infection transmission. Considerations should include patient separation (i.e., single-bedded or multibedded configurations, spacing between patients), proximity of vulnerable patient populations to construction activity, need for relocation of patients during the work, separation of clean and contaminated activities, and potential impact of services (HVAC, plumbing) in active patient care areas. The anticipated need for air sampling for ambient fungal spores should be discussed during the development of the ICRA (i.e., projects in close vicinity of high-risk patients where there is clinical concern of fungal infections) so that this may be incorporated into project budget. An important part of the ICRA is the preventive measures analysis, which takes into consideration the type of construction activity (i.e., the scope of work), and the population risk group (i.e., individuals in the vicinity of work), to provide a class or level of precautions. The preventive measures analysis process has been described previously [1, 2, 26].

It is important that IPAC requirements are communicated early in the planning process and included in project documentation, as they may have costing implications. Policy and procedure documents should be established and clearly communicated to Planners, Project Managers, Facility Operations and Maintenance Personnel, Consultants, and Constructors. A comprehensive construction policy should support the IPAC Professional, outlining roles and responsibilities, communication plans, minimum preventive measures, approval and inspection requirements, notification timelines, required documentation, education plans, and construction breach processes, among others [29].

Design

Physical design elements, including patient separation, specialized isolation rooms, support spaces, HVAC, and plumbing systems, are critical to IPAC efforts. The unique operating characteristics of healthcare facilities, including frequent cleaning and disinfection of surfaces, year-round control of humidity levels, and continuous operation, result in considerable stress placed on building materials. Appropriate selection of fixtures and finishes is of utmost importance, not only to help prevent the spread of infection, but also to extend the life cycle of the space. Major IPAC design elements to be considered for healthcare construction/renovation projects are listed in Table 35.2. There are several well-established healthcare design guidelines detailing these requirements

Table 35.2 Select elements of design with IPAC significance

Element	Considerations	References
Airborne isolation rooms (AIRs)	Number and location Minimum one AIR per inpatient unit based on patient population and functional program Emergency department and Intensive Care Units may require more Ambulatory/outpatient units based on patient population and functional program.	[21, 27, 28, 30]
Protective environment rooms	Number and location Based on patient population and function program Typically specific to burn, oncology, and bone marrow transplant units	[21, 27, 28, 30]
Patient separation Critical care Inpatient Ambulatory/outpatient (e.g., emergency, dialysis) and recovery areas	100% private rooms 100% private rooms Typical curtained bay verses 3-sided hard-walled cubicle, or fully enclosed rooms	[27, 28, 32–34]
Washrooms	Number and location One washroom for every inpatient Separate washrooms for patients, staff, and visitors	[27, 28]
Waste management systems Clinical flushing rim sinks/hoppers Macerators Washer/disinfectors	Type, number, and location Provided in every patient room or common soiled utility	[12, 27, 28]
Hand hygiene sinks	Number and location In every room where physical patient care is provided For provision of hand washing only Design and materials Nonaerating faucet Off-set faucet and drain Hands-free controls Increased depth of basin, shaped to reduce splash-back Stand-alone, not built into millwork, min. 3 feet from any fixed surface or equipment/supplies	[12, 27, 28]
Support spaces Soiled utility Clean supply Housekeeping rooms Equipment storage	Number, size, location Minimum one of each in patient care areas/units	[27, 28]
Medical device reprocessing	Centralized or decentralized	[27, 28, 35]
Waiting rooms	Layout and spacing	[27, 28]
Plumbing fixtures		[12]
Sinks	Shaped to prevent splash-back Off-set faucet and drain No overflow	
Faucets	Nonaerating faucets Hands-free controls considered based on location	
Toilets	Wall hung for ease of cleaning	
Shower accessories	Nonaerating for high-risk patient populations	
Material finishes		[27, 28]
Counter tops	Solid surface	
Flooring	Resilient, easily cleaned, minimal seams	
Wall protection	Impact resistance and protection from water/moisture	
Furnishing and equipment selection	Nonupholstered surfaces that are easily cleaned/disinfected Only water-resistant, wipeable materials compatible with hospital-approved disinfectants	[27, 28]
Personal protective equipment storage	Location Outside every patient room Stand-alone versus recessed units	[27, 28]
HVAC systems Air change rate Pressurization Filtration Dedicated systems Redundancy	Based on Class of facility and location served within the facility Use of alternative filtration technologies (e.g., electronic air purifiers that utilize particle control/charged particle filtration) should be carefully evaluated Ultraviolet germicidal irradiation can supplement traditional filtration systems	[27, 28, 30, 31]

Table 35.2 (continued)

Element	Considerations	References
Plumbing systems Materials Temperatures Filtration Redundancy	Ensure systems are designed to prevent the introduction, growth, and spread of microorganisms Use of adjunct disinfection technologies such as UV disinfection, silver-copper ionization, and ozonated water should be carefully evaluated	[12, 27, 28]
Biophilic architectural features Wood Plants Water features	Wood and plants are not recommended in high-risk areas Water features are not recommended in healthcare facilities	[12, 27, 28, 36, 37]

that can be used as guidance for the IPAC Professional [12, 27, 28, 30, 31]. The Functional Program will help inform the specific building/unit requirements.

Pandemic Planning

Recent events with the COVID-19 pandemic have emphasized the importance of including pandemic planning in the healthcare design process. Important considerations include separate building entrances for staff and patient entry, provision for screening space at entrances, zoning of HVAC systems, establishing or maintaining pressure relationships between spaces (i.e., positive or negative pressure to protect or contain), need for dedicated systems, and ability for 100% exhaust or 100% return air depending on the threat. Respiratory pathogens are concerning due to their modes of transmission (droplet, airborne) making appropriately designed HVAC systems critical to response efforts. Designing negative pressure zones or units with the facility, in addition to an adequate number of airborne isolation rooms, allows facilities to respond more readily to emerging respiratory pathogens. Retrofitting of existing areas can be challenging to achieve the required HVAC parameters [30, 31]. Designing for flexibility of spaces is crucial to allow for expansion of departments (e.g., emergency departments, Intensive Care Units) in the event of a large influx of patients. Stand-alone biocontainment units such as field tents can assist facilities with limited space but require unused land and provision of infrastructure services (HVAC, plumbing, power) and can be expensive to operate.

Construction, Renovation, and Maintenance

Preconstruction

Once a project moves from planning and design to implementation, a Project MDT must be established. The Project MDT may have similar representation as the Planning and Design MDT, with a few notable changes (i.e., addition of a Project Manager and the constructor that will be performing the work). An Environmental Consultant may also be engaged if the risks of the project warrant additional oversight and/or environmental monitoring. The objective of the Project MDT is to assess project-specific risk associated with the construction process and provide guidance to mitigate the risks. In many jurisdictions, the constructor is required to submit an Infection Control (IC) Plan detailing the means and methods that they will utilize to address the risks identified in the ICRA [2, 26]. The MDT must review the plan prior to work commencing and provide comment or further direction if needed. An example of elements for inclusion in the IC Plan can be found in Table 35.3.

During Construction

The constructor is required to follow the IC Plan and implement the preventive measures identified during planning. Once the barriers have been erected, the IPAC Professional must inspect the enclosures to ensure they have adequate seals and the requirements of the IC plan are being adhered to prior to any work commencing. Routine inspections should be conducted by the IPAC Professional, or another knowledgeable member of the MDT. Barrier seals, both above and below the ceiling plane, negative pressure, and general cleanliness in and around the site must be verified as a part of the inspection. The frequency of the inspections will be project dependent and determined by the MDT. The IPAC professional or any member of the MDT shall have the authority to stop construction if there is a significant failure to adhere to the required preventive measures and there is significant patient or staff safety risk present. The constructor must also perform internal daily site inspections to identify any breaches in containment or other preventive measures. Where negative pressure must be maintained within a high-risk construction site, a log of differential pressure measurements must also be kept by the contactor and submitted to the MDT as determined by the IC Plan. Planned disruptions to negative pressure are permitted if they are coordinated in advance and have approval of the MDT.

Active plumbing lines within the construction site must be thoroughly flushed at regular intervals throughout the construction project (e.g., at least twice a week) and on com-

Table 35.3 Example of elements for inclusion in the Infection Control (IC) Plan

Element
Applicable standards and guidelines
Communication plan
Education plan for trades and subtrades completing the work
Shipping, handling, and storage of construction materials
Traffic plan for workers
Plan for any outdoor excavation work needed
Hoarding layout, material, and assembly Location of barriers above the ceiling Alternative hoarding materials (modular systems)
Construction air handling units (CAHUs) Exhaust locations Testing requirements Monitoring plan
Protection of the HVAC system Within the construction zone Adjacent pressure-critical spaces (i.e., ORs, AIRs)
Protection of the potable water system[a] Identify systems that should be drained of water and isolated Flushing and/or disinfection requirements
Debris removal path/plan
Cleaning requirements Routine cleaning of site Routine cleaning around site Final construction clean Wall cavities and above ceiling infrastructure before enclosure

[a]Before a water system or portion of a water system is shut down for construction or maintenance work, a risk assessment should be conducted to determine methods to ensure microorganism growth and leaching of metals is minimized [12]. Plumbing lines remaining active within the site must be flushed at regular intervals (see During Construction below). Flushing frequency and duration as well as disinfection requirements prior to turnover should be determined by the MDT prior to start of the project. The requirement for disinfection of plumbing lines at the completion of construction will depend on several factors including length of piping affected, age of infrastructure, amount of scale and sediment in the system, history of contamination, length of shutdown (if applicable), and vulnerability of patient population [12]
Sites within the healthcare facility that will be turned over to the constructor for construction, renovation, or maintenance work must be made safe prior to construction occupancy. All patient equipment, supplies, and confidential information must be removed from the space. The area must also be thoroughly cleaned (i.e., with hospital-grade clinical or terminal clean) prior to handover to the constructor

pletion of construction [12]. Thorough flushing involves replacing the water in the line several times over to restore the water supply equal to the quality of the rest of the system.

Post Construction

Once deficiency walk-throughs have been performed and construction is complete, the constructor must perform a final construction clean. All surfaces, including the inner layer of barriers, must be cleaned of dust and debris. Duct cleaning would also be completed at this juncture. The IPAC Professional must inspect the site for cleanliness prior to barrier removal. If deemed acceptable, the barriers may be removed ensuring any potential for dust generation is minimized. Environmental Services must then perform a hospital-grade clinical or terminal clean of the area and disinfect all surfaces. There are instances where a hospital-grade clinical or terminal clean may be required both before and after removal of construction barriers. This requirement would be project dependent and based on the population risk group in the vicinity of work. The IPAC Professional would perform a final inspection post terminal/clinical clean to ensure the area is safe for occupancy.

At the end of the project, the MDT should conduct an infection control procedures quality review to determine what was successful in the process and where improvements could be made in future projects. The quality review should include review of the IC Plan, the effectiveness of the preventive measures that were undertaken, and documentation and communication of any improvements for future use.

Commissioning

Commissioning is the systemic verification, documentation, and training process to ensure the building/area is functioning as designed. Commissioning is an integral part of the design and construction process and must be incorporated early into planning documents to ensure expectations are clear and adequate time and resources have been accounted for [38]. The unique nature of a healthcare facility presents considerable risk should system failure occur. It is necessary to validate performance in a dynamic environment where the systems are challenged, and not just static conditions. There are several commissioning requirements specific to IPAC that must be verified prior to turnover. These are summarized in Table 35.4.

Table 35.4 IPAC commissioning requirements

Element
Above ceiling infrastructure and wall cavities have been cleaned prior to enclosure
Final construction clean activities have been completed and verified
The HVAC system and ducts in the construction zone are clean
The HVAC system has been balanced and physically restored to the original or new design as applicable
Mechanical waste disposal systems have been tested and commissioned
Disinfection and/or flushing of the plumbing system has been completed
Completion audit of the IC Plan has been performed

Operations and Maintenance

Aging infrastructure and deferred maintenance can contribute to conditions favorable for microorganism growth and proliferation. Adherence to a regularly scheduled preventive maintenance program in line with building system manufacturer recommendations is essential to maintaining a safe environment of care. A Site MDT should be established to address standardization issues and develop policies and procedures related to facility construction, renovation, and maintenance. There should be representation from Project Planning, Project Management, Facility Operations and Maintenance, IPAC and Occupational Health and Safety to address IPAC issues such as water shutdown procedures, HVAC shut-down procedures, process for routine preventive maintenance of building systems (e.g., water management plan), and process for leak/flood response. The Site MDT should also perform an education needs assessment and plan for ongoing education of both in-house facilities personnel as well as external contractors to ensure all performing work are knowledgeable in the IPAC requirements.

Summary

The significant morbidity and mortality related to healthcare-associated infections underscores the importance of infection prevention and control input during all phases of health care facility projects. It is essential for IPAC Professionals to be involved early in the planning and design process as integral members of the multidisciplinary team. IPAC planning and design elements such as single room accommodation, increased number of airborne isolation rooms, durable fixtures and finishes, and upgraded plumbing and HVAC systems can increase upfront capital costs, but the potential for reduction in healthcare-associated infections and associated cost savings over the long-term demonstrates the necessity of these features. These elements will also increase the resiliency of healthcare facilities to respond to new, emerging infectious diseases and pandemic situations.

Thoughtful planning, incorporating design elements to support IPAC efforts, along with implementation of appropriate control measures during facility construction, renovation, and maintenance activities, can significantly reduce the risk of construction- and infrastructure-related infections.

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Aerosol-Generating Medical Procedures: Controversies in Definition, Risks, and Mitigation Strategies

36

Alon Vaisman and Susy Hota

General Principles

Aerosols are defined as a collection of biological particles containing microbes, liquid, or dust that are diffused in the air. The size of these aerosols can vary from 2 μm up to 100 μm [3]. Aerosols larger than >5 μm, which may colloquially be referred to as "droplets," rapidly descend toward the ground after being emitted by patients due to the force of gravity and will typically travel up to 2 meters from their site of origin [4, 5]. In contrast, smaller particles measuring less than or equal to 5 μm in diameter, sometimes colloquially referred to simply as "aerosols," may evaporate to form droplet nuclei that are small and light enough to remain suspended in the air for hours [6]. Whether or not these small aerosols are capable of carrying viable pathogens to susceptible hosts over prolonged distances and durations depends on a wide variety of variables, including the ventilation and airflow in the space, the biological characteristics of the microbe and the infection it causes, and environmental factors such as temperature, humidity, and presence of UV light [7–9]. For example, experimental studies involving MERS-CoV and SARS-CoV-2, the etiologic agent for COVID-19 infection, show that these viruses can remain viable for at least 60 minutes after artificial aerosolization [7, 10, 11]. Due to the prolonged period of suspension time, there is an increased concern that these particles have an increased risk of travelling to and contaminating contiguous spaces. While many respiratory pathogens may be found in aerosols at varying distances from their source in different settings, the role of aerosolization in person-to-person transmission remains unclear for many. Pathogens that have been established to transmit predominantly via these aerosols currently include only measles, disseminated varicella zoster, and tuberculosis of the respiratory tract. These pathogens are therefore commonly referred to as "airborne" pathogens due to their clear capability to transmit via aerosols.

Aerosol-based transmission can be driven by naturally occurring aerosols, which are generated while speaking, breathing, coughing, and sneezing, or by aerosols that are artificially generated by medical procedures. These medical procedures, which stimulate production of a relatively high degree of small or droplet nuclei, are aptly deemed "aerosol-generating medical procedures." They present an increased risk for "opportunistic" airborne transmission of pathogens not otherwise predominantly spread by the airborne route or increase the risk of transmission via organisms believed to be transmitted primarily via the airborne route [12].

There are numerous definitions for AGMP. These include, "...any medical procedure that can induce the production of aerosols of various sizes, including droplet nuclei [13]" and "Procedures that stimulate coughing and promote the generation of aerosols..." [14]. It is unclear what factors predict whether a procedure can generate these small aerosols, and what distinguishes these procedures from others. Currently, there are no clear criteria that define whether a procedure is aerosol generating or not. Many of the studies examining this question measure ambient particle sizes to infer aerosol generation while patients are undergoing the studied procedures [15]. Interpretation of these studies is challenging given the diversity of sampling techniques and technologies. Another approach is to determine whether expectorant originates from the most distal locations in the lungs, where the smallest droplet sizes are located, as in the case of lower lung manipulation [12]. Others have used criteria of high airway pressure, distal airway collapse, and the generation of shear forces in the airway [9], while another approach takes into account four factors: forced air, severity of disease, distance, and procedure duration [16]. One possible criterion for AGMP is the induction of forceful coughing [17–19], a poorly defined concept, as a source for aerosol generation.

Complicating matters further is that even when a procedure results in production of small particles (e.g., bronchos-

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G. Bearman et al. (eds.), *Infection Prevention*, https://doi.org/10.1007/978-3-030-98427-4_36

copy, suctioning, bronchoscopy), it may not produce detectable pathogen genetic material or viable virus [15]. Finally, considering the view that droplet to aerosol generation occurs along a spectrum, and that even speaking can generate droplet nuclei, the term AGMP is inadequate, since the risk of infection transmission is not based solely on whether aerosols are generated, but rather the extent of aerosol generation [16]. On top of all these considerations is the often unanswered subsequent question of whether these procedures actually increase the risk of infection among exposed patients and staff – which is ultimately the purpose of distinguishing these procedures from all others routinely performed.

Studies Supporting Aerosol Generation From Specific Procedures

Although there is uncertainty about the precise definitions of an AGMP, categorization of some AGMPs has a high degree of consensus between international guidelines. Procedures with a high degree of agreement include intubation/extubation, airway suctioning, bronchoscopy, noninvasive ventilation, and nebulized therapy; however, the evidence base supporting each one of these is variable [17]. Often the studies examining these procedures are limited in generalizability by a narrow sample size, differences in sampling technique, and challenges in technologies' ability to accurately capture bioaerosols.

Intubation and extubation are one of the most cited examples of AGMPs, but new studies yield conflicting results. Notably, in elective settings, where measures are well controlled, it was demonstrated that nonurgent tracheal intubation generated, on average, 500-fold lower concentration of aerosols compared to a volitional cough (but 3.5 fold higher than baseline) [20]. Extubation, on the other hand, produced a mean concentration that was 35-fold less than a volitional cough. This evidence suggests that coughing associated with extubation is of higher concern than elective intubations routinely performed on sedated patients. Somewhat conflicting evidence demonstrated 30–50-fold increase in aerosol generation by tracheal tube insertion compared with 12–125 for extubation [21].

Although often cited, evidence for aerosol generation from bronchoscopy and nebulizer therapy is limited. In one study, bronchoscopy produced the highest amount of aerosols, followed by suctioning and then intubation [15]. In this sampling study, procedures not found to have significant aerosol generation included nebulization, chest physiotherapy, and noninvasive ventilation. In another study, six procedures were investigated for their potential to generate aerosols using biosamplers (extubation, bronchoscopy, mechanical ventilation, noninvasive (NIV), lower airway suctioning, and nebulized medication administration). Of these, only nebulized therapy and bronchoscopy with nebulized therapy were found to generate any significant aerosols [22]. Data around the generation of aerosols for nebulized therapy also appear to be conflicting, with one study of a single patient with a large volume nebulizer showed negative SARS-CoV-1 viral PCR results on filters placed approximately 30 cm above a patient's head [23].

The generation of aerosols with the use of high flow nasal cannula (HFNC) therapy has also been studied, with evidence for significant aerosol generally lacking [24, 25]. While some studies have shown an increase in the distance of cough droplets for patients on HFNC [26], studies have not shown an increase in pathogen environmental contamination when patients are on HFNC [27]. Compared to the control of 6 liters of oxygen via nasal prongs, HFNC showed no increase in aerosol generation in a study of volunteer subjects receiving HFNC with up to 60 L/min gas flow [28, 29].

Other procedures with moderate evidence supporting aerosol generation include bag mask ventilation, which has demonstrated a 15–300-fold increase in aerosol generation during intubation and extubation [21] and certain dental procedures, including high-speed hand piece, pneumatic scaler, ultrasonic scaler, and triple syringe, found to have a high degree of aerosol dispersion, with use of high-speed devices thought to be a main risk factor [30].

Several procedures, though generally accepted to be AGMPs, have a very narrow evidence base for aerosol generation. For example, studies of continuous airway pressure (CPAP) setups have shown limited dispersion of droplets with tight fitting masks with pressures up to 15–20 cm of H_2O [24, 28, 31]. Despite inclusion in numerous guidelines and expert recommendations, there has never been a study formally investigating the risk of aerosol generation from tracheostomies [9, 32, 33]. Lower airway suctioning has commonly been cited as an AGMP; however, although increased numbers of particulate matter, and fungal/bacterial elements, have been identified in the air after suctioning, increased risk of infection transmission (e.g., from SARS-Cov-2) has not been demonstrated [34, 35]. Lastly, a study of outpatient laryngoscopy did not demonstrate the generation of significant aerosols [36].

Several procedures have never been found to generate significant aerosols (nor demonstrated to increase transmission risk to patients or staff) – including nasopharyngeal swabbing, upper gastrointestinal endoscopy, transesophageal echocardiography, chest physiotherapy, and chest compression [1, 35].

Thus, although there has been a significant increase in the attention paid to AGMPs, there is still diversity in opinions on what constitutes an AGMP from international guidelines.

A recent review by Jackson et al. showed that the following procedures had >90% concordance between official guidelines/academic recommendations: autopsy, postmortem procedures with high speed devices, intubation/extubation, sputum induction, and bronchoscopy – the remaining had varying levels of agreement [17]. Procedures with less than 80% agreement between guidelines (deemed AMGP or possible AGMP) include oral and dental procedures, upper gastrointestinal endoscopy, thoracic surgery, and nasopharyngeal/oropharyngeal swabbing. Many of these guidelines provide recommendations based on expert opinion and scarce substantial citation of the actual risk of transmission associated with the aerosol-generating procedures. Table 36.1 outlines common procedures and the view of major national and international bodies on whether they are deemed an AGMP. There are several notable procedures with wide agreement as being an AGMP; however, as demonstrated above, the evidence base for some is lacking (specifically open suctioning and cardiopulmonary resuscitation).

Table 36.1 Concordance on procedures deemed an AGMP according to major national and international public health bodies

Procedure	Centres for Disease Control (CDC) [37]	World Health Organization (WHO) [38]	Public Health Agency of Canada (PHAC) [39]	National Health Service (NHS) [40]
Open suctioning of airways Sputum induction Cardiopulmonary resuscitation Endotracheal intubation and extubation Noninvasive ventilation Bronchoscopy Manual ventilation	Yes	Yes	Yes	Yes
Tracheotomy	No	Yes	No	Yes
Autopsy procedure	No	Yes	No	Yes
High flow oxygen	Uncertain	Uncertain	No	Yes
Nebulized Therapy	Uncertain	Uncertain	Yes	Yes
Upper GI endoscopy with airway suctioning	No	No	No	Yes
High-frequency oscillatory ventilation	No	No	No	Yes
Dental procedures (using high-speed devices, e.g., ultrasonic scalers/ high-speed drills)	No	No	No	Yes

Studies Demonstrating Increased Risk of Infection from AGMPs

Naturally, the next area of interest is to determine whether the aerosols generated by AGMPs pose a risk of infection transmission to nearby healthcare personnel (HCPs) and patients. Due to the recent COVID-19 pandemic, special focus has been placed on the risk of AGMP and SARS-CoV-2 transmission. For procedures such as high flow oxygen via nasal cannula and noninvasive ventilation (NIV), the interest is particularly high given their potential mortality benefit and prevention of severe outcomes in treating COVID-19 [41, 42].

Early work summarizing the risk associated with AGMPs included a comprehensive systematic review in 2012 by Tran et al. that was updated in 2020 (focusing only on pandemic coronaviruses) on studies answering this question [1, 41]. These studies were based on early experiences during the SARS-CoV-1 outbreak where knowledge of transmission risk was limited. Data on other pathogens are far more limited, partly due to the increased awareness of risk around these procedures since that time and therefore increased uptake of pre-emptive measures by facilities to protect their staff. Thus, when interpreting these exposure data, it is critical to understand what measures were taken by staff to protect themselves – particularly respiratory protection use such as N95 respirator or FFP3 masks – to understand how risky these procedures truly are. These limitations make it more challenging to understand whether AGMPs pose a higher risk to frontline staff or increase their risk of infection when compared to providing routine care for patients.

The number and variety of organisms, which have been demonstrated to have capacity to transmit via AGMPs, is limited. Thus far, outside of tuberculosis [43, 44], only viral pathogens have definitively been demonstrated to transmit via AGMPs. The pathogen with the most evidence thus far is SARS-CoV-1, as demonstrated by several studies during the pandemic in 2003 in Toronto [45–48]. Middle Eastern Respiratory Virus–related coronavirus (MERS) has also been suspected to transmit via AGMP in numerous observational studies in the last decade, primarily in Saudi Arabia [49–52]. Evidence supporting aerosolization of influenza via AGMP is limited. Although aerosol generation and possible transmission has been noted outside of AGMPs [53–55], person-to-person transmission as a result of an AGMP is not definitive. One notable study showed no differences in influenza H1N1 positive air samples between baseline and high-risk AGMP (bronchoscopy and suctioning) [15]. Thus, the role of AGMPs in influenza transmission is unclear and yet to be definitively proven.

In the aforementioned systematic review of the 2003 SARS-Cov-1 pandemic, a variety of AGMPs were shown to increase risk of infection transmission (overall quality of evidence by GRADE: low), and these were tracheal intubation, lower airway suctioning, NIV, and manual ventilation before intubation [1]. Procedures not associated with increased risk were endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, administration of oxygen, high-flow oxygen, defibrillation, insertion of nasogastric tube, and collection of sputum endotracheal aspiration, suction of body fluids, bronchoscopy, nebulizer treatment, administration of oxygen, high-flow oxygen, defibrillation, insertion of nasogastric tube, and collection of sputum. The updated systematic review in 2020 did not include any additional studies of high quality [41] but did include a few more cases of possible transmission due to AGMP attributable to MERS [56, 57]. One of the larger studies, involving 250 HCWs working in a hospital with numerous patients with MERS, showed no increased relative risk of acquiring infection between staff performing and not performing AGMP [50]. One key conclusion to draw from this largest of systematic reviews is that studies examining transmission risk from AGMPs are not rigorous or standardized in the measurement of exposure time, personal protective equipment (PPE) worn by the HCW, environmental measures used to mitigate risk, and symptom status of the index patient cases. These details are often missing, making it very challenging to understand risk associated with the procedures.

In lieu of rigorous studies, there are many incidental observations noted when patients with infective virus underwent AGMPs unbeknownst to the healthcare personnel who were not wearing appropriate PPE [49, 58]. For example, in a study of 41 healthcare personnel (85% of whom wore surgical masks rather than N95s) exposed to a patient with SARS-CoV-2 during their period of infectivity undergoing AGMPs that included intubation, extubation, NIV, and exposure from an open circuit, none acquired COVID-19 [59]. Similarity, when exposed to a patient with COVID-19 receiving CPAP in a hemodialysis center (4 sessions lasting 8 hours), none of the 11 exposed patients or 12 staff contracted COVID-19 despite wearing only surgical masks [60]. Another study examined 37 staff (none wore eye protection, gown, or N95 respirators) after incidental exposure to a patient with COVID-19 (3 of whom subsequently tested positive) [61]. They found that 2/5 staff present during nebulization treatment were infected with COVID; however, infected staff also spent significantly more time with patient performing non-AMGP activities. Other AGMP observed among these staff that did not appear to lead to infection included bronchoscopy, NIV, manual ventilation, and bronchoscopy.

Tracheal intubation has been one of better-studied AGMPs with regards to risk associated with viral infection. Pooling 8 studies, it was demonstrated to have the highest odds ratio (6.6) for SARS-CoV-1 transmission to HCWs of any AGMP [1]. One study from China showed increased risk associated with SARS-CoV-2 due to intubation and spinal anesthesia during Caesarian section when staff were not wearing full, "Level 3" PPE (likely defined as wearing N95, full body gown including head and neck, and eye protection), which dropped the risk from 57% to 2% [62]. Transmission of MERS was documented among four HCW cases of present during intubation when not wearing N95s or PAPRs [63] while another three acquired MERS while participating intubation, open suctioning of airways, and/or cardiopulmonary resuscitation.

Another common AGMP that has been studied is HFNC. So far, there have yet to be any systematic reviews definitively showing increased risk of transmission associated with HFNO from SARS-CoV-1 or SARS-Cov-2 [1, 64]. For example, a study of 25 patients with H1N1 influenza showed no secondary HCW cases (all HCWs used gloves, gowns, eye protection, and FFP3) [65].

Evidence for infection transmission for other specific procedures and pathogens is otherwise lacking. For example, tracheostomy performed on patients with SARS-CoV-1 appeared to be associated with a low risk to HCWs who were in direct contact with the patients in the operating room, when all were wearing N95 respirators [66]. However, one single case-control study, based on survey data, found an OR 4.15 (1.50–11.50) associated with tracheostomy in a patient with SARS-Cov-1 infection although no specific data on PPE worn was provided [67]. Incidental HCW exposure of a small cluster of medical students to patients with SARS-Cov-1 undergoing jet nebulization therapy lead to no increase in transmission [68]. One case of transmission of MERS was reported during cardiopulmonary resuscitation; however, the presumed mode of transmission may have not been aerosols, but rather direct inoculation of the mucous membranes via fluid exposure [69].

Mitigating Risk from AGMP

Despite some scarcity in evidence linking AGMPs to increased transmission risk to staff, several strategies have been developed to help protect staff against the risk of infection. Acknowledging the scientific gaps, many have chosen to follow the precautionary principle in this area to proactively protect HCWs. A commonly used approach in devising mitigation strategies is to consider a hierarchy of control measures, starting with the most effective: elimination, substitution, engineering control, administrative measures, and the use of personal protective equipment (PPE).

The first step in reducing risk is to eliminate the need for AGMPs in the first place – that is, hospital staff should be instructed to perform these particularly high-risk procedures

only when necessary. Thus, to help guide decisions on which patients should undergo these procedures, special protocols can be created to define which patients are at lower risk to potentially transmit pathogens – that is, those with noninfectious presentations, those who are nearly resolved in their infectious processes, etc. As well, when possible, AGMPs should be substituted for other procedures of lower risk – for example, avoiding intubation to perform HFNC [70]; not performing bronchoscopy on patients with acute respiratory disease; and delaying tracheostomy in patients going through infectious periods [32].

The next level in protection is applying engineering controls. As it pertains to AGMPs, the main focus in this realm is the ventilation of the space in which AGMP is being performed, with the underlying understanding that particles can be carried long distances by air currents and thus be distributed widely throughout a unit. For standard hospital rooms, the American Society of Heating, Refrigerating and Air-Conditioning Engineers (AHSRAE) and Canadian Standards Association (CSA) have made recommendations around minimum requirements to appropriately ventilate rooms. A variety of other recommendations have been made pertaining to ventilation, including increasing percentage of outdoor air supply to the system, limiting demand-controls on the ventilation to minimize decreases in airflow, ensuring that outflow of air is not impeded, improving exhaust, and increasing the air exchanges in a room [71]. Understanding any given room's air exchanges per hour via air balancing will also help define fallow times for specific rooms – that is, periods where risk is elevated due to lingering aerosols, while the ventilation is clearing out infected particles. This will allow proceduralists to plan for when the next patient may enter the room to avoid exposure to suspended aerosols generated by the previous patient.

Using a negative pressure room has also become standard for certain high-risk AGMPS, with the rationale being the decreased contamination of areas outside the room where the procedure is being performed [13]. In the absence of negative pressure rooms, using single bedrooms with closed doors helps to minimize exposure to other patients and other staff in other spaces on medical units. Barring this, the use of a barrier may be considered when emergent AGMPs need to be performed in settings where other patients and staff may be exposed. Portable HEPA filters have also been proposed as a mitigation strategy, although the evidence supporting these measures is limited. Their value may be greatest in nonacute medical settings where AGMPs are performed and are therefore not designed to evacuate suspended aerosols [72].

The next level of control measures is administrative. These include having the most experienced staff perform the AGMP to minimize complications and time of exposure. Furthermore, minimizing the number of people in the room during the procedure is also an easily implemented measure. For elective AGMPs such as outpatient bronchoscopy and dental procedures, patient pre-visit screening or testing can help avoid performing AGMPs on patients with potentially infectious pathogens [73]. Designating specific rooms or times of the day for such procedures can also reduce exposure to staff and other patients.

Other administrative controls are targeted at specific AGMPs. For example, during the use of nebulizers, employing a tent around the nebulized medication can decrease droplet contamination [74]. For intubation, applying a viral filter is recommended after the procedure is completed in order to decrease environmental contamination [75]. Renewed interest in dental procedures as AGMPs arose out of the COVID-19 pandemic, with multiple bodies making recommendations on reducing aerosol generation by avoiding the use of ultrasonic hand instruments, three-way syringes, and high-speed handpiece, if possible [76]. In the use of HFNC, a surgical mask appears to be protective in reducing droplet generation [77].

Finally, PPE provides the last line of defense after all other measures have been put in place to protect staff. Specifically, the use of filtering facepiece respirators such as FFP2, FFP3, or N95 type respirators has been emphasized by various guidelines [37]. These are the mainstay of protection against aerosol inhalation for HCWs (most cited National Institute for Occupational Safety and Health respirators used in healthcare settings being N95, while the European Norms commonly used respirator is the FFP3 respirator). Though N95 respirators have shown no superiority to surgical masks in non-AGMP and non–airborne-transmitted infections [78], they are believed to better protect staff when aerosols are present due to their superior airborne particle filtration and superior fit. In laboratory simulated conditions, N95s have been shown to block particles <5 um laden with influenza virus [79]. The same study also demonstrated that surgical masks performed as well as poorly fitted respirator masks. In the most comprehensive review of its kind, use of N95 respirators did not appear to have increase protection against MERS during AGMP (RR = 0.45 (0.16–1.29), $p = 0.16$)) but covering the mouth and nose using any type of mask did [50]. Wearing a complete hood, as in the use of a PAPR, has also been shown to be totally protective during bronchoscopic intubation with patients with COVID-19 [80]. Face shields also demonstrate efficacy in reducing exposure to aerosols [79, 81]; however, it should be noted that this PPE is standard for patients who have suspected or confirmed respiratory infections, and therefore does not change the PPE recommendation for AGMP (which also includes donning a full waterproof gown and gloves [13]).

Conclusion

The understanding of AGMPs has rapidly expanded over the last year due to renewed interest triggered by the onset of the COVID-19 pandemic. Although there are still controversies about what precisely an AGMP constitutes, to what degree it augments the risk of transmission, and what interventions are necessary to reduce that risk, significant progress in the last year has been made to help clarify some of these issues.

Future research should investigate the degree of aerosol generation for some of the procedures with less agreement – including nebulized medical therapy, high flow oxygen, and upper airway suctioning. More studies are also required to determine the benefits of some commonly used mitigation strategies, such as the use of portable HEPA filters. Given persistence of COVID-19 and the possibility of new viral pandemics, understanding the risks of procedures, which are routinely performed in hospitals, will be critical to optimize resource allocation (such as PPE and negative pressure isolation rooms) and protect patients and HCWs.

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