# Common Approaches to the Control of Multidrug-resistant Organisms Other Than Methicillin-resistant *Staphylococcus aureus* (MRSA)

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**KEYWORDS**

- Multidrug-resistant organisms
- Vancomycin-resistant enterococcus
- Multidrug-resistant gram-negative infection
- *Clostridium difficile*

Curbing the spread of antibiotic resistance is one of the greatest challenges in health care today. Infections caused by multidrug-resistant organisms (MDRO) such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and vancomycin-resistant enterococci (VRE) are estimated to result in 12,000 deaths and 3.5 billion dollars in excess health care costs in the United States each year.[1] Multidrug-resistant bacterial infections are a growing problem. Surveillance studies of infections in intensive care units (ICU) demonstrate a 47% increase in *Klebsiella* species resistant to third-generation cephalosporin and a 12% increase in VRE from 1999 to 2003.[2] However, drug resistance in human pathogens is by no means new; penicillin-resistant *S aureus* was first isolated only 4 years after the drug became widely available. In the last half century as new antibiotics have been developed, bacteria continue to express new resistance mechanisms to escape them. With this in mind, it is clear that new drug development alone is no panacea. Effective and sustainable strategies to prevent the spread of these potentially lethal pathogens are urgently needed, especially in hospitals and other health care facilities. Although

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a great deal of the literature has focused largely on just 1 pathogen, MRSA, there are several other clinically and epidemiologically significant pathogens for which practical and systematic infection control strategies have been examined.

Resistant strains of *Enterococcus* are a relatively recent discovery, but these strains are now widespread and are associated with significant morbidity and mortality.[3] VRE accounts for 28.5% of ICU isolates of *Enterococcus* in the United States.[2] VRE infection has been associated with increased mortality compared with infection with vancomycin-susceptible strains.[4] Some VRE strains have demonstrated resistance to even the newest antimicrobial options, including linezolid, thus complicating management.[5]

Gram-negative bacterial resistance is a growing problem in American hospitals.[6] Although gram-negative resistance is not new, there has been increased concern recently for multidrug-resistant gram-negative (MDRGN) isolates, specifically those harboring genes for extended spectrum β-lactamases (ESBLs), inducible β-lactamases (AmpC), and carbapenemases. Some of the broadest spectrum antibiotics are rendered ineffective by these resistance mechanisms and unfortunately, few antibiotics to treat gram-negative infections are in development.[7] The results of studies that examine the consequences of MDRGN infections are somewhat conflicting; however in general these infections seem to be associated with increased length of stay, hospital cost, and mortality.[8,9]

*C difficile* is also an important health care–associated pathogen. Although not usually considered to be an MDRO, it has been suggested that the proliferation of this organism may be partly a result of the development of resistance to multiple classes of antibiotics.[10] *C difficile* infection was first reported in the 1970s, and was initially believed to be associated with clindamycin use, however it is now well known that most antibiotics can precipitate *C difficile* disease.[11] *C difficile* is currently the leading cause of infectious diarrhea in hospitalized patients[12] and the incidence is increasing.[13] The mortality associated with *C difficile* infection has also been increasing.[14] More recently, an epidemic strain of *C difficile* has emerged that has increased virulence, adding to the difficulty of controlling this serious infection.[15]

This article focuses on relevant infection control measures for VRE, MDRGN, and *C difficile*. The rationale and available evidence for common control strategies specifically targeting these pathogens are reviewed and opportunities for new research and more effective deployment of existing tools are highlighted. When there is less extensive evidence available from the published literature, the experience with MRSA is discussed as it might apply to these other pathogens. (MRSA control is discussed separately elsewhere in this issue).

## RATIONALE FOR COMMONLY USED MDRO CONTROL STRATEGIES

To best appreciate the general approach to MDRO control, it is useful to first review the epidemiologic and biologic underpinnings that inform the strategies that have been developed in the past half century. MDRO prevention measures generally fall into 2 categories: control of transmission and antimicrobial stewardship. Transmission control is focused on preventing the spread of clinically significant pathogens, principally via the contaminated hands of health care workers (HCWs) and the environment (particularly contaminated surfaces and equipment). In 1938 a landmark paper categorized the microflora of human skin into transient and resident flora.[16] Resident flora are found mostly on nonexposed skin, and represent a fairly stable population of low virulence organisms. Resident flora are difficult to remove through hand washing and are generally not spread through routine contact with patients or the environment. In

contrast, transient flora tend to be found on exposed skin and have been associated with health care–associated infections. These transient bacteria are generally picked up through contact with contaminated surfaces and are much more easily removed by hand hygiene. The hands of HCWs have been implicated in the spread of hospital-acquired infections, including those caused by MDRO, in several reports including point prevalence surveys, laboratory models, and particularly in epidemics and clusters.[17] Even in cases in which HCW are colonized with resistant pathogens (including those from whom MRSA can be isolated from nasal swabs), the hands represent the most common and potentially most effective means by which to transfer such pathogens to vulnerable patients.

Although hand hygiene is the cornerstone of transmission control, additional measures are necessary for many serious health care–associated pathogens. An increasing number of well-designed studies have demonstrated a potentially important role for the transmission of such pathogens on inanimate objects, including the clothing and personal equipment of HCWs. In these studies, pathogens have been recovered from physicians' white coats, pagers, and cell phones.[18–20] In addition, MDRO have been cultured from environmental surfaces such as sinks, bedrails, and ventilator water (**Table 1**).[21] Health care–associated pathogens have been found to persist for months on inanimate surfaces.[22] The consequence of contamination of inanimate surfaces was highlighted in a recent retrospective study by Huang and colleagues.[23] They showed that a patient admitted to a hospital room previously occupied by a patient with MRSA or VRE were themselves at increased risk for MRSA or VRE infection. With this in mind, it is recommended that patients with MDRO be isolated and their health care providers use barrier protection with gowns and gloves. This is necessary to prevent the HCW from contaminating hands and clothing by coming in contact with an infected or colonized patient and to decrease the potential for the HCW to come in contact with contaminated surfaces in the patient's rooms.

Complimenting transmission prevention as a tool for MDRO control is antimicrobial stewardship. Fundamentally, it has been recognized that antibiotic use, and particularly misuse and abuse, is the primary precipitant to the emergence of antimicrobial resistance. Exposure to antibiotics has been shown in animal models to increase the risk of colonization with resistant bacteria including VRE and ESBL-producing organisms.[24,25] Given that at least one-third of patients admitted to the hospital will be treated with a course of antibiotics, opportunities for inappropriate use abound.[26] One study documented antibiotic misuse in 37.4% of hospital prescriptions.[27] The effect of antimicrobial exposure does not just affect the individual taking the drug but also has been shown to increase the risk of MDRO colonization among close contacts.[28] By addressing these issues, stewardship programs that promote judicious antimicrobial use can have a major effect on MDRO control. Antimicrobial stewardship is discussed in detail elsewhere in this issue.

**Table 1**
**Environmental sampling**

| Inanimate Objects from Which MDRO have been Recovered | | | |
|---|---|---|---|
| **MRSA** | **VRE** | **MDRGN** | ***C difficile*** |
| Pagers[18]<br>White coats[19]<br>Blood pressure cuffs[110] | Stethoscopes[58] | Bedrails, sinks, ventilator water[21]<br>Computer keyboards[109] | Bed frames[108] |

## EVIDENCE OF EFFECTIVENESS FOR SPECIFIC MDRO CONTROL STRATEGIES

### *Hand Hygiene*

Hand hygiene has been recognized as an essential element of infection control for more than a century. The potential benefit of hand hygiene was first documented by Semmelweis in his initial reports on childbed fever in 1846.[29] As is true for many of the strategies discussed in this article, some of the best evidence for the effectiveness of hand hygiene in MDRO control comes from the experience with MRSA. In 2000 Pittet and colleagues[30] instituted a multidisciplinary hospital-wide program to improve hand hygiene. They documented an improvement in hand hygiene adherence from 48% to 66%, but most impressively they demonstrated a 50% reduction in the incidence of MRSA transmission.

More recently, alcohol-based hand rubs (ABHR) have been promoted for hand hygiene. In some studies they have been found to be more effective than soap and water and have been definitively shown to increase HCW adherence to hand hygiene standards.[31,32] Although there is not an extensive body of literature on ABHR for control of all MDRO, it is reasonable to believe that they would be as effective for these organisms as for other pathogens (with the exception of *C difficile*, discussed later). Consequently, ABHR promotion should have a role in any comprehensive infection control program. Hand hygiene is discussed in detail elsewhere in this issue.

### *VRE*

VRE can easily pass onto HCW hands and then contaminate another environmental surface or the patient, sustaining the cycle of transmission.[33] In a recent study, VRE was found on 52% of those HCWs who touched only the environment and 70% of those who touched the environment and the patient.[34] In epidemiologic studies, VRE has been documented on the hands HCWs between 13% and 41% of the time[35] and can persist on the hands for at least 60 minutes.[36] VRE is successfully removed from hands with soap and water and with ABHRs.[36,37]

The specific effect of hand hygiene on VRE transmission has been examined in mathematical models and has been suggested to be an essential element of a comprehensive infection control program.[38] However, according to at least 1 model, the effect is dependent on compliance rates greater than 50% which, unfortunately, may be difficult to sustain in many centers. The effect of hand hygiene on VRE transmission was measured in a 2-hospital observational study completed in 2000.[39] Interventions at the study hospital focused on changing organizational culture to increase hand hygiene adherence. The other hospital served as a control. During the study period, hand hygiene adherence increased at the intervention hospital significantly. Simultaneously, the incidence of VRE infections decreased by 85% at the intervention hospital compared with a decrease of 44% at the control hospital.

### *MDRGN*

Like VRE, gram-negative organisms can commonly be found on environmental surfaces as well as on the hands of HCWs. Gram-negative pathogens seem to survive longer on inanimate objects than on hands.[40] However, they have been shown to be carried persistently on the hands of 21% of HCWs.[41] Wearing artificial fingernails has also been shown to increase the risk of carriage of gram-negative organisms among HCWs.[42]

The specific role of hand hygiene in controlling the incidence of MDRGN infections has not been as extensively studied as for the other pathogens discussed here. An outbreak of multidrug-resistant *Pseudomonas aeruginosa* in Germany was controlled with the implementation of strict hand hygiene, together with enhanced deployment of

isolation precautions.[43] In contrast, an improvement in hand hygiene adherence did not result in a decrease in MDRGN infection or colonization among neonatal ICU patients in a resource-poor setting with very high rates of MDRGN colonization.[44]

### *C difficile*

Like VRE and MDRGN, *C difficile* has been recovered from the hands of HCWs and can transfer between HCW hands and patients.[45] *C difficile* can be distinguished from the other pathogens discussed in this article by its capacity to form spores. This has significant implications for transmission control strategies in general and for hand hygiene in particular. Antiseptic hand rubs and antimicrobial soaps are not effective against *C difficile* because they lack sporocidal activity.[46] Physical removal of spores by washing with soap and water has been shown to be the best way to clean hands after caring for a patient with *C difficile*.[47] Not surprisingly, studies have shown little effect on *C difficile* infection rates after the introduction of ABHRs even when they decrease the rate of other health care–associated pathogens.[48,49] However, it is equally important to note that the widespread use of ABHRs does not seem to increase the incidence of *C difficile* infection.[50] This could be because increased awareness of the importance of hand hygiene through promotion of ABHR might also enhance the likelihood of using soap and water.

An effective hand hygiene campaign against *C difficile* should include an intervention to educate HCWs on the importance of using soap and water when caring for those patients with *C difficile* infection. This was illustrated in a study by Abbett and colleagues[51] in which a central element of the intervention program was promotion of soap and water as primary hand hygiene after care of a patient with *C difficile*. Implementation of the program was accompanied by a significant decrease in the incidence of *C difficile* infection. Recent guidelines have recommended hand hygiene with soap and water for *C difficile* particularly in epidemic settings.[52]

## *Isolation Precautions and Personal Protective Equipment*

Isolating people with serious infections from healthy individuals is one of the oldest forms of infection control. The Old Testament documents the practice of isolating those with leprosy from the general population and more recently, in the late nineteenth and early twentieth centuries, isolation of patients with tuberculosis was viewed as one of the few effective methods to curb spread.[53] Modern medicine has moved away from isolating patients from society and instead isolation precautions have been integrated into routine hospital care to prevent propagation of resistant or highly infectious pathogens. One key element of isolation precautions in the hospital is the use of personal protective equipment. It has been shown that HCWs who don gloves during patient encounters have a significantly decreased risk of hand contamination.[54] Jernigan and colleagues[55] showed that when patients were not placed in precautions (gowns and gloves), the transmission rate of MRSA to uncolonized patients was 0.14 transmissions per day. In contrast, when patients were cared for using isolation precautions the transmission rate was significantly lower (0.009 per day). Although these methods have been widely applied and endorsed by expert authorities, the overall evidence in support of isolation precautions remains somewhat lacking. A 2004 systematic review of the literature concluded that there was insufficient evidence supporting a benefit of isolation precautions in controlling MRSA, largely as a result of a lack of well-designed studies.[56] Isolation precautions and specifically the use of personal protective equipment for control of VRE, MDGRN, and *C difficile* are discussed in detail later.

### *VRE*

Current guidelines recommend contact isolation for patients with VRE.[26,57] However, as was the case for MRSA, there are few large, well-executed, controlled trials of VRE and contact isolation. Nonetheless, there is a significant amount of circumstantial evidence in favor of wearing gowns and gloves to prevent VRE transmission. One study documents contamination of gloves, gowns, or stethoscopes after 67% of encounters with a patient with VRE[58] and gloves have been shown to reduce the risk of contamination of hands with VRE by 71%.[59] As has already been noted, VRE contamination of a patient's room can also be an important risk for transmission.[23]

Most specific evidence for the effectiveness of contact precautions to prevent VRE acquisition comes from intervention studies and particularly from the experience with outbreaks. However, nearly all successful intervention studies enforced contact precautions along with active surveillance and antibiotic restriction, which makes it difficult to determine the specific contribution of contact isolation to overall effectiveness.[60–63]

The relative contribution of gowns versus gloves in preventing the transmission of VRE has also been evaluated separately. Srinivasan and colleagues[64] examined the incidence of hospital-acquired VRE in an ICU. There was a significant increase in the acquisition of VRE when HCWs were encouraged to wear only gloves and not gowns. In the same year Puzniak and colleagues[65] also showed that acquisition of VRE in a medical ICU was higher during a no gown period. Overall the evidence suggests that the use of both gowns and gloves are important in the prevention and control of VRE.

### *MDRGN*

There are a relatively few studies that specifically support the use of contact precautions in decreasing the incidence of MDRGN. French investigators demonstrated an increase in the incidence of infection with *Acinetobacter* spp during a period in which the use of contact isolation was discontinued.[66] After reinstituting the practice, the incidence of *Acinetobacter* infections returned to baseline. When infection control measures, including isolation and contact precautions, were instituted at a Canadian hospital, the incidence of health care–associated infections caused by ESBL-producing organisms remained stable despite an increase in ESBL-producing organisms in the surrounding region.[67] In contrast with these findings, a Belgian study showed that instituting contact precautions during an outbreak of infections with ESBL-producing *Klebsiella* spp had little effect.[68] The outbreak was only contained once additional measures were instituted, including room decontamination, restriction of broad-spectrum antibiotics, and creation of patient cohorts with dedicated nursing.

Despite the uncertainly of the relative effectiveness of contact precautions for controlling the spread of MDRGN, the continued application of these measures is likely justified by the lack of alternatives. As has already been noted, antibiotic treatment options are limited for MDRGN, and as new resistance mechanisms emerge these options will continue to dwindle. A conservative approach that attempts to limit the spread of these potentially lethal pathogens is appropriate, even while additional confirmation of effectiveness is sought.

### *C difficile*

Current guidelines recommend that patients with diarrhea who are known or suspected to have *C difficile* infection should be placed under contact precautions.[69] Several studies support this approach. A before-after intervention study in 1998 showed that with institution of infection control measures including contact

precautions, the incidence of *C difficile* dropped significantly, by 60%.[70] Unfortunately without a control group it is difficult to separate the effect of contact precautions from other concurrent interventions. In 1990 a prospective controlled trial evaluated the effect of universal glove use while caring for all patients on the incidence of *C difficile*. On wards where glove use was instituted, incidence fell significantly from 7.7 *C difficile* infection cases per 1000 discharges to 1.5 per 1000 but remained unchanged on the control wards.[71] More recently, Salgado and colleagues[72] described their experience with an outbreak of *C difficile*. By instituting several infection control strategies including isolation for patients with suspected *C difficile* and targeted hand hygiene with soap and water, they observed a decrease in incidence of *C difficile* infection of 45.3%.

Although randomized controlled trials regarding the specific benefit of contact isolation for *C difficile* are for the most part lacking, the available evidence still generally supports barrier precautions for reducing horizontal spread. However, it remains to be seen which measures are the most important at reducing transmission.

#### *Limitations to isolation and contact precautions*

Even when successful at preventing the spread of disease, the isolation of patients should not be viewed as an entirely benign procedure. Several studies have highlighted the potentially negative effects of patient isolation. Stelfox and colleagues[73] found that several quality of care measures for patients who are in isolation precautions are significantly worse than for those who are not. In addition, patients on precautions may be more likely to experience signs and symptoms of depression and anxiety.[74] These are serious consequences that must be weighed against the potential benefit of isolation precautions and carefully considered when formulating hospital-wide infection control policies.

### *Active Surveillance*

Recently, considerable attention has been focused on the usefulness of active surveillance, in which patients are screened for carriage of MDRO, as an important adjunct to the transmission control strategies already introduced. What remains uncertain is the relative benefit of this approach for the range of MDRO commonly encountered in the hospital setting. Ultimately, the overall effectiveness of these basic measures is limited by the ability to detect all those patients who are colonized or infected with MDRO. One useful way to examine this limitation is by calculating the undetected ratio, which is the proportion of patients not identified by routine clinical cultures among all those who are colonized or infected.[75] The greater the proportion, the greater usefulness of active surveillance to detect colonized individuals who could be a reservoir for transmission. For MRSA, studies have found this proportion to be as low as 30% and as high as 90%.[75] Despite the wide range of these estimates, targeted surveillance for MRSA has been successful in helping to control this organism in many settings (**Table 2**). Routine surveillance in the ICU accompanied by the implementation of appropriate precautions has been shown to effectively reduce MRSA bacteremia by 75%.[76] Universal hospital surveillance of MRSA has also been shown to decrease overall incidence.[77] Although the effectiveness of surveillance has largely been confirmed for MRSA (and is discussed in detail elsewhere in this issue), this is not the case for all MDROs, as is summarized in the following sections.

#### *VRE*

VRE poses a unique challenge because of the very high undetected ratio associated with the organism.[78] Put another way, many more patients are colonized than clinical

**Table 2**
**Evidence for efficacy of active surveillance**

| | MDRO | Level of Surveillance |
|---|---|---|
| Ostrowsky et al[62] | VRE | Region |
| Bode et al[111] | MRSA | Patient |
| Robicsek et al[77] | MRSA | Single hospital |
| Calderwood et al[112] | VRE | Single hospital ward |
| Huang et al[76] | MRSA | Single intensive care unit |

cultures would detect. Finding and isolating those colonized patients may be an important part of VRE control. Byers and colleagues[79] found that unprotected proximity to a patient with VRE was a significant risk factor for VRE acquisition but proximity to a patient colonized with VRE who was isolated was not.

Price and colleagues[80] compared the incidence of VRE at 2 hospitals, 1 that used active surveillance and 1 that did not, and showed that VRE bacteremia was significantly less common in the surveillance hospital. Ostrowsky and colleagues[62] documented an initiative to control VRE in a 3-state area through active surveillance and isolation. They were successful at decreasing incidence of VRE from 2.2% to less than 1% in only 2 years. Because of the strong evidence in support of active surveillance for VRE, organizations such as the Society for Healthcare Epidemiology of America (SHEA) recommend active surveillance for those at high risk for colonization.[26] The decision whether or not to deploy an active surveillance program for VRE should be primarily influenced by the overall burden of disease (in terms of incidence and clinical consequences) at a given institution.

***MDRGN***

Although most hospitals have not used active surveillance as a routine control strategy for MDRGNs, some studies have tested the feasibility of this approach. One obstacle to screening for MDRGNs is the heterogeneity of the various organisms involved in terms of microbiological characteristics and even the epidemiology of colonization and infection. Strategies such as the use of selective media for screening surveillance specimens have been used to try to isolate only relevant organisms.[81] Another approach is to use molecular testing. There are polymerase chain reaction (PCR) protocols for *Klebsiella pneumoniae* carbapenemase (KPC)- and ESBL-producing organisms but these are each specific for one type of MDRGN. Deciding which MDRGN to address and how to target it is a daunting first step in the surveillance of MDRGN. Specific MDRGNs can be targeted individually. For example, the Centers for Disease Control has suggested point prevalence surveillance if a single case of a KPC-producing organism is detected at a hospital.[82]

As with VRE, many studies of MDRGN surveillance have been performed to better understand the epidemiology so that appropriate infection control strategies can be implemented. Other studies have been specifically designed to determine if MDRGN surveillance can help clinicians choose appropriate empirical antibiotic therapy. Papadomichaelakis and colleagues[81] performed biweekly surveillance cultures of ICU patients and found that there was good concordance between MDRGN detected by active surveillance and the causal organisms in ventilator-associated pneumonia and blood stream infections. There was a significantly increased rate of appropriate empirical antibiotic therapy in those who underwent active surveillance screening.

Other studies of active surveillance for MDRGN have provided mixed results. Gardam and colleagues[83] instituted an active surveillance program for

Enterobacteriaceae only to find that almost all isolates were genotypically unique and it was unlikely that there was any horizontal spread. They concluded that the costs of such a program outweighed any potential benefit. Currently there are no specific recommendations to survey for MDRGN on a routine basis, only in the case of an outbreak.

#### *C difficile*

The epidemiology of colonization with *C difficile* remains an area of intense study and considerable uncertainty. At least 1 study has found that colonization may actually be associated with a decreased risk of symptomatic disease.[84] Nonetheless, carriers of *C difficile* can still serve as a reservoir for health care–associated spread of *C difficile* and prevalence of asymptomatic carriage can be as high as 20% of inpatients.[85] Given these conflicting findings, and the challenges of interpreting and acting on the results of such an active surveillance program, active surveillance has not been recommended for *C difficile* in any recent guidelines.

#### *Limitations to active surveillance*

Because the effectiveness of active surveillance for MDRO control depends on more stringent deployment of basic practices such as isolation precautions, even an effective program may be associated with the same issues regarding patient safety and satisfaction associated with isolation precautions that were discussed in the preceding section. However, there are also several potential downsides that are unique to active surveillance. Patients may believe that they are being unfairly labeled, especially if without routine active surveillance they would not have been put in isolation.[86] Other practical concerns exist. For example, implementation of precautions for a large number of patients may disrupt patient flow between units and facilities, and could conceivably strain the capacity of some institutions in terms of staffing, laboratory resources, and patient bed spaces.

### *Antimicrobial Stewardship*

Considering the growing number and incidence of antimicrobial-resistant pathogens and the increasingly limited range of antibiotic agents available to treat them, one of the most crucial MDRO control strategies is the rational use of currently available antibiotics. The fundamental goal of antimicrobial stewardship is to promote the selection of antimicrobial therapy that will treat infection, at the same time avoiding toxicity as well as the risk of emerging resistance.[87] Considerable economic benefits have also been reported in many cases as a result of decreased drug acquisition and administration costs as well as the avoidance of expenses related to monitoring and adverse events. Two of the most basic approaches to antimicrobial stewardship, prospective auditing/feedback and preauthorization, are discussed here in the context of MDRO control. A more detailed discussion of the subject is provided elsewhere in this issue.

Antimicrobial stewardship has been used in the hospital setting for decades.[88] In a 1988 study of streamlining therapy, the investigators found that for 54% of cases for which narrower coverage was recommended, the change was adopted by providers more than 80% of the time. This led to total cost savings of about 40,000 dollars. As early as 1974, McGowan and Finland[89] described a system of restricting new and costly antibiotics. They showed that by requiring physicians to contact an infectious diseases consultant before prescribing restricted agents they were able to substantially decrease the use of these drugs. A more recent addition to these approaches uses computerized decision support. By moving the stewardship function to the computerized record, it becomes easier to reach the physician at the time the

clinical decision is being made. These programs have been shown to decrease costs associated with antimicrobials and decrease excess antibiotic use.[90]

In the subsections that follow, the specific rationale and evidence for the usefulness of stewardship in curbing the spread of VRE, MDGNR, and *C difficile* are discussed.

### *VRE*

Not surprisingly, exposure to vancomycin has been commonly linked to subsequent VRE acquisition. However, a meta-analysis of epidemiologic studies found that although there was a small effect of vancomycin on infection or colonization with VRE, the association was not statistically significant once adjusted for confounding factors.[91] It is not at all clear that limiting vancomycin use alone will decrease VRE incidence. A review of the literature in 2007 examined all randomized controlled trials or quasi-experimental studies that documented a decrease in vancomycin use.[92] The investigators concluded that it was impossible to determine the specific role of vancomycin usage in preventing VRE colonization or infection as a result of conflicting data. Vancomycin is not the only antibiotic that has been linked with VRE. In a study by Smith,[93] a decrease in VRE was observed after the institution of a hospital-wide initiative to decrease cephalosporin use. In another study, third-generation cephalosporin use was found to be significantly associated with risk of VRE acquisition.[94] However, in this same study, when the prevalence of VRE colonization was greater than 50%, the effect of cephalosporin use on time to VRE acquisition was negligible. Restricting the use of certain antimicrobials is certainly part of a comprehensive infection control strategy for control of VRE infection, however in hospitals where colonization rates for VRE run high, antibiotic stewardship may not be as effective in curbing the spread of VRE.

### *MDRGN*

Several studies show the benefit of restricting antibiotic use to help decrease the incidence of MDRGNs. In 2000, a cross-over study performed in 2 neonatal ICUs showed that when empirical sepsis coverage with amoxicillin + cefotaxime was enforced, rates of resistant gram-negative colonization were significantly higher than when penicillin + tobramycin was used.[95] Another study looked at an outbreak of ceftazidime-resistant *Klebsiella* spp, which was believed to be associated with increased ceftazidime use.[96] By implementing ceftazidime restriction and other infection control measures the investigators documented a 60% reduction in resistant isolates.

The experience with antimicrobial stewardship in control of MDRGN has highlighted the difficulty in controlling resistance in the hospital setting. Although restricting 1 class of antibiotics can decrease the incidence of bacteria resistant to that class it often results in an increase in resistance to the alternative agent. A study by Rahal and colleagues[97] highlighted this difficulty. A program intended to decrease cephalosporin resistance in *Klebsiella* spp by restricting cephalosporins had the unintended consequence of increasing carbapenem resistance by indirectly encouraging the use of this class of antibiotic. Despite these challenges, antimicrobial stewardship can be important for MDRGN control. With dwindling therapeutic options, it is prudent to try to limit use of broad-spectrum antibiotics whenever possible to retain those antibiotics for use when others have failed.

### *C difficile*

Because *C difficile* in the hospital is usually associated with antibiotic use, one of the most important strategies to decrease the incidence of *C difficile* is to limit unnecessary use of antibiotics. The most convincing evidence for stewardship in general is probably for the control of *C difficile*. Several reports highlight the potential importance of limiting unnecessary antibiotic use, even without regard to the restriction of specific

classes. In a report of a severe outbreak of *C difficile* Polgreen and colleagues[98] found that of the patients with *C difficile* who had been given antibiotics for pneumonia, 50% did not have evidence of lung infection. In this case, excessive antibiotic use may have contributed to avoidable infection and death.

Although an overall decrease in antibiotic exposure might be of greatest benefit, limiting the use of specific classes of antibiotics, such as third-generation cephalosporins, has also been shown to decrease *C difficile* incidence. In 2002, Khan and Cheesbrough[99] tracked the incidence of *C difficile* infection when empirical pneumonia treatment was changed from ceftriaxone to levofloxacin. They demonstrated a decrease in the proportion of positive *C difficile* tests from 14.5% to 8.6%. McNulty and colleagues[100] reported on an outbreak of *C difficile* that could not be controlled with transmission control measures. However, when broad-spectrum cephalosporin use was limited and narrower spectrum antibiotics were used, the incidence of *C difficile* decreased significantly. A more recent study by Valiquette and colleagues[101] instituted a nonrestrictive antimicrobial stewardship program to control an outbreak of the hypervirulent strain of *C difficile*, NAP1/027. Their policy included recommendations to decrease the use of second- and third-generation cephalosporins, ciprofloxacin, clindamycin, and macrolides. They found that there was a reduction in the use of targeted antibiotics and, in addition, *C difficile* incidence decreased by 60%. More specific associations between exposure to particular antimicrobial agents and epidemic *C difficile* infection continue to be explored. For example, the NAP1 strain is more likely to demonstrate resistance to certain fluoroquinolones than non-NAP1 strains.[15] A recent study described an intervention to decrease fluoroquinolone use in an outbreak involving the NAP1 strain.[102] By decreasing fluoroquinolone use by 66% the investigators demonstrated a 22% decrease in the percentage of NAP1 *C difficile* isolates. In addition, there was a nonsignificant decrease in the incidence of all *C difficile* strains after this intervention was undertaken.

### *Limitations to antimicrobial stewardship*

Antimicrobial stewardship programs are effective in curbing costs, medical errors, and unnecessary antibiotic use,[88,103] but there have been relatively fewer studies that have convincingly demonstrated a meaningful and sustained decrease in the overall burden of antimicrobial resistance at hospitals that have deployed such programs. In part this limitation is a result of the difficulty in separating out the benefit of antimicrobial stewardship from other interventions initiated concurrently, especially in the setting of an outbreak. In addition, it is possible that limiting antibiotic use in a hospital without simultaneously addressing community antibiotic misuse may fail to have an overall effect on the resistance of isolates in the hospital.[104] It can also be difficult to predict which antibiotics should be restricted to decrease the incidence of a particular targeted organism. For example, prior fluoroquinolone exposure has been found to be a significant risk factor for MRSA acquisition,[105] an association that may not be intuitively clear to many providers. Similarly, as has been noted, cephalosporin use may be more closely associated with the emergence of VRE than even exposure to vancomycin itself. These unexpected relationships may come about through as yet unappreciated molecular phenomena or a more complex interaction between drug, host, and pathogen. However, whatever the cause, the development of rational stewardship recommendations to predictably influence the epidemiology of antimicrobial resistance remains elusive.

## CHALLENGES AND OPPORTUNITIES

The measures described in the previous sections offer considerable promise to clinicians and other stakeholders committed to the control of pathogens such as VRE,

MDRGN, and *C difficile* in the hospital setting. However, it is important to acknowledge several limitations to the interpretation of the evidence that has been presented in support of the effectiveness of the various prevention strategies (**Table 3**). These limitations undoubtedly present a challenge to those responsible for formulating and deploying a rational and cost-effective MDRO control program in both small and large facilities. Simultaneously, recognition of these limitations allows for a more focused and rigorous approach to future investigations to ensure that the beneficial effects of these strategies are maximized across the spectrum of care.

One serious limitation to the available evidence for various MDRO control strategies relates to the design and execution of the studies in which these measures have been tested. One principle issue is that many reports describing the effect of control measures were conducted in the setting of outbreaks and clusters. Fundamentally, the epidemiology (and in some cases the biology and pathogenicity) of a microbe is altered in the setting of an epidemic. As such, it is difficult to know for certain the extent to which the findings of interventions tested in this context can be applied to the control of endemic disease in other settings. MDRO control measures are often deployed (particularly in the setting of an outbreak) in a multimodal fashion in which several separate interventions are implemented simultaneously. Because of this, it is impossible for those reporting the experience to quantify the relative contribution of any 1 specific measure to a successful outcome. Partially as a result of this phenomenon, control measures have frequently been promoted as bundles leaving clinicians to guess as to which elements of the intervention are truly effective and which are no more than a waste of resources. In general, the design and analysis of the intervention studies on which the entire discipline of MDRO control is based remains somewhat lacking. Many investigators continue to rely on relatively unsophisticated study designs (most typically, before-and-after studies) that limit the interpretability and generalizability of findings. Moreover, more sophisticated statistical methods have not yet come into widespread use by many in the infection control field, further hindering definitive analysis and conclusions.

There are more practical and everyday limitations to the available evidence as well. One of the most common (and uncomfortable) challenges to the application of the control strategies described here relates to the continued failure of HCWs to adhere to even basic measures to prevent the spread of infection. This shortcoming has largely been accepted and even acknowledged in the scientific examination of these

**Table 3**
**Limitations to infection control strategies**

| MDRO Control Method | Limitations |
|---|---|
| Hand hygiene | Poor adherence by providers |
| Isolation precautions | Poor adherence by providers<br>Psychological stress for patients<br>Diminished quality of care and safety<br>Diminished patient satisfaction |
| Active surveillance | Psychological stress for patients caused by isolation precautions<br>Disruption in patient and laboratory flow<br>Lack of standardized methods and analysis |
| Antimicrobial stewardship | Poor adherence to policies and standards by prescribers<br>Unintended increase in the incidence of antimicrobial resistance among nontarget MDRO |

strategies. For example, many reports of the effectiveness of hand hygiene in preventing the spread of antimicrobial resistance describe adherence rates of less than 70% after the deployment of an intervention. The lack of adherence to basic measures is compounded when more intensive and sophisticated methods are studied or deployed. For example, although active surveillance programs in part rely on the timely availability of the results of microbiological sampling (often through the use of PCR or other rapid testing methods), the entire effectiveness of this approach absolutely depends on the adherence of providers to more basic practices such as hand hygiene and the use of personal protective equipment. Shortcomings in adherence to these standards will ultimately limit the overall effectiveness of even the most sophisticated control strategy.

Fortunately, these limitations are not unavoidable and there is already ample and growing evidence that the study and practice of MDRO control is moving to a higher level of sophistication. Several investigators and methodologists have championed the use of more rigorous study design and statistical analysis,[106] including the use of more sophisticated measures to determine the cost-effectiveness of MDRO control interventions.[107] Similarly, collaborative studies are pooling the resources and expertise across centers to allow for more rigorous investigation of the epidemiology (and prevention) of endemic disease. It is likely that competition for enhanced federal and private support for investigation into the control of MDRO will promote even greater improvements.

Unfortunately, improvement in adherence to control practices will not come about simply through the use of more sophisticated statistical techniques and multicenter collaborations. However, the opportunity exists to apply the same level and intensity of sophisticated, rigorous, and well-designed investigations to a greater understanding of the barriers that limit the adherence of bedside providers to these critical measures. Reliable research into the diffusion, dissemination, and adoption of best practices will rely on collaboration from many other disciplines than microbiology and clinical infectious diseases including behavioral science, economics, and psychology. Only when the gap between actual and ideal adherence is closed will we be able to truly measure the effectiveness of the tools at our disposal.

## SUMMARY

Antibiotic resistance will continue to be a problem as long as selective antibiotic pressure gives a competitive advantage to resistant strains and contaminated hands pass these strains along to new and vulnerable hosts. Comprehensive infection control strategies are vital. Despite a relative dearth of prospective randomized studies of transmission prevention measures and antimicrobial stewardship for the control of VRE, MDRGN, and *C difficile*, there is a growing amount of evidence supporting specific interventions. It is imperative that the rigorous examination of the performance and consequences of these strategies continue to determine which are the most influential. Given the limits of the available evidence, clinicians and other leaders must continue to balance the benefit of these potentially life-saving strategies against any unintended consequences and the expenses that are associated with their implementation.

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