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Is patient isolation the single most important measure to prevent the spread of multidrug-resistant pathogens?

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Isolation, or cohorting, of infected patients is an old concept. Its purpose is to prevent the transmission of microorganisms from infected or colonized patients to other patients, hospital visitors and health care workers, who may subsequently transmit them to other patients or become infected or colonized themselves. Because the process of isolating patients is expensive, time-consuming, often uncomfortable for patients and may impede care, it should be implemented only when necessary. Conversely, failure to isolate a patient with multidrug-resistant microorganisms may lead to adverse outcomes, and may ultimately be expensive when one considers the direct costs of an outbreak investigation and the indirect costs of lost productivity. In this review, we argue that contact precautions are essential to control the spread of epidemic and endemic multidrug-resistant microorganisms, and discuss limitations of some available data.

Historical Background

The term "isolation" in infectious diseases refers to the possibility to separate infected (or suspected to be infected) people from other subjects not affected by the disease, a concept practiced in many ancient societies.[1] Around seven hundred years ago, the strategy of "quarantine" was introduced, originating from the Italian *quaranta giorni*, meaning "forty days": the 40-d isolation of ships prior to entering the harbor of Dubrovnik, as a measure to prevent the spread of plague. Other infectious diseases (e.g., leprosy and cholera) lent themselves to the practice of quarantine.[2] Although the concept was crystal-clear, implementation was never easy, even before the emergence of antibiotic resistance. For instance, after the promulgation of the first Quarantine Act (1710), the protective practices in England remained unsystematic for many years. After an international sanitary convention was concluded in Paris in 1912, the strict quarantine doctrine for ships was abandoned, an approximation to the principles advocated by Great Britain due to economic considerations.[2]

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Although leprosy hospices were part of many cities in medieval Europe, isolation in healthcare facilities was practiced only inconsistently during the past centuries. This changed completely in the 20th century with the recognition of bacterial and viral pathogens as vehicles of spread of infectious diseases. The emergence of *Staphylococcus aureus* as a hospital pathogen in the 1950s and 1960s prompted the development of infection control programs in US hospitals. In 1968, the first edition of the American Hospital Association's manual presented a simple scheme of barrier precautions for patients with communicable diseases, listing the need for gloves, gowns, masks and visitor screening.

Definitions

Nowadays, the concept of "patient isolation" has been much refined. The Centers for Diseases Control and Prevention (CDC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) updated in 2007 a previous guideline and developed a two-level system for isolation precautions:[3] standard precautions (SP), which apply to all patients, and transmission-based precautions (contact, droplet and airborne), put in place for patients with suspected or proven colonization or infection with certain microorganisms at risk of spreading. Neither SP nor droplet or airborne precautions among those transmission-based precautions will be reviewed in detail, but the definitions of SP and contact precautions (CP) are herein summarized.

SP combine the major features of universal precautions [designed in 1987 to initially prevent HIV transmission and one year after, hepatitis B virus and other bloodborne pathogens transmission, to the healthcare workers (HCWs)] and body substance isolation (designed in 1987 to prevent pathogen transmission from moist body surfaces to the HCWs).[4] SP apply to all patients, regardless of suspected or confirmed infection status, in any setting in which health care is delivered: they include the performance of hand hygiene according to pre-specified guidelines, use of personal protective equipment, respiratory hygiene/cough etiquette, safe injection practices, use of masks for catheter insertion and lumbar puncture procedures, safe handling of contaminated equipment, textiles and laundry and routine cleaning and disinfection of environmental surfaces.[3] Avoiding the exposure to potentially infectious sources such as blood, wounds, mucous membranes and excretions is the primary goal of SP.

Transmission-based precautions, and CP among those, apply only to some patients, are more restrictive and often require physical patient isolation.[3] The application of such precautions requires that gowns and gloves should be worn when entering the patient's room and removed before leaving it. Dedicated equipment such as stethoscopes or blood pressure cuffs should remain in the isolation room and not be used for other patients. If supported by the hospital and laboratory information systems, electronic alerts that notify admitting personnel of patients who were colonized/infected with a resistant pathogen on a previous admission can help expedite isolation of patients.[5] CP may include single-room isolation, an entire isolation ward, or cohorting of a group of patients (with or without designated staff). CP are aimed at preventing transmission of epidemiologically important pathogens from a colonized or infected patient through direct (the patient) or indirect (surfaces or objects in the patient's environment) contact. Contact isolation is mostly indicated for patients colonized or infected with multidrug-resistant microorganisms (MDRO) that have a high risk of exogenous cross-transmission, such as methicillin-resistant *S. aureus* (MRSA) or vancomycin-resistant enterococci (VRE). These guidelines stipulate that patients colonized or infected with clinically important MDRO should be isolated during hospitalization, to prevent nosocomial MDRO transmission from carriers to other patients, hospital visitors and HCWs.[3] Together with hand hygiene, appropriate CP measures are sought to be of the utmost importance to decrease the risk of MDRO transmission in various health care settings.

Several interventions and strategies that have been documented in the literature as being successful in the prevention and control of MDRO transmission have been recently reviewed.[6] Whereas it is unclear which bundles of interventions are effective, there is a clear suggestion that multiple simultaneous interventions can be effective in reducing MDRO infections. Among these, continued educational programs including feedback to HCWs are important tools to improve compliance with hand hygiene,[7] SP and CP.[8,9]

Methodological Limitations

Although isolation measures are based on the current understanding of the mechanisms of transmission of organisms, few data are available to demonstrate their efficacy. First, mathematical models of transmission have allowed predictions about the effectiveness of various interventions that would be difficult or impractical to study in large clinical trials.[10-12] Because healthcare-associated infections are relatively uncommon events, any study designed to demonstrate efficacy requires samples sizes that are often prohibitively large. Thus, studies evaluating the efficacy of isolation measures often lack the power to allow one to conclude confidently that there has been a lack of effect. Second, many clinical studies were conducted during epidemics while the majority of hospitals confronting these pathogens now face endemic resistance; the epidemiology of MDRO and the effectiveness of control measures are different in these two situations. Third, most studies implemented multiple interventions either simultaneously or sequentially, making it impossible to determine which were linked to the outcome. Which of the following components is critical for successful control may therefore not be obvious:

- identifying an at-risk patient;
- obtaining a specimen for culture or PCR;
- testing the specimen for multi-resistance;
- providing the nurse or physician with the result;
- placing the patient in a private room or cohorting the patient with other carriers;
- posting signs indicating that the patient is in isolation;
- stocking the patient's room with isolation supplies;
- requiring visitors and HCWs who care for the patient to wear gloves and gowns;
- enforcing strict hand hygiene;
- providing for adequate environmental hygiene, including waste removal.

Fourth, most of the information available comes from quasi-experimental studies that may have failed to take into account stochastic or secular changes, that did not adequately control for bias or confounding, or that may have had very short periods of follow-up.[13] Fifth, in studies of infection control interventions that require the active participation of HCWs in a clinical setting, such as studies of the effect of contact isolation on acquisition of colonization by a MDRO, compliance monitoring was rarely performed. Studies that did monitor compliance often found it to be poor, raising questions about the validity of the causal inferences made by the authors. Finally, the reason for the success of isolation measures is not known definitively. The outcome could be related to improved hand hygiene and decreased transmission, a positive intended effect, or to fewer HCW contacts with colonized or infected patients, an unintended effect with potentially negative consequences.[14-16]

Another limitation on the effectiveness of CP to stop cross-transmission of MDRO is due to epidemiological differences among MDRO themselves. The location of the MDRO in the host [mainly anterior nares and skin for MRSA; gastrointestinal tract for VRE and multidrug-resistant Gram-negative bacteria (MDR GNB)], the amount of MDRO, their propensity to spread in the environment and their survival in the environment can help to explain the various effectiveness of SP and CP reported in the literature.[17]

Current Controversies

Despite historical experiences and sound plausibility, the routine use of CP to prevent MDRO transmission remains controversial. Although most experts would agree that patients with purulent discharge of MRSA from wounds or with VRE-positive diarrhea, indeed, would require single-room isolation and CP to prevent the spread of the pathogen, it remains unclear whether patients only colonized, rather than infected, with those MDROs should be subject to isolation. Yet another unresolved question is whether colonized patients should be identified by active screening and isolated to prevent or minimize transmission to other patients. Given the lack of high-quality evidence, current practices are variable: some institutions carry out selective surveillance and

isolation of patients, whereas other institutions isolate only patients diagnosed with infections caused by these pathogens. Moreover, existing evidence supports infection prevention and control interventions as cost effective in decreasing transmission of MRSA and VRE in Intensive Care Units (ICUs),[18] but there remains skepticism on whether these measures are cost-effective or even detrimental to the quality of patient care in non-ICU wards.[19] For instance, a recent study evaluated the impact of CP on compliance with individual and composite process of care quality measures, and found that contact isolation was associated with lower adherence to the composite pneumonia process-of-care measure, whereas other composite measures were not affected.[20] Another issue addressed by several systematic reviews is the impact of contact precautions on patients' well-being: troubling common themes of harm emerge from these reviews and drawbacks associated with CP have sometimes been reported.[21-23] For example, Kirkland et al. reported that HCWs who treated patients in contact isolation entered their rooms less frequently, and had significantly less direct contact with them, than those caring in SP.[14] Stelfox et al. reported that compared with controls, patients isolated for infection control precautions experience more preventable adverse events, express greater dissatisfaction with their treatment, and have less documented care.[16] One additional finding is the higher level of depression and anxiety among patients placed under CP or isolation.[15,24,25] There can be also difficulty for HCWs in communicating with patients as it was shown during the Canadian outbreak of severe acute respiratory syndrome in 2003.[26] The ethical considerations of such an intervention which balance patient autonomy with protection of the population have been discussed in detail elsewhere.[27]

Therefore, in 2006, the American Institute of Architects, in its Guidelines for Design and Construction of Health Care Facilities, made single-patient rooms the standard.[28] Hospitals that have single-patient rooms exclusively are able to isolate patients with transmissible diseases without disrupting patient flow.[29] However, existing facilities, especially in Europe, often have a significant proportion of double- or multi-bed patient rooms.

Despite these ongoing controversies, we will discuss in the following sections evidence arguing in favor of CP as the single most important measure to prevent the spread of MDROs. We will first focus on sporadically occurring MDRO and then discuss the effectiveness of CP in settings with hyperendemic MDRO. Each major section has been divided into two subsections relative to MRSA and VRE, for which more studies and data are available, and MDR GNB.

The role of CP to control sporadic or epidemic MDRO transmission. *MRSA and VRE.* During the past 50 years, CP have been successfully advocated and implemented in settings with low prevalence or small-scale outbreaks of MRSA and VRE.[13,30-34] Frequently, CP were linked with other control measures, including implementation of active surveillance cultures (ASC) or decolonization procedures. For instance, the University of Geneva Hospitals in Switzerland evaluated several intensive infection control measures on a hospital outbreak of MRSA occurring between 1990 and 1993.[32] These measures included patient screening, on-site surveillance, contact isolation, decolonization, a computerized alert system and hospital-wide promotion of hand hygiene, and had a substantial impact on both the reservoir of MRSA patients and the attack rate of MRSA bacteremia.[32] Similarly, an active infection control intervention, which included the obtaining of surveillance cultures, education, communication and the isolation of infected patients reduced the transmission of VRE in health care facilities of the Siouxland region of Iowa, Nebraska and South Dakota between 1996 and 1999.[31] Other prominent examples of the effect of CP on the successful control of MDRO clusters (mostly stopped at an early stage) are listed in **Table 1**. As mentioned above, it remains difficult to ascertain the unique role of CP in the control of sporadic or epidemic MDRO transmission, because of the multimodal intervention character of these studies. Nevertheless, most experts would agree that they are an essential component of the "search-and-destroy" strategy to prevent further spread of MRSA in a healthcare setting.[35] This latter policy has been successfully applied in countries with low to very low prevalence of MRSA, notably the Netherlands.[36] In a 5-year study, control of MRSA was accomplished by the use of active surveillance cultures for persons at risk (patients or HCWs), by the preemptive isolation of patients at risk, and by the strict isolation of known MRSA carriers and the eradication of MRSA carriage. For unexpected cases of MRSA colonization or infection, patients placed in strict isolation or contact isolation and HCWs were screened. In a survey of 231 Dutch hospitals inquiring about MRSA control, those who had implemented an isolation cohort (i.e., index cases were isolated on hospital admission) had only 4/73 (5%) cases of secondary MRSA transmission. By contrast, the non-isolation cohort (i.e., high-risk patients not put into isolation on admission) had 19/95 (20%) cases of secondary MRSA transmission.[37] Interestingly, the Netherlands achieved MRSA control despite generally rather low hand hygiene compliance. In an observational survey in ICUs and surgical departments of five hospitals of varying size in the Netherlands, hand hygiene compliance of 65 nurses, attending physicians, medical residents and medical students was monitored, with an overall compliance of only 19%.[38]

MDR GNB. The prime value of CP to control outbreaks of MDR GNB has also been demonstrated (**Table 1**). In the past, intensified CP measures controlled the outbreak of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae before these bacteria became endemic.[39,40] Several studies have demonstrated that outbreaks of ESBL-producing *Klebsiella pneumoniae* could be due to a same single strain or clone, depending on the microbiological technique used for identification, and these bacteria could spread into an ICU[41] or several units of the same hospital.[42] In one study,[41] reinforced control measures (cohorting and dedicated staff in addition to CP and screening of patients at admission and weekly) allowed to end an outbreak of 32 cases of ESBL-producing *K. pneumoniae* colonization or infection. However, environmental screening had not been performed. Clearly, if the source is not identified and eliminated, infection control measures could be ineffective. For readers seeking additional background information, they can refer to standard sources.[43-46]

Table 1. The effect of contact precautions on the successful control of selected MDRO outbreaks

Country	Organism	No. of patients	Duration	Measures	Reference
Israel	MRSA	15	14 mo	Isolation/cohorting Hand washing/hand disinfection Patient screening/surveillance Personnel screening/surveillance Decolonization	82
USA	Multidrug-resistant *Enterococcus faecium*	37	18 mo	Isolation/cohorting Patient screening/surveillance Protective clothing Change in antibiotic therapy	83
Germany	Multidrug-resistant *Klebsiella pneumoniae*	9	7 mo	Isolation/cohorting Protective clothing Patient screening/surveillance Personnel training Restriction of workload	84
Kuwait	Multidrug-resistant *Acinetobacter baumannii*	24	1 y	Patient screening/surveillance Closure of affected location Isolation/cohorting Environmental screening Personnel screening/surveillance Hand washing/hand disinfection Disinfection/sterilization	85
USA	Multidrug-resistant *Serratia marcescens*	18	5 mo	Personnel training Hand washing/hand disinfection Disinfection/sterilization Isolation/cohorting Closure of affected location Environmental screening Patient screening/surveillance Personnel screening/surveillance	86
Belgium	Multidrug-resistant *Acinetobacter baumannii*	30	11 mo	Patient screening/surveillance Personnel screening/surveillance Isolation/cohorting Hand washing/hand disinfection Disinfection/sterilization	87
Brazil	Multidrug-resistant *Pseudomonas aeruginosa*	5	1 mo	Handwashing Contact precautions	88
Belgium	Multidrug-resistant *Enterobacter aerogenes*	34	9 mo	Isolation/cohorting Protective clothing Hand washing/hand disinfection Disinfection/sterilization Patient screening/surveillance Personnel screening/surveillance	89

The latest fatal outbreak of carbapenem-resistant *K. pneumoniae* at the US National Institute of Health Clinical Center[47] underscores that infection control precautions were the only effective measure that eventually stopped the outbreak. This outbreak led to 18 affected patients and 6 deaths attributable to *K. pneumoniae*. Whole-genome-sequencing performed after the end of the outbreak revealed that infections control practitioners failed to appreciate that the most important transmitters of MDROs were asymptomatic carriers and not sick cases (infection control measures were, in fact, not intensified for the carriers) and they failed to identify an environmental source (improperly disinfected respiratory equipment) of the MDR *K. pneumoniae*. The outbreak was ultimately contained by implementing strict cohorting of colonized patients to minimize sharing of hospital equipment and of care providers between outbreaks patients and the other patient in the hospital and adequate screening of patients.

For carbapenem-resistant Enterobacteriaceae (CRE), in settings with low prevalence and localized outbreaks, the aim of infection control measures should be the complete eradication of CRE, according to an adaptation of the classic "search and destroy strategy," whereby patients considered to be at risk of

Table 2. The added value of personal protective equipment (PPE) to decrease the likelihood of MDRO contamination of HCWs (adapted from Snyder et al.[56] and Morgan et al.[55])

Organism	HCW Room Entries	Hands contamination before pulling on PPE (%)	Contamination of gown and/or glove after patient care activities (%)	Hands contamination after removal of PPE (%)	Effectiveness of PPE
MRSA	84	2%	18.5%	2.6%	85%
VRE	94	0%	8.5%	0%	100%
MDR *A. baumannii*	202	1.5%	38.7%	4.5%	88%
MDR *P. aeruginosa*	134	0%	8.2%	0.7%	90%

CRE carriage are isolated upon hospital admission pending the outcome of admission screening.[48] Reliable detection of the first CRE index case in a hospital is crucial in order to implement interventions in a timely fashion. Isolation precautions should be implemented and strictly applied to already identify carriers, although in several settings simple contact isolation was not sufficient to stop local outbreaks, and cohorting of patients with dedicated staff was warranted.[49]

International spread of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* from Greece has occurred to at least 9 European countries since 2007 with further transmission documented in some case.[50] For example, Germany experienced an outbreak of KPC-producing *K. pneumoniae* in 2008. Despite the introduction of infection control measures, transmission occurred in 8 patients. A common source for the outbreak could not be established and the increasing risk of transmission with increasing contact times suggests that transmission via the hands of HCWs was the most likely mechanism of spread. The outbreak resolved after implementation of strict isolation of the cases for the whole period of hospitalization and two prevalence screenings to search for asymptomatic carriers.[51]

Thus, effective tactics to control the spread of CRE include (1) cohorting CRE-colonized and -infected patients, (2) assigning dedicated staff to cohort units, (3) performing active surveillance for CRE by rectal swabs or stool cultures and (4) intensifying hand hygiene and environmental cleaning. In order to be effective in a region with epidemic CRE, infection control guidelines should be uniform for all involved hospitals, and drawn up by a central public health authority invested with the statutory power to oversee and enforce their implementation.

The role of CP to control endemic MDRO transmission. Endemic MDRO occurrence is also frequently the result of inappropriate antimicrobial prescribing, leading to excessive antimicrobial consumption and selection pressure. Antimicrobial classes for which resistance has become a major problem include fluoroquinolones, cephalosporins and glycopeptides. Extended fluoroquinolone prophylaxis in urology and hematology settings, for example, is among the most important drivers not only of fluoroquinolone-resistant but also of ESBL-producing Enterobacteriaceae, since many of these strains also express β-lactamases that confer cephalosporin resistance.[52] Meyer et al. observed that carbapenem use almost doubled despite the absence of significant change in total antibiotic use—expressed as defined daily doses per 1,000 patient-days—in 53 German ICUs between 2001 and 2008.[53] The exponential increase of third-generation cephalosporin resistance among Enterobacteriaceae in this study led to switching empirical therapy of infections to carbapenems, and carbapenem-resistant *Klebsiella pneumoniae*, carbapenemase-producing Gram-negative pathogens and imipenem-resistant *Acinetobacter baumannii* emerged as a direct consequence. Glycopeptide resistance has been largely restricted to nosocomial *Enterococcus faecium* strains, the spread of which is promoted by ineffective infection control mechanisms for fecal organisms and the widespread use of VRE-colonization promoting antimicrobials (especially cephalosporins and antianaerobic antibiotics). Therefore, selecting the most appropriate antibiotic choice with the least impact on the microbial environment and host flora may help reduce the risk of MDRO spread.

In settings with hyperendemic MDRO prevalence, CP are also an essential part of MDRO control. In a landmark study performed 25 years ago, CPs including gowns and gloves have been shown to delay colonization by 5 d and reduce the rate of healthcare associated infections by 2.2 times.[54] More recently, Morgan et al. and Snyder et al. have demonstrated the added value of personal protective equipment to decrease the likelihood of MDRO contamination of HCW (**Table 2**).[55,56] Of interest, masks may reduce colonization of HCWs with MDRO, although it is not included in the CDC definition of contact precautions.[57]

MRSA and VRE. Observational studies have shown beneficial effects of isolation on acquisition of MDRO, especially for MRSA and VRE colonization and infection.[58-61] Often, enhanced infection-control strategies were associated with increased compliance.[62-64] However, the value of CP has been questioned by some studies. Aboelela et al. conducted in 2006 a systematic review of literature pertaining to the use of barrier precautions/patient isolation and surveillance cultures to prevent the transmission of MDROs and attributed a quality score to these studies. Only 7 studies with highest quality scores (≥ 90%) were selected, four studies[59,65-67] were in favor of barrier precautions and surveillance culture and three studies[64,68,69] did not report a difference (**Table 3**).[70] This lack of difference may have been explained by a number of factors including low screening compliance, delays in notification of results, poor compliance with general infection control measures such as hand hygiene and understaffing. These

Table 3. Studies with highest quality scores (≥ 90%) testing the effectiveness of barrier precautions and surveillance culture in preventing transmission of multidrug-resistant organisms

Study	Setting and study population	Design	Intervention(s)	Major findings
Cepeda et al., 2005[68]	Three medical-surgical ICUs in two London teaching hospitals	Two sets concurrent, Untreated control group design that uses dependent pretest and posttest samples	First 6 mo, MRSA patients moved to single rooms or cohort bays; second 6 mo not moved Other interventions: gloves, gowns, visitor education, hand hygiene monitored	No difference in MRSA acquisition rates between patients moved and patients not moved
Chaix et al., 1999[65]	Medical ICU of a French university hospital	Retrospective cost-benefit analysis	Surveillance culture, gloves, gowns, plastic aprons, masks	Control program found to be beneficial: mean cost attributable to MRSA infection was $9275, cost of program was $340-$1480/patient, 14% reduction in infection rate
Silverblatt et al., 2000[66]	Veterans nursing home	1-Group pretest-posttest design	Transfer patients screened, contact isolation and oral antibiotic for those colonized Other interventions: patients in single rooms, patient cohort, handwashing	No new VRE carriers from time 1 to time 2
Slaughter et al., 1996[64]	Medical ICU of 900-bed urban teaching hospital	Untreated control group design that uses dependent pretest and posttest samples (no pretest)	Precautions changed from use of gloves and gowns to use of gloves alone Other interventions: Surveillance culture, HCW education, visitor education, environmental cleaning, feedback to HCW regarding compliance	No difference in VRE colonization rates among use of gloves with gowns compared with glove use alone
Srinivasan et al., 2002[59]	16-bed, medical ICU in a university teaching hospital	1-Group pretest-posttest design	VRE isolation precautions were changed from gowns and gloves to gloves alone Other interventions:Surveillance culture, patients in single rooms, patient cohort, HCW education	VRE acquisition rate was lower (1.8 cases/100 d) with gowns and glove use compared with glove use alone (3.78 cases/100 d)
Trick et al., 2004[69]	667-bed acute and long-term care facility, 283 subjects	Randomized clinical trial	Use of 2 infection control strategies: gloves with and without contact isolation Other interventions: Surveillance culture, patients in single rooms, patient cohort, HCW education	No difference in transmission of VRE or MRSA among glove use with or without use of contact precautions, cost was 40% less without
Wernitz et al., 2005[67]	German 700-bed acute care teaching hospital	1-Group pretest-posttest design	Surveillance culture for all high-risk patients upon admission	A 48% reduction in the frequency of patients positive for hospital-acquired MRSA

Adapted with permission from Aboelela et al.[70]

factors emphasize the importance of institutional measures (such as architecture, staffing and education) required to support CP interventions. As mentioned above, this isolation debate is also influenced by research demonstrating that isolation is associated with adverse effects in terms of patient satisfaction and level of care provided by HCWs.[71]

Uncertainty still remains about the effectiveness of ASC programs to better guide isolation of suspected or confirmed MDRO carriers. Two important studies have produced conflicting results on the implementation of ASC and their effectiveness in MRSA control. Harbarth et al.[72] found no reduction in the incidence of nosocomial MRSA infections among surgical patients enrolled in a single, large institution crossover cohort trial, whereas Robicsek et al.[73] found that the use of ASC reduced MRSA infections by nearly 70% in an observational cohort study performed in two affiliated hospitals. More recently, two important studies performed in the United States have highlighted not only the efforts in prevention of MDROs but also the difficulties in gaining sustained and reproducible results.[74,75] Jain et al.[74] evaluated the effectiveness of a quality improvement initiative in preventing the acquisition and spread of MRSA among nearly 2 million patient admissions; the study included data from 196 ICUs in the US. During the intervention period, an important decrease in infections caused not only by MRSA but also by

other pathogens was observed. Huskins et al.[75] evaluated more than 9,000 patients in 18 ICUs with a cluster-randomized intervention aimed at implementing barrier precautions, carrying out ASC, and feeding back adherence information to personnel; however, the final result of the intervention showed no effect on MRSA and VRE colonization or infection rates, despite the improvement in compliance with precautions and procedures.

MDR GNB. Currently, the expansion of ESBL resistance into the community presents challenges for prospective identification of colonized patients upon admission and infection control. A recent systematic review has examined the efficacy of infection control interventions for the control of ESBL-producing Enterobacteriaceae in hospitals in non-outbreak settings. Although four uncontrolled, retrospective studies were included, no well-designed prospective study capable of informing infection control practice was identified.[76] Although several studies in ICUs have supported the hypothesis that patient-to-patient transmission does not play an important role in ESBL-producing Enterobacteriaceae acquisition,[77,78] a recent study has highlighted the importance of patient-to-patient transmission in the acquisition of ESBL- producing *E. coli* during hospitalization in rehabilitation centers and the varying dissemination potential of different clones.[79] As CP have not been implemented in their institution, authors believe that infection control practices should be adapted and implemented in these rehabilitation centers. There is an urgent need for research in this area and future infection control studies should differentiate species of ESBL-producing Enterobacteriaceae.

A recent review about control of endemic CRE reported various successful attempts in endemic settings.[80] Although some differences in approach did exist, the interventions implemented were largely based on the rationale of surveillance cultures, isolation and cohorting, CP and assignment of dedicated staff. Interpretation of the published data, however, suggests that application of a bundle of infection control measures may be required for maximum containment of CRE. Therefore, a group of experts suggested a multifaceted approach with different components.[48] At the local level, control measures should include (1) physical separation of carriers from non-carriers, (2) dedicated staff, (3) active surveillance of high-risk patients, (4) training and measures to keep staff and hospital administration informed and (5) ongoing CRE surveillance with prospective data collection and daily census of CRE carriers. Crucial to a successful CRE control program is a national task force coordinated and supported by a central public health authority with competence in hospital infection control. The aims of this task force are multifaceted and include top priority action items as providing (1) isolation guidelines for carriers, (2) monthly progress reports about CRE control for concerned institutions and (3) evaluation of concerned hospitals and identification of problem areas. Controlled studies and more mathematical modeling of CRE transmission and prevention[11,81] are needed to specify the most appropriate procedures for containment or even eradication of CRE.

Conclusions

The cornerstone of control measures attempting to prevent MDRO transmission is the uniform use of SP and hand hygiene, along with CP and appropriate environmental cleaning for specific pathogens and situations, especially for outbreaks. When these practices are inadequate to control the spread of MDROs, a more intensive approach should be implemented. The combination of a comprehensive infection control strategy and an effective antimicrobial stewardship program may be complementary and lead to the prevention of emergence and transmission of MDRO. This includes multimodal strategies, variably combined, such as hand hygiene promotion, barrier precautions and asymptomatic patient decolonization, prevention bundles, environmental decontamination and "high quality" antimicrobial prescription. To be potentially effective, such programs must be strongly supported by the hospital administration.

In summary, contact precautions probably remain the most effective and essential method of preventing transmission of MDROs, especially at the early stage of dissemination. They are extensively recommended by scientific societies and governmental authorities. Therefore, isolation measures should be integral part of any MDRO control program, despite the fact that they are often not applied consistently and rigorously.

Disclosure of Potential Conflicts of Interest

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