Multidrug-Resistant Gram-Negative Bacteria

Infection Prevention and Control Update

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KEYWORDS

• Gram-negative bacteria • MDR-GNB • CRE • Nosocomial infections
• ESKAPE pathogens • Infection control

KEY POINTS

- Multidrug-resistant Gram-negative bacteria (MDR-GNB) infections constitute a great threat to human health because of their propensity for human-to-human spread and limited therapeutic options
- The lack of standardized microbiological definitions of resistance among certain Gram-negative bacteria (GNB) leads to nonuniformity in infection control established recommendations
- Infection control interventions should be implemented in parallel in both acute-care hospitals and connected long-term care facilities (LTCFs) to maximize the effectiveness of prevention interventions among high-risk patients across the continuum of care
- Clinical cultures only identify a minority of patients colonized with MDR-GNB; active surveillance is necessary to detect asymptomatic MDR-GNB carriage
- Screening methods for active surveillance of extended-spectrum β-lactamases (ESBL) and carbapenem-resistant Enterobacterales (CRE) colonization are more sensitive than methods for the detection of carbapenem-resistant *A. baumannii* (CRAB) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
- Hand hygiene (HH), contact precautions (CPs), and cohorting are key containment measures for MDR-GNB prevention
- CPs are recommended for all carriers of CRE, CRPA, and CRAB
- In settings of high endemic rates, cohorting with dedicated staff is recommended for carbapenemase-producing CRE carriers. It is also recommended for CRAB (or *A. baumannii* in general) prevention, depending on local endemicity
- Cohorting carriers of different MDR-GNB together may result in cross-transmission of resistance elements and adversely impact antimicrobial resistance in a facility

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Infect Dis Clin N Am 35 (2021) 969–994
https://doi.org/10.1016/j.idc.2021.08.001
id.theclinics.com

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- The environment likely plays a role in MDR-GNB acquisitions. Establishing strict terminal cleaning protocols and regular monitoring of the effectiveness of cleaning are important components of successful prevention programs. The use of advanced "no-touch" technologies [automated ultraviolet C (UV-C)–emitting and H2O2-based devices] with terminal room cleaning may provide additional benefits
- Endoscopes, particularly duodenoscopes and bronchoscopes, have been associated with multiple MDR-GNB outbreaks; appropriate reprocessing of these devices is crucial to prevent the transmission of MDR-GNB and serious infections
- Antimicrobial stewardship (AMS) programs must be part of all infection control programs in all facilities and in community health settings; they have been associated with a 50% reduction in MDR-GNB incidence in hospital settings
- Selective oral and digestive decontamination are not recommended for MDR-GNB prevention. The use of colistin for these purposes could be hazardous. Chlorhexidine gluconate bathing reduces MDR-GNB incidence. Fecal microbiota transplantation (FMT) may play a future role in CRE prevention

PEARLS

- Performance of active surveillance for carbapenem-resistant Enterobacterales (CRE) among high-risk populations can facilitate early detection and cohorting of cases, limiting the risk of transmission
- Identifying high-risk populations based on local/regional epidemiology is crucial to determining what patients warrant active surveillance for CRE
- *Acinetobacter baumannii* is notorious for widespread environmental contamination. Enhanced environmental cleaning and use of novel "no-touch" technologies can reduce the risk of environmental persistence and potentially transmission
- Consider endoscopes and environmental water sources as potential reservoirs of multidrug-resistant Gram-negative bacteria (MDR-GNB) during outbreak investigations

PITFALLS

- Active surveillance for carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and carbapenem-resistant *A. baumannii* (CRAB) is challenging because of the low sensitivity of cultures from any single anatomic site. Multiple sites may need to be cultured to optimize detection.
- Reliance on phenotypic testing alone to detect carbapenem-resistant Enterobacterales (CRE) may fail to detect epidemiologically important resistance genes
- Cohorting patients colonized with different MDR-GNB can potentially result in patient-to-patient cross-transmission of genetic resistance elements
- Data do not support the use of contact precautions (CPs) for patients colonized with extended-spectrum β-lactamases–producing GNB. High utilization of CPs is associated with lower health care worker adherence.
- The use of colistin for selective digestive decontamination (SDD) has the potential to promote colistin resistance

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA: NOMENCLATURE

Multidrug-resistant Gram-negative bacteria (MDR-GNB) comprise many of the urgent threats identified by the Centers for Disease Control and Prevention (CDC)'s 2019 Antibiotic Resistance report.[1] Most of the "ESKAPE" pathogens[2], which cause a large preponderance of hospital infections although effectively "escaping" the effects of most available therapeutics, are Gram-negative bacteria (GNB), including *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Escherichia coli*. In this review, MDR Gram-negative ESKAPE bacteria will be referred to as MDR-GNB, although these isolates are frequently extensively drug resistant (XDR), or even pan-drug resistant.[3]

Although antimicrobial resistance among GNB includes many classes of antibiotics, this review will focus specifically on β-lactam resistance.[4] Beta-lactam agents are among the oldest, safest, and cheapest therapeutic options[5] and are bactericidal with an established track record against the most common infectious syndromes.[6] This review will summarize evidence-based infection control measures aimed at halting the emergence and spread of 4 resistance phenotypes among the ESKAPE MDR-GNBs (**Table 1**): (1) Enterobacterales resistant to extended-spectrum cephalosporins: such as pathogens expressing various types of β-lactamases, including the Ambler-A extended-spectrum β-lactamases (ESBL) and the Ambler-C bla_{AmpC} (AmpC); (2) carbapenem-resistant Enterobacterales (CRE); (3) carbapenem-resistant *P. aeruginosa* (CRPA); and (4) *A. baumannii* [including but not solely limited to carbapenem-resistant *A. baumannii* (CRAB)].

MICROBIOLOGICAL DEFINITIONS AND MECHANISMS OF β-LACTAM RESISTANCE

Surveillance of β-lactam resistance among GNB is challenging because of a lack of standardized definitions for MDR-GNB. Different antimicrobial susceptibility testing breakpoints have been set by different international committees (Clinical and Laboratory Standards Institute vs European Committee on Antimicrobial Susceptibility Testing), and these breakpoints have changed over time to optimize the detection of β-lactam resistance.

CRE can be detected either phenotypically by MIC breakpoints or by molecular detection of carbapenemases. Both the Israeli Ministry of Health and the US CDC recommend carbapenemase production testing on all CRE isolates because results can inform local CRE epidemiology and guide appropriate infection control measures.[7,8]

Resistance to extended-spectrum cephalosporins among Enterobacterales can also be detected by either phenotypic third-generation cephalosporin resistance or ESBL production testing.[9,10] There are other prevalent resistance mechanisms to third-generation cephalosporins, most notably bla_{AmpC}.[11] ESBLs are encoded on transmissible mobile genetic elements, whereas AmpC is frequently encoded on chromosomal genes that are upregulated in the setting of antibiotic exposure.[12] Although ESBLs may be acquired in hospitals by patient-to-patient transmission[13], among AmpC, the most common mode of acquisition is by the emergence of resistance due to antimicrobial selective pressure, which might influence the bundle of infection control measures that should be used.

MODES OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA ACQUISITION

Prevention tool kits for the acquisition of MDR-GNBs address 2 modes of resistance acquisition: (1) patient-to-patient transmission of MDR-GNB and/or their mobile

Table 1
Multidrug-resistant gram-negative bacteria nomenclature and abbreviations

	Abbreviation	Definition	Examples
Multidrug-Resistant Gram-Negative Bacteria	MDR-GNB	Gram-negative bacteria nonsusceptible to ≥3 classes of antimicrobials	
Extensively Resistant Gram-Negative Bacteria	XDR-GNB	Gram-negative bacteria nonsusceptible to ≥1 agent in all but ≤2 antimicrobial classes	
Enterobacterales			
Carbapenem-Resistant Enterobacterales	CRE	Enterobacterales phenotypically resistant to ≥1 carbapenem -OR- detection of carbapenemase	
Nonfermenting Gram-Negative Bacteria	NF-GNB	Gram-negative bacteria incapable of fermenting glucose	*P. aeruginosa*, *A. baumannii*, *S. maltophilia*, *Burkholderia cepacia* complex
Carbapenem-Resistant *P. aeruginosa*	CRPA	*P. aeruginosa* phenotypically resistant to ≥1 carbapenem	
Carbapenem-Resistant *A. baumannii*	CRAB	*A. baumannii* phenotypically resistant to ≥1 carbapenem	
Beta-Lactamases			
Extended-Spectrum Beta-Lactamases	ESBLs	Enzymes capable of hydrolyzing third- and 4th-generation cephalosporins in addition to penicillin agents	CTX-M, TEM, SHV
AmpC Beta-Lactamases	AmpC	Inducible enzymes (usually chromosomal) that when upregulated confer resistance to first- to third-generation cephalosporins & BL/BLIs	Frequently found in: *E. cloacae, C. freundii, S. marcescens, P. aeruginosa, A. baumanii*
Carbapenemase-Producing Organisms	CPOs	Gram-negative bacteria that produce enzymes capable of hydrolyzing carbapenems	KPC, NDM, OXA, VIM

S. maltophilia, *Stenotrophomonas maltophilia*; *Burkholderia cepacia*, *B. cepacia*; *C. freundii*, *Citrobacter freundii*; *S. marcescens*, *Serratia marcescens*; *E. cloacae*, *Enterobacter cloacae*. KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-beta-lactamase.

genetic elements (eg, carbapenemases) (often through an intermediary such as health care staff, the proximal environment, or shared equipment) or (2) *de novo* evolution of resistance, in which susceptible isolates, under antibiotic selective pressure, newly express an MDR phenotype, often mediated by the upregulation of chromosomal

gene expression (eg, AmpC) or alterations in outer membrane porin channels or efflux pumps due to certain stressors.[5,14]

Infection control measures in hospitals that address patient-to-patient transmission include (1) hand hygiene (HH), (2) contact isolation precautions, (3) patient cohorting and dedicated staff, (4) environmental cleaning, (5) active surveillance programs to identify asymptomatic carriage, and (6) decolonization protocols. In contrast, tackling *de novo* emergence of resistance requires enforcing adherence to effective antimicrobial stewardship (AMS) policies.[14]

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA EPIDEMIOLOGY

Acute-care hospitals

ESBL-producing GNB were first described in acute-care facilities, specifically in intensive care units (ICUs), in the 1980s.[15,16] By the mid to late 1990s, ESBL-producing strains had become prevalent in outpatient settings.[17,18] This rapid global dissemination has been largely driven by the clonal expansion of *E. coli* sequence type 131, which frequently harbors the CTX-M beta-lactamase.[19] ESBL colonization prevalence ranges from 2% to 56% among patients admitted to ICUs, depending on the geographic region.[20–22]

Infections due to the nonfermenting MDR-GNB CRAB and CRPA primarily affect patients with prolonged and complicated stays in acute-care hospitals.[23–25] Prolonged prior hospital or ICU stay, recent surgery/procedures, presence of invasive devices, and recent exposure to antibiotics all serve as independent predictors for the acquisition of CRE, CRPA, or CRAB.[23–27]

Long-term care facilities

Long-term care facilities (LTCFs) became a pivotal part of the health care system over the past 3 decades and are now providing more complex post–acute-care management to greater numbers of patients.[28] Today, elderly patients with multiple risk factors for MDR-GNB acquisition, such as multiple comorbidities, indwelling devices, recent exposure to hospitals, and broad-spectrum antibiotics, are frequently managed in LTCFs.[23,24,29,30] Moreover, patients from LTCFs frequently cycle back and forth from acute-care facilities, resulting in additional complexities in terms of transmission and spread.[29,31] Above all, lower adherence with HH and barrier precautions in LTCFs, along with a paucity of infection control resources and expertise, can facilitate the spread of MDR-GNB.[32]

The first reported outbreak of bacteria resistant to ceftazidime in the United States occurred among patients in a chronic-care facility in Massachusetts in 1990.[33] Since that time, ESBL-producing Enterobacterales have become endemic in LTCFs throughout most of the world. Risk factors for ESBL colonization in LTCFs include (1) poor functional status, (2) percutaneous endoscopic gastrostomy tube placement, (3) pressure ulcers, (4) use of ciprofloxacin and/or trimethoprim-sulfamethoxazole (TMP-SMZ), and (5) increased length of stay.[34,35]

CRE have also been identified among LTCF patients, and risk factors for acquisition include the prolonged length of stay in acute care, sharing rooms with known carriers, and the degree of colonization pressure on certain wards.[8]

Resistant *P. aeruginosa* infections, particularly CRPA catheter-associated urinary tract infections (UTIs) and skin and soft-tissue infections, were identified in LTCFs more than 2 decades ago.[8] CRPA infections in this setting have been associated with intermittent urethral catheterization, chronic indwelling urinary catheters, and postsurgical drains.[36,37] CRAB have been detected among ventilated patients in

long-term acute-care hospitals (LTACHs) and also in LTCFs in general.[38,39] Importantly, *Acinetobacter* spp. may persist on dry inanimate surfaces for days to months.[40]

Community settings

MDR-GNB infections are considered community acquired (CA) if they occur outside of the hospital or LTCFs or are diagnosed within the first 72 hours of hospitalization. However, the boundary between community settings and health care–associated settings may be blurred as patients with recent health care exposure often resemble patients in acute-care hospitals and LTCFs.[41] Cases of CRE, CRPA, and *A. baumannii* present or incubating at the time of hospital admission were previously termed CA although they often occurred among a population with heavy recent prior exposure to health care.[25] Exclusively CA infections caused by CRE, CRPA, or CRAB remain very rare in most countries.[42]

In contrast to carbapenem-resistant pathogens, CA-ESBL infections have become relatively commonplace in many parts of the world.[5] The community prevalence of ESBL colonization is highly variable. The community prevalence of ESBLs is as high as 46% to 63% in parts of Asia and Africa and as low as 2% in North America.[43] Although the role of patient-to-patient transmission in ESBL acquisition in the community is unclear[13], ESBL infections are clearly associated with worse outcomes,[44] mainly because of the frequent delays in initiating appropriate therapy (DAAT).[11]

Infection control measures to curb the continued emergence and spread of ESBLs in the community are speculative. Developing robust AMS programs in outpatient ambulatory settings, for example, targeting fluoroquinolones, might reduce the emergence and spread of ESBLs in the community.[45,46] In addition, restricting antimicrobial usage in agriculture and food industries is a critical measure.[45]

Table 2
Epidemiologic and biological characteristics of colonization by MDR-GNB

	Anatomic Locations for Screening	Duration of Colonization	Risk for Transmission	Risk of Clinical Infection
ESBL & CRE	Rectum, inguinal, urine.	144 d 50% positivity rate by 3–6 mo, 25% by 6–24 mo in *K. pneumoniae*[162]	Health care acquisition/ community onset ratio 59/52 in *E. coli*[50]; 37/35 in *K. pneumoniae*[163]	44/520 (8.8%)[164] and 42/464 (9%)[165] in *K. pneumoniae*
CRAB	Rectum, respiratory tract, skin, urine[48,49]	20 mo[48]	Health care acquisition/ community onset ratio 32/16	Bacteremia in 108/200 (54%)[166]
CRPA	Rectum, oropharynx, urine, sputum		Health care acquisition/ community onset ratio 70/46[167]	Clinical infection in 41/213 (19.2%)

Abbreviations: CRE, carbapenem-resistant Enterobacterales; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL, extended-spectrum β-lactamase-producing Enterobacterales; GNB, Gram-negative bacteria; MDR, multidrug-resistant.

THE "ICEBERG PHENOMENON": THE ROLE OF COLONIZATION IN THE EPIDEMIOLOGY AND PREVENTION OF MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA TRANSMISSION

Asymptomatic colonization of humans occurs among almost all of the MDR-GNB, and several studies have determined the anatomic locations of colonization, duration of colonization, and the relationship with transmission and clinical infection (**Table 2**).

Anatomic locations of colonization

The colon is the natural habitat of Enterobacterales, and sampling colonic content by rectal (or less preferably perirectal) cultures is the most sensitive and efficient method for identifying CRE and ESBL carriers.[47]

There is less certainty regarding the optimal screening location for CRAB and CRPA.[48] Sampling of several anatomic sites, including the rectum, pharyngeal/respiratory tract, and skin sampling, may increases the yield[48,49] and also the labor and cost burden of surveillance.

Risk of transmission and clinical infection among colonized patients

Surveillance cultures of patients during their hospital stay combined with molecular analysis have traced the clonal transmission of ESBL-producing *E. coli* in only 50% of ESBL acquisitions (see **Table 2**).[50]

The risk of overt clinical infection for carriers varies tremendously between CRE (~9%) and CRAB (54%) (see **Table 2**). Although this difference may be related to virulence potential, it is also a reflection of differences in the patient population of carriers (eg, ICU patients with CRAB vs the general wards with CRE) and the possible lower detection of CRAB colonization than CRE based on surveillance cultures.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA CONTAINMENT

Hand hygiene

HH is a principal component of standard precautions and the cornerstone of infection prevention (**Table 3**).[51] Many studies have demonstrated isolation of the same MDR-GNB from patients and the hands of the health care workers caring for them.[52–54] Therefore, investing in HH compliance among staff is an important intervention to control outbreaks of MDR-GNB.[55–57] Although the isolated impact of improving MDR-GNB acquisition is difficult to quantify,[58] HH is efficacious, inexpensive, and easy to perform. Following the performance of HH either with water and antiseptic soaps or with alcohol-based hand rub, there are significant reductions in the inoculums of MDR-GNB.[59] A recent modeling analysis in the ICU setting demonstrated that HH is the most efficient measure in controlling ESBL acquisitions. This model showed that improving HH compliance from 55% before patient contact and 60% after patient contact to 80% before and after patient contact would reduce the proportion of patients who acquire ESBLs within 90 days by 91%.[60]

Although simple and fundamental to good patient care, compliance with HH is often suboptimal[58] and further interventions need to be implemented to increase compliance among staff, including the use of advanced technologies.[61,62] HH compliance among staff is a core performance measure of every infection control program and it is important to recruit leaders to invest and allocate preventive resources to this task.[63]

Contact precautions

Contact precautions (CPs) include wearing a gown and gloves on entry into the patient environment and removing the gown and gloves before exiting the patient's immediate

Table 3
Evidence-based MDR-GNB infection prevention and control measures

IPC Intervention	Definition	Comments
Hand Hygiene	Washing or sanitizing hands before and after patient care	Highly effective but adherence is often suboptimal. Monitoring and feedback are essential to maintaining high HCW adherence
Contact Precautions	Gown and glove use for all patient care	Data supporting use in endemic settings are strongest for CRE and *A. baumannii.* Data do not support the use of CPs for ESBL prevention.
Environmental Cleaning	Surface disinfection of patient environment and equipment	Crucial to monitor compliance. Consider potential water sources (eg, sinks) in MDR-GNB outbreaks, particularly *P. aeruginosa* and *A. baumannii.* No-touch terminal room technology can reduce the risk of MDRO infection in subsequent room occupant.
Medical Device Reprocessing	HLD/sterilization of invasive medical devices	Duodenoscopes associated with CRE transmission even when following the manufacturer's IFU
Antimicrobial Stewardship	System to limit inappropriate use & optimize antimicrobial prescribing	Associated with 50% absolute risk reduction in MDR-GNB infection/colonization. Most effective when combined with infection control measures.
Active Surveillance	Screening cultures (eg, rectal/perirectal swab) to detect asymptomatic MDR-GNB colonization	Universal vs targeted. Effective in reducing CRE transmission in epidemic and some endemic settings. Unclear role in the prevention of NF-GNB.
Patient and HCP Cohorting	Segregating MDR-GNB–infected or MDR-GNB–colonized patients in one geographic location with the use of dedicated HCP	Effective for epidemic CRE control when bundled with other interventions. Low HCP morale has been reported.
Patient Decolonization	Topical CHG cutaneous decolonization or SDD/SOD	CHG data are strong for MRSA/VRE but more limited for MDR-GNB. Utility of SDD/SOD depends on baseline antibiotic resistance prevalence and carries the risk of increased drug resistance. FMT for this purpose is still experimental.
Interfacility Collaboration	Enhanced communications between facilities regarding patient MDR-GNB status & coordination with state health authorities	Improves early detection of silent MDR-GNB carriers. Strong data supporting a coordinated approach to epidemic CRE control. Crucial to incorporate acute-care hospitals and LTCFs.

environment (see **Table 3**). CPs are preferably used for patients in single rooms. Performing HH before wearing gloves and after removing them is a mandatory part of CPs. Most supportive studies for the prevention of the spread of MDR-GNB include the use of CPs in combination with other infection control strategies and measures.[64,65] Universal use of CPs in ICU patients does not seem to be more effective than targeted CP for MDR-GNB–positive patients. A large cluster-randomized trial of universal gowns and glove use versus standard hospital policies for CPs among ICU patients found a nonstatistically significant 10% reduction in the incidence of MDR-GNB acquisition [risk ratio (RR) = 0.90, confidence interval (CI) = 0.71–1.12, $P = .34$].[66] In addition to being an important component of bundled interventions to limit the epidemic spread of MDR-GNB, CPs are simple and inexpensive and are one of the only tools available in the hospital, other than HH, to reduce the pathogen inoculum and limit transmission of pathogens from patient to patient.

Patients colonized or infected with CRE should always be subjected to CPs[47,67] per CDC recommendations. Current guidelines do not differentiate between carbapenemase-producing CRE and non–carbapenemase-producing CRE in terms of applying CPs (as opposed to cohorting and dedicated staff).

Limited data exist examining the role of CP in the prevention of the spread of nonfermenting MDR-GNB. The use of CPs is recommended for all patients infected or colonized with CRAB or CRPA by the World Health Organization.[68] *A. baumanii* is notorious for causing widespread environmental contamination and has been associated with higher rates of health care worker acquisition on gowns and gloves than *P. aeruginosa.*[69] Furthermore, one quasi-experimental study in a French hospital found an increase in the annual incidence of *A. baumannii* infections after discontinuing their CP policy, with a subsequent reduction after reinstituting the CP policy.[70] Controversy exists over whether CPs should be used for all *A. baumannii* or only cases of CRAB. For *P. aeruginosa*, carbapenem resistance occurs through *de novo* evolution and patient-to-patient transmission. Most facilities subject only patients with CRPA to CPs because carbapenems are regarded as such an important cornerstone antibiotic in the hospital and widespread carbapenem resistance throughout the hospital could be catastrophic.[71]

Although still used in many American hospitals, accumulated data suggest that CPs for ESBL are ineffective in preventing transmission, likely related to the high incidence of undetected CA colonization with these endemic organisms.[72,73] In a US study involving 11 teaching hospitals, as the proportion of patients on CPs exceeded 40% of the unit's occupancy, the compliance with CP and HH recommendations decreased dramatically, and only 5 of these 11 centers continued to implement CP for ESBL carriers following the study.[74] In a controlled study conducted at 2 hospitals in France, the rate of ESBL acquisitions was not associated with CP implementation.[75] However, some national guidelines (eg, in Switzerland) recommend CPs for hospitalized ESBL carriers; and during outbreaks or among high-risk populations (eg, neonates, severely immunosuppressed), CPs may still play a role in preventing ESBL acquisition.[76–78]

Overuse of CPs has the potential to cause harm. Prior studies have found that isolated patients receive less frequent personal contact from health care workers because of the additional effort required in adhering with CPs.[79,80] CPs may be stressful for patients and their families, and isolated patients are prone to higher rates of anxiety, depression, adverse events, and medical errors.[81]

ACTIVE SURVEILLANCE

The use of surveillance cultures to identify asymptomatically colonized patients has become an essential tool in infection prevention and control programs, not only during outbreaks but also as a routine measure for some endemic MDR-GNB.[8] Active surveillance, paired with preemptive contact isolation, reduces colonization pressure, risk of patient-to-patient transmission, and DAAT.[8,82,83] As the reliance on clinical cultures alone has been found to significantly underestimate CRE prevalence, the use of active surveillance cultures will more accurately estimate the colonization pressure of a given health system or unit.[83,84]

In many regions, the endemic prevalence of ESBL colonization in the community is so high that active surveillance is considered of questionable benefit. Efficacy data pertaining to the utility and yield of screening for ESBLs are derived primarily from outbreak settings or from certain high-risk populations such as in the neonatal ICU[85] or among immunosuppressed individuals. A recent large European cluster-randomized trial of ICU infection prevention strategies failed to find benefit of ESBL active surveillance in reducing the incidence of ESBL-producing *E coli* infections in the context of high compliance with hand hygiene and CHG bathing.[86] Moreover, as not all ESBL acquisitions are associated with patient-to-patient transmission, we believe that active surveillance should be limited only to situations in which its benefit outweighs the burden, such as in outbreak settings. In countries where ESBLs are endemic in community settings, the role of ESBL screening before elective abdominal surgery, to direct the presurgical prophylactic regimen for certain surgical procedures, can be considered.[87]

Screening for CRE among high-risk populations is a practice recommended in some scenarios by most of the national and international bodies.[8,47] As with any screening policy, local policies of which patients to screen should be based if possible on regional epidemiology and risk factor stratification.[47] Populations that may be targeted[25–27] include patients admitted directly from LTACs, patients from other LTCFs with known endemicity, patients with prior travel to foreign countries with high endemic rates, or those transferred directly from another hospital. Both the CDC and Israel Ministry of Health recommend screening close contacts of known CRE carriers.[7,88] Recent hospital stay (in the previous 6 mo) and functional dependency are additional screening candidates. Additional periodic screening policies (eg, weekly) for hospitalized patients in certain high-risk units (eg, ICUs) may be considered during periods of epidemic spread.[47]

The role of active surveillance to prevent spread of nonfermenting MDR-GNB such as CRAB and CRPA is unclear and is not currently recommended by the WHO guidelines for the prevention and control of MDR-GNB.[68] Screening for *A. baumannii* has 2 major limitations: (1) the best anatomic site for colonization detection has not yet been established (especially among nonventilated patients) and (2) the sensitivity of the diagnostic methods, by using traditional microbiologic methodologies, is known to be low.[48,82] In a study that prospectively screened proven *A. baumannii* carriers from 6 different anatomic sites, using routine conventional methods, the sensitivity of identifying carriers was only 55% after combining all 6 sites.[48] Because of the poor sensitivity and unclear benefit, most institutions do not screen routinely for *A. baumannii* carriage. However, there are multiple quasi-experimental studies supporting active surveillance (typically using sputum or rectal cultures) to reduce the incidence of CRAB in endemic or epidemic settings.[89,90] In a Monte Carlo simulation analysis, even with a sensitivity of 55%, active screening reduced *A. baumannii* transmissions, infections, and deaths by 48%. As screening sensitivity approached 90%,

the reduction in transmissions, infections, and deaths reached 78%. For all simulations, active surveillance was also cost-saving, except when carrier prevalence was equal or less than 2% and the sensitivity of the screening test was less than 55%.[82] Recent publications report higher performances for screening the skin with specified sponges and simple sampling procedure.[91]

Cohorting and dedicated staff

Physically cohorting patients infected or colonized with MDR-GNB in a contained area and using dedicated staff to treat only these patients during any given shift may reduce the risk of transmission (see **Table 3**).[67] The resource expenditure required to implement these measures is substantial, and supportive evidence for these practices for MDR-GNB prevention exists primarily in the control of CRE outbreaks and, to a lesser extent CRAB, largely as part of multifaceted bundles that also included active surveillance and additional interventions.[92,93]

Modeling has shown that cohorting was the second most effective intervention in reducing ESBL acquisition in the endemic ICU setting, following HH.[60] In Israel, the establishment of dedicated CRE cohort units with dedicated nursing staff nationwide curbed the emergence and spread of new CRE acquisitions.[67] Cohort units for CRE patients are also common in many facilities in the US and in other countries.[94]

Extrapolation of this practice led Detroit Medical Center to establish a "united cohort unit," in one of its facilities, for all patients with carbapenem-resistant GNB in 2008.[95] Soon thereafter, it became evident that the cocolonization of CRE with *A. baumannii* or *P. aeruginosa* was significantly associated with increased antimicrobial resistance (particularly to colistin and increased MICs to carbapenems[95]) and increased overall mortality.[94] Mobile genetic elements are easily transferrable in these settings and can cross the interspecies barriers.[96,97] This concept of cross-contamination of carbapenemases has also been demonstrated in shared room cohorting of CRE in LTACs.[98] In Israel, even inside the CRE cohort units, patients are separated based on the type of carbapenemse, that is, a carrier of bla_{KPC} is separated from a carrier of bla_{NDM}.

As with CPs, the possible negative psychological impact of cohorting must be considered and quantified longitudinally.[81]

THE ROLE OF THE ENVIRONMENT AND SHARED EQUIPMENT

Environmental contamination

MDR-GNB environmental contamination can occur on virtually any hospital surface, including the floor, the bed frame, the furniture, monitor screens and cables, the various pumps from which parenteral fluids and diet products are administered, the patients' clothes, and the bedsheets (see **Table 3**).[99,100] This most commonly occurs by a colonized patient shedding into his/her immediate vicinity.[100,101] This can result in patient-to-patient transmission primarily through health care workers, whose hands come in contact with the contaminated environment, particularly when HH is suboptimal. The non–glucose-fermenting GNB *A. baumannii* and *P. aeruginosa* have historically been associated with environmental reservoirs.[100,102] Both pathogens survive prolonged periods in low-nutrient environments and are relatively more resistant to some routine cleaning and disinfection products. CRAB can easily be cultured from every high-touch surface surrounding a CRAB carrier in acute-care settings.[103,104]

CRE have been found to contaminate the immediate vicinity of colonized patients as well, with the toilet and the floor around the toilet most frequently testing positive.[105,106] Water sources have also been increasingly implicated in the transmission of MDR-GNB in recent years, with sinks being recognized as a frequent source of

hospital-acquired infections.[107] A recent systematic review of MDR-GNB outbreaks originating from water sources found *P. aeruginosa* most commonly implicated, followed by *K. pneumoniae*, *A. baumannii*, and *Enterobacter* spp.[108] Drains, sink surfaces, and faucets were implicated as environmental sources by molecular techniques in the vast majority of cases.

Environmental cleaning

In many outbreak investigation reports of MDR-GNB, preventive bundles applied to successfully contain the outbreak included environmental cleaning, sanitation, and disinfection.[109–112] The CDC recommends that hospitals optimize baseline institutional policies relating to environmental cleaning.[113] Such policies must ensure the adequacy of cleaning and define responsibility for and frequency of cleaning and disinfection of equipment and surfaces and adequate training and retraining of all staff members that have responsibilities for cleaning and disinfection.

Rooms occupied by patients with MDR-GNB should be cleaned and disinfected at least once per day, and dedicated or single-use equipment should be used when possible. Cleaning policies should include the use of an Environmental Protection Agency–registered hospital-approved disinfectant.[113,114] Such surface disinfectant cleaners have been found to be effective against MDR-GNB.[115] Automated "no-touch" technologies such as automated ultraviolet C–emitting (UV-C) and H2O2-based devices are increasingly used for terminal room cleaning after discharge and as part of bundled response to new MDR-GNB outbreaks.[114,116] A recent cluster-randomized trial of standard quaternary ammonium terminal room disinfection versus bleach versus UV-C found that UV-C resulted in a lower incidence of MDRO infection or colonization among the subsequent occupants of the studied rooms.[117] Limited data exist for the prevention of MDR-GNB specifically; however, one study did find that UV-C resulted in less *A. baumannii* surface contamination after a terminal room clean than quaternary ammonium alone.[118]

Following the discharge or transfer of MDR-GNB–colonized patients, formal cleaning and disinfection of the room, its contents, and bathroom should be completed including the laundering of privacy curtains, cleaning, and disinfection of mattresses. Many facilities create specific terminal cleaning protocols for this purpose. Standard precautions do however apply for management of linen and waste from patients with MDR-GNB.[119,120]

Monitoring of cleaning

Monitoring of compliance with environmental cleaning via audits or other measures and distribution of regular cleaning audit reports[113,121] are now fundamental requirements in hospitals.[122] Invisible fluorescent marker or adenosine triphosphate (ATP) bioluminescence can be used to objectively evaluate the thoroughness of cleaning activities in patient rooms by confirming that surface cleaning or disinfection involves contact with all contaminated surfaces. Using ATP bioluminometers has provided quantitative evidence of improved cleanliness of high-touch surfaces after the implementation of an intervention program.[123,124] However, the general utility of ATP monitors is unclear in the absence of validated cleaning benchmark values.[124] Data connecting the level of cleaning to clinical outcomes including the acquisition of MDR-GNB are only recently starting to evolve.[125] Quantifying the exact contribution of improved cleaning on MDR-GNB acquisition will enable stakeholder administrators to weigh the benefits associated with investments aimed at improving the level of cleanliness.

Shared medical equipment

Shared equipment should be minimized in hospitals, particularly among patients with epidemiologically significant pathogens such as the MDR-GNB. Private phones, pens, and computer keyboards are all established vectors for MDR-GNB transmission.[126]

Various types of endoscopes, in particular, duodenoscopes and bronchoscopes, have been linked to multiple outbreaks of CRE and MDR *P. aeruginosa.*[127,128] Appropriate reprocessing of these devices is crucial to prevent the transmission of MDR-GNB. High-level disinfection (HLD) or sterilization should be performed by trained personnel and include visual inspection, manual cleaning, and leak inspection. Pathogen transmission has been described even when following the manufacturer's instructions for reprocessing; enhanced cleaning and reprocessing may be required in some instances and can include a double HLD process or liquid chemical sterilization and/or periodic performance of surveillance microbiologic cultures.[129]

Protocols for cleaning, disinfecting, and sterilizing shared equipment should be established and audited for compliance. Although single-patient-use stethoscopes and blood pressure cuffs are advocated for use among patients with MDR-GNB and in dedicated cohort units, evidence for the benefit of these items is lacking.[130,131]

THE ROLE OF ANTIMICROBIAL STEWARDSHIP

AMS is the core measure in the prevention of MDR-GNB[132] and is a core recommendation of the WHO Antimicrobial Resistance strategy (see **Table 3**).[133] AMS includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy administration, to maximize clinical cure or prevention of infection while limiting unintended consequences such as the emergence of resistance. The ultimate goal of AMS is to improve patient care and health care outcomes.[134]

The rationale for AMS programs is that when properly implemented, they can result in large reductions in the overall use of some antimicrobials[135,136] and reductions in MDR-GNB colonization or infection, both by decreasing the risk of *de novo* resistance evolution and reducing the likelihood of exogenous acquisition.[137,138] The benefit of hospital-based AMS has been replicated in many studies. A meta-analysis of 32 studies of the effect of AMS on infection or colonization with MDROs found an overall risk reduction of 51% for MDR-GNB acquisition (incidence ratio = 0.49, 95% CIs = 0.35–0.68).[139] An AMS program in China with restriction of broad-spectrum beta-lactams significantly reduced ceftazidime resistance among *P. aeruginosa* and *A. baumannii* and ciprofloxacin resistance among *P. aeruginosa.*[140] Similarly, in Denmark, the restriction of cephalosporins, fluoroquinolones, and carbapenems has resulted in a sustained reduction in the incidence of both colonization and infections caused by ESBL-producing GNBs.[141]

Hospital-based AMS strategies to reduce the risk of MDR-GNB are described in-depth in the chapter (Chapter 11: Antimicrobial Stewardship and the Infection Control Practitioner: A Natural Alliance. Available at: https://pubmed.ncbi.nlm.nih.gov/34362543/). LTCFs represent a particularly high-yield target because of high rates of antibiotic overuse and high MDRO colonization rates among residents.[142] Barriers to AMS in LTCFs include limited expertise and resources. Successful programs historically have included education campaigns, collaboration with local academic health systems or infectious disease physician groups, and buy-in from LTCF administrative leadership.[143,144]

THE ROLE OF DECOLONIZATION

Therapeutic options to treat and eradicate XDR-GNB (CRE, CRAB, and CRPA) are scarce with very few options available for decolonizing patients (see **Table 3**).[145] Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are measures that have been shown to reduce rates of ventilator-associated pneumonia and mortality among ICU patients in studies performed in low-MDRO prevalence settings in Holland.[146] Typical agents used for SDD and SOD include colistin, aminoglycosides, and amphotericin B. Evidence that the use of colistin as SOD[147,148] or SDD[149] can lead to the emergence of colistin resistance among human pathogens has limited use of this practice to a handful of countries including the Netherlands, where the rates of CRPA and CRAB are known to be low.[150]

In a small randomized, double-blind, placebo-controlled trial of SDD using oral gentamicin and oral colistin for the eradication of CRE carriage, the percentages of rectal cultures positive for CRE were significantly reduced at 2 weeks following the SDD regimen compared with the placebo arm [odds ratio (OR) = 0.13, $P<.01$].[151] The authors concluded that this SDD regimen could be a suitable decolonization therapy for selected patients colonized with CRE, such as transplant recipients or immunocompromised patients undergoing chemotherapy and patients who require major intestinal or oropharyngeal surgery.[151] A larger randomized trial with 8000 patients in European ICUs with a high prevalence of antimicrobial resistance did not find that SOD or SDD (colistin, tobramycin, and nystatin) reduced the risk of MDR-GNB bloodstream infections compared with daily CHG bathing.[152] We believe it could be potentially hazardous to administer colistin for decolonization purposes because it remains an essential therapeutic option for the treatment of invasive XDR-GNB bloodstream infections[153] and resistance to colistin is emerging in many parts of the world.[95,154]

The use of daily bathing with CHG 4% solution among functionally dependent (bathed in bed) or ICU patients may reduce the risk of MDR-GNB spread and new acquisitions, and it has shown efficacy in preventing additional HAIs (predominantly CLABSI).[155,156] This is a sensible infection prevention strategy for endemic units, among functionally dependent, mechanically intubated patients or patients with central lines.[157]

Fecal microbiota transplantation (FMT) could impact the prevention of CRE and ESBL infections and acquisitions because it has a track record of proven efficacy in *Clostridium difficile* infection.[158] Early trials of FMT for the decolonization of MDR-GNB have shown promise in reducing MDR-GNB colonization.[159] Efficacy and safety data on larger cohorts of carriers, for prolonged periods, will inform whether FMT should be recommended for reducing colonization with MDR-GNB, particularly considering recent reports of donor-to-recipient ESBL transmissions that have highlighted the importance of screening FMT donors for MDR-GNB colonization.[160]

COLLABORATION WITH LONG-TERM CARE FACILITIES

Because of the interconnectedness of hospitals and LTCFs, infection control interventions should ideally be implemented in parallel in both settings to maximize the effectiveness of prevention interventions among high-risk patients across the continuum of care.

In the Israeli nationwide CRE epidemic from 2006 to 2007, a stable decrease in new acquisitions was only evident after broadening the national prevention plan to include LTCFs.[8,67] This experience highlights the importance of close collaboration and communication between infection control programs in acute-care hospitals and surrounding LTCFs. Restrictions put in place to halt patient-to-patient transmission in

LTCFs should ideally be tailored to a facility, based on its structure, its residents' characteristics, the local colonization pressure, and the overall level of care provided in the facility. Sharing of resources, standardizing education and training, and improving interfacility communication regarding MDRO colonization status can allow for a more integrated infection prevention approach across different health care settings.[161]

SUMMARY

Antimicrobial resistance is a global iatrogenic complication of modern medical care. MDR-GNB are prevalent in most facilities, and their containment and treatment pose an enormous challenge. The authors' suggestions are as follows:

1. Active surveillance: screening to detect asymptomatic colonization
   a. ESBL: not routinely recommended
   b. CRE: establish populations who warrant screening based on local and regional CRE epidemiology. We also recommend using molecular assays to determine the presence and type of carbapenemases.
   c. CRAB: should be considered in endemic ICUs, on admission to the unit, and periodically thereafter. Respiratory samples (only from ventilated patients) and skin samples (from wide areas using designated sponges or wipes according to established methodology) are the basic body sites to target.
   d. CRPA: not routinely recommended
2. Containment
   a. HH is a core component in the prevention of MDR-GNB spread
   b. Contact isolation precautions
      i. ESBL: not routinely recommended
      ii. CRE: recommended for carbapenemase-producing and non–carbapenemase-producing CRE isolates
      iii. *A. baumannii*: recommended for all CRAB. Consider use for carbapenem-susceptible isolates in outbreaks or endemic settings
      iv. CRPA: recommended for all carriers
   c. Cohorting with dedicated staff
      i. Avoid "united cohort units" for more than a single MDR-GNB
      ii. ESBL: not routinely recommended
      iii. CRE: recommended for carbapenemase-producing CRE during epidemic spread and in hyperendemic regions.
      iv. CRAB: not routinely recommended, unless during outbreaks or high endemic states in ICU settings or LTACs.
      v. CRPA: not routinely recommended, unless during outbreaks.
3. Environmental cleaning and shared equipment
   a. Establish unit-specific cleaning protocols for units with unique features (eg, hemodialysis, operating rooms, certain outpatient clinics).
   b. Establish strict protocols for terminal cleaning following discharge of an MDR-GNB carrier.
   c. Regularly monitor the level of cleaning (preferably by quantitative processes) and disseminate the results for quality improvement purposes.
   d. Audit compliance with protocols for HLD or sterilization of high-risk shared medical devices such as duodenoscopes and bronchoscopes
4. AMS
   a. Establish an institutional AMS program, monitor adherence, and provide feedback to prescribing providers at regular intervals

5. Decolonization of MDR-GNB carriage
   a. SDD and SOD are not recommended for the routine prevention of MDR-GNB infections among ICU patients
   b. Daily bathing with topical CHG is recommended for functionally dependent patients bathed in bed, mechanically intubated patients, patients with central lines, and ICU patients in general, although efficacy data pertaining specifically to MDR-GNB prevention are limited

DISCLOSURE

This study was not supported financially by any external source. D. M. has received payments previously for lectures and research grants from Merck and GAMA Health care (unrelated to this study). J. P. M. has no potential conflicts of interest.

ACKNOWLEDGMENTS

None.

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