REVIEW ARTICLE

Carbapenem-Resistant *Enterobacteriaceae*: A Strategic Roadmap for Infection Control

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The incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) has increased worldwide with great regional variability. Infections caused by these organisms are associated with crude mortality rates of up to 70%. The spread of CRE in healthcare settings is both an important medical problem and a major global public health threat. All countries are at risk of falling victim to the emergence of CRE; therefore, a preparedness plan is required to avoid the catastrophic natural course of this epidemic. Proactive and adequate preventive measures locally, regionally, and nationally are required to contain the spread of these bacteria. The keys to success in preventing the establishment of CRE endemicity in a region are early detection through targeted laboratory protocols and containment of spread through comprehensive infection control measures. This guideline provides a strategic roadmap for infection control measures based on the best available evidence and expert opinion, to enable preparation of a multifaceted preparedness plan to abort epidemics of CRE.

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BACKGROUND

The incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) has markedly increased worldwide over the last decade. While almost unheard of at the beginning of the 21st century, in 2014, 7% of *Klebsiella pneumoniae* bloodstream isolates reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net) were carbapenem resistant.[1] Infections caused by CRE are associated with crude mortality rates of 44%–70%, due in part to limited therapeutic options.[2–6] Risk factors identified for carbapenem-resistant *K. pneumoniae* acquisition and infection include underlying medical conditions, critical illness, intensive care unit stay, poor functional status, and receipt of antibiotics.[3,7–9]

In developed countries, the epidemiology of CRE followed a pattern typical for hospital-acquired pathogens.[10] Initial sporadic occurrences were followed by single-hospital outbreaks, then spread along hospital patient referral routes (Figure 1). Hospitals that share the same patients are at a high risk of admitting colonized or infected individuals, providing sources for future outbreaks.[10] This natural history of CRE spread was well demonstrated in Europe, where between 2010 and 2013, 17 of 31 countries reported increased spread or endemicity of CRE.[11] The cardinal role of long-term care facilities (LTCFs) in the epidemiology of CRE, especially long-term acute-care hospitals (LTACHs) caring for mechanically ventilated patients, has also been demonstrated. Such facilities often serve as reservoirs and amplifiers of resistance.[12]

Proactive and adequate preventive measures are needed locally, regionally, and nationally to contain the spread of CRE, particularly in countries where CRE are not yet endemic.[13] This guideline, based on the best available evidence and expert opinion, updates the global epidemiology of CRE, summarizes experience with implementation of measures for the control of outbreaks caused by CRE, and creates a roadmap for infection control measures.

We performed an informal systematic review of the literature by searching PubMed between January 2006 and December 2015 for the terms "carbapenemase," "*Klebsiella pneumoniae* carbapenemase," or commonly used acronyms (eg, KPC, CRE, CPE, NDM, VIM, IMP, OXA) in combination with the names of individual countries and "detection" or "prevention" or "contact isolation" or "infection control."

THE GLOBAL EPIDEMIOLOGY OF CRE

The epidemiologically relevant carbapenemases can be grouped into 3 classes. In class A, *K. pneumoniae* carbapenemase (KPC) is clinically and epidemiologically the most important.[10] KPC-producing *K. pneumoniae* was first isolated in the United States in 1996.[14] KPC is spread primarily by clonal outbreaks in

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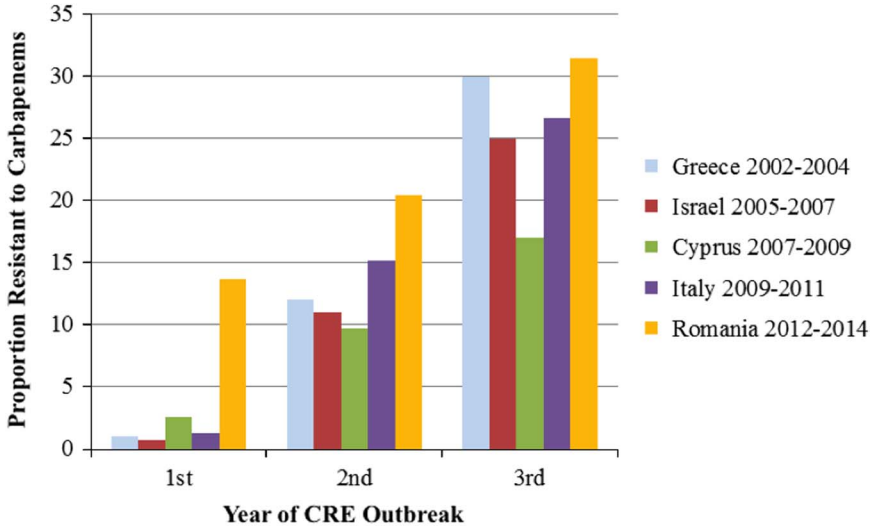

FIGURE 1. Natural history of carbapenem-resistant *K. pneumoniae* spread in 5 different countries during the first 3 years of the outbreak. This graph depicts the spread of carbapenem-resistant *K. pneumoniae* in Europe based on precise data by country and year available from European Antimicrobial Resistance Surveillance Network (EARS-Net).

healthcare facilities, with a single *K. pneumoniae* clonal complex, CC258, having played a major role in the dissemination of 2 KPC isoenzymes: KPC-2 and KPC-3.[14]

As of January 2015, at least 1 KPC-producing CRE isolate had been reported from 48 US states, and KPC has gained a foothold globally,[10,11,14,20–38] with established endemicity in the northeastern United States, Puerto Rico, China, Israel, England, Italy, Romania, Greece, Brazil, Argentina, and Colombia (Figure 2).[14–19]

Class B carbapenemases include the metallo-β-lactamases (MBLs), imipenemase IMP), verona integrin-encoded MBL (VIM), and New Delhi MBL (NDM-1). IMP producers were initially identified predominantly in Asia with more recent spread elsewhere (Figure 2).[16,17,21,36–43]

VIM enzymes were discovered in *P. aeruginosa* in Verona, Italy, in 1997, and were first reported in *Enterobacteriaceae* in 2002, in Athens. *K. pneumoniae*–producing VIM is endemic in Greece,[16,44] and VIM-producing *Enterobacteriaceae* are now spreading elsewhere, especially in Italy and Spain.[10,11,16,17,20,21,32,37–40,43–48]

NDM-1 spreads within and between species on a transposon. The main reservoir of NDM-producing *Enterobacteriaceae* is the Indian subcontinent (Pakistan, India, Sri Lanka, and Bangladesh),[49] where NDM is widespread both in healthcare settings and the community, spread in the latter is likely due to limitations in sanitation and hygiene.[25] Elsewhere, NDM was initially introduced via patients with recent hospitalization in the Indian subcontinent.[10,36,49,50] NDM is now emerging worldwide (Figure 2).[11,16,17,22,37–42,47,51–58]

Class D β-lactamases include the oxacillinases (eg, OXA-48–like enzymes).[10] The OXA-48 gene is primarily plasmid-based and is associated with clonal and nonclonal multispecies spread. OXA-48–producing *K. pneumoniae*, first described from a patient in Istanbul,[11,59] arose in the Mediterranean basin, likely in the community. Elsewhere, OXA-48 has led to healthcare-associated outbreaks.[16,39,60] OXA-48 is endemic in Malta,[11] and it is the most frequently detected carbapenemase in The Netherlands, France, and Belgium.[11,14,16,22] Outside Europe, it is spreading across all other continents (Figure 2).[11,16–19,32,37,40,46,55,61–73]

OXA-181 is a variant of OXA-48, which shares similar carbapenemase activity, and it has been identified in isolates from India or of Indian origin, often coexisting with NDM in single strains of *K. pneumoniae*. OXA-181 is present in much of Asia and has been sporadically detected in the United Kingdom, The Netherlands, Norway, France, South Africa, New Zealand, Oman, and Nigeria.[22,67,74,75] As the description above suggests, CRE are identified wherever antimicrobial resistance data exist.

STEPS IN THE CRE ROADMAP

This review provides a stepwise roadmap of infection control measures that are required to contain CRE in acute-care hospitals, LTCFs, and the community. Table 1 outlines the steps in the roadmap.

Step 1: Determine Whether CRE Have Been Isolated

The first step is to determine periodically whether CRE have been isolated from patients at the institution and the timing of cultures relative to admission dates (within 48 hours of admission or more than 48 hours after admission). On a regional or statewide level, CRE prevalence surveys should be completed under the guidance of public health authorities.[76]

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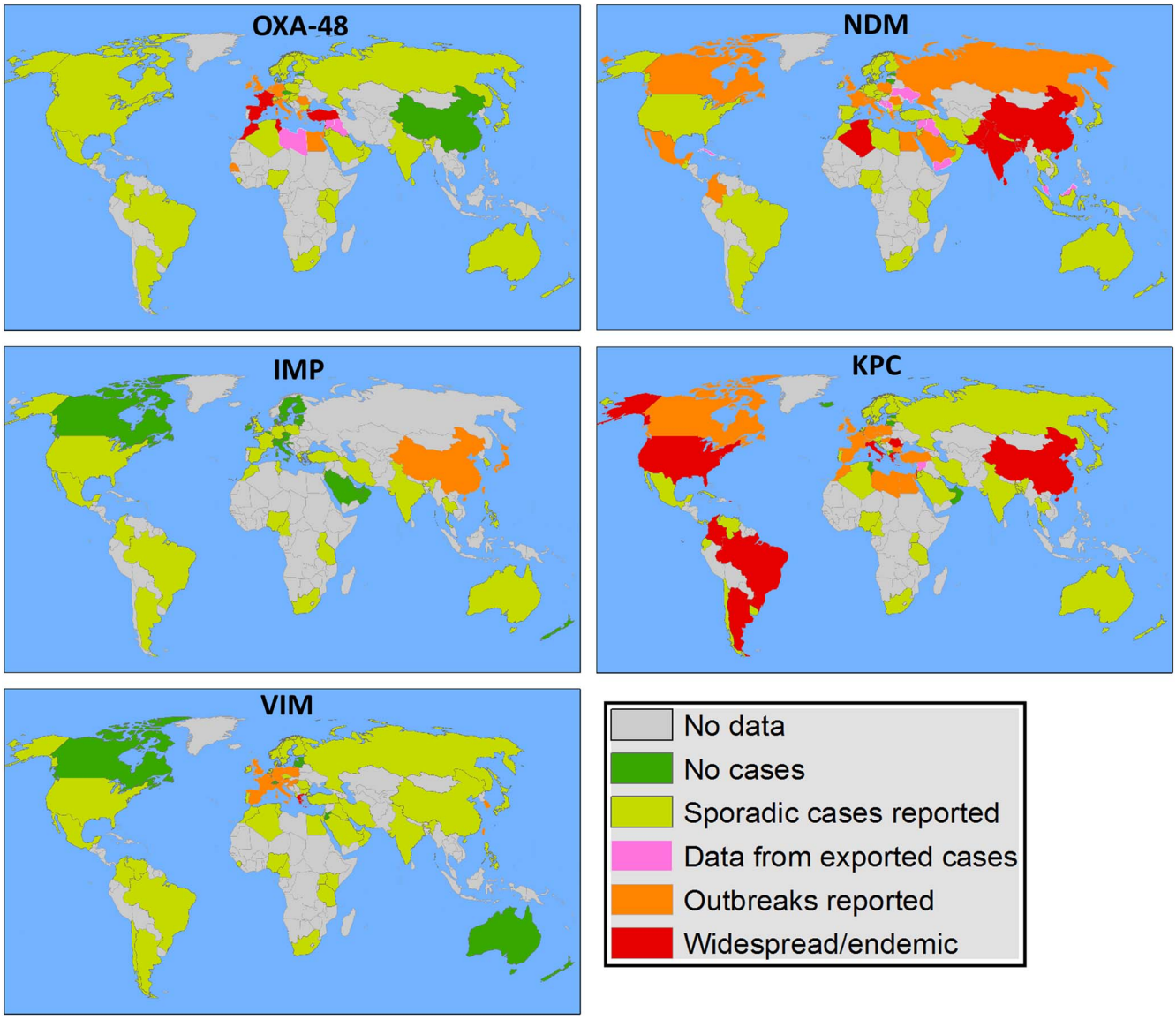

FIGURE 2. Occurrence and geographic distribution of carbapenemase-producing *Enterobacteriaceae* (CPE) worldwide by resistance mechanism, based on literature review, 2015. These maps are based on literature review. In some countries, the scale used may underestimate the true extent of the spread of CPE because of an absence of detailed data, making it difficult to distinguish between sporadic cases and outbreaks. Results presented here reflect reporting at the time of preparation of this review.

Facilities without this information should review archived laboratory results from the prior 6–12 months.[77]

CRE Have Not Been Isolated

If CRE have never been reported, highly sensitive detection criteria plus an early warning system and a preparedness plan should be put in place according to the steps in this roadmap.[10] The primary requirement is the microbiological laboratory capability to identify CRE phenotypically and genetically using uniform selective media and confirmatory tests (according to guidelines for detection) and a reference laboratory capable of timely molecular characterization of isolates.[10,76,78–82]

Step 2: Determine Affected Wards and Occurrence of Intrafacility Transmission

If CRE have been isolated, determine which wards are affected and whether evidence exists for intrafacility transmission. If data are not available, an audit is required to determine the proportion of all *Enterobacteriaceae* in the facility that are CRE. In known CRE-positive patients, the following factors should

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be determined: demographics, diagnoses, and wards, as well as risk factors such as surgery and antibiotics.

A simple, 5-level numerical staging system, proposed by Grundmann et al,[10] should be used to grade the epidemiology of carbapenem resistance in institutions, regions, states, and/or countries (Table 2). While recommended infection control measures adopted to confront CRE in different settings vary greatly,[13] the interventions chosen should be guided by the epidemiological stage.[10]

Sporadic CRE

If CRE have been identified sporadically, the goal should be to completely eradicate that CRE according to the 'search and destroy strategy' described by Wertheim et al[83] in reference to methicillin-resistant *Staphylococcus aureus* (MRSA) in 2004. This Dutch strategy, when utilized against CRE, is more accurately termed a "search and isolate" strategy, that incorporates active surveillance, contact tracing, and strict contact isolation in single rooms.[84] A suggested action plan for rapid implementation of infection control measures in settings with sporadic occurrence of CRE includes the following elements[78]:

- Screening of all contacts of index cases
- Epidemiological investigation of nosocomial cross-transmission events with >2 secondary cases
- Communication with staff and hospital administration
- Stringent infection control measures aimed at containment and eradication of nosocomial clusters
- Coordination and supervision by public health authorities

TABLE 1. Steps in the Carbapenem-Resistant Enterobacteriaceae (CRE) Preparedness Roadmap

Step 1	Determine whether CRE have been isolated
Step 2	Determine affected wards and occurrence of intra-facility transmission
Step 3	Implement early CRE detection and CRE containment measures
Step 4	Enhance existing infection control requirements • Healthcare worker education • Limit patient transfers • Environmental surface decontamination • Sanitary measures in the outpatient setting • Minimize the use of invasive devices to the extent medically feasible
Step 5	Regional strategy • Screening protocols • Infection control measures • Antimicrobial stewardship • Local laboratory capacity • Dedicated reference laboratory • Mandatory reporting • Centralized surveillance data collection and communications network • International considerations
Step 6	Investigate for community spread of CRE

Single-Hospital Outbreak of CRE

In suspected hospital CRE outbreaks in nonendemic settings, infection control teams must commence their investigations by ensuring that situations fulfill outbreak criteria by having 2 or more cases that are epidemiologically related.[10] Development of outbreak management teams is recommended to coordinate investigation of possible sources and mechanisms of transmission and to coordinate communication, education, contact screening, and expansion of infection control measures (Table 3). Consideration should also be given to closure or reduction in activity of high-risk units and to investigation for possible environmental reservoirs.[85–88]

Step 3: Implement Early CRE Detection and CRE Containment Measures

For sporadic hospital outbreaks or regional spread of CRE, infection control teams should be trained to implement measures to contain spread based on premises of early CRE detection and containment. Interventions must be adapted to local conditions, and institutions must decide which to implement first.

TABLE 2. Epidemiological Scale and Stages of Healthcare-Associated Carbapenem- Non-Susceptible *Enterobacteriaceae*[a]

Stage	Epidemiological Scale	Description
0	No cases reported	No cases reported
1	Sporadic occurrence	Single cases, epidemiologically unrelated
2a	Single hospital outbreak	Outbreak defined as ≥2 epidemiologically related cases in a single institution
2b	Sporadic hospital outbreaks	Unrelated hospital outbreaks with independent, ie, epidemiologically unrelated, introduction or different strains, no autochthonous interinstitutional transmission reported
3	Regional spread	>1 epidemiologically related outbreak confined to hospitals that are part of a regional referral network, suggestive of regional autochthonous interinstitutional transmission
4	Interregional spread	Multiple epidemiologically related outbreaks occurring in different health districts, suggesting interregional autochthonous interinstitutional transmission
5	Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources

[a]Adapted from Grundmann et al, Euro Surveillance 2010.[10]

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TABLE 3. Managing a Hospital Outbreak of Carbapenem-Resistant *Enterobacteriaceae* (CRE)

- Define the existence of an outbreak: ≥2 epidemiologically related cases in a single institution.[10]
- Establish a case definition.
- Develop an outbreak management team and plan a communication strategy.
- Implement early secondary case finding via screening of contacts.[87]
- Expand infection control measures including strict contact isolation ± patient cohorting and dedicated staffing.
- Epidemiological investigation to define the index case, local reservoirs, risk factors and transmission dynamic.[78,85]
- Review laboratory processes for CRE detection and molecular characterization.
- Develop in-house education modules for staff.[86]
- Consider investigating for an environmental reservoir as the source of the outbreak.[88]
- Monitor outcomes and communicate findings.

TABLE 4. Examples of High-Risk and Medium-Risk Patients for Carbapenem-Resistant *Enterobacteriaceae* (CRE) Screening Purposes

High-Risk Patients[87]	Medium-Risk Patients[7,9,94]
Ward contacts of newly discovered CRE carriers. Determination of contacts to be screened should be based on proximity to the index case, duration of exposure, and shared nursing staff.	Patients with a history of recurrent urinary tract infections
Patients transferred from another medical facility with known or suspected CRE prevalence, or having been cared for at such a facility in recent months. The exact timing of recent hospitalization needs to be defined.	Patients with a history of previous extensive antibiotic exposure in the community
Patients hospitalized in wards with high incidence and/or prevalence of CRE carriage	Older men and women
Patients who reside in a PACH or other LTCF (dependent on the known prevalence of carriage of CRE at these facilities)	Patients with underlying medical conditions, such as diabetes mellitus
Patients who have received medical care in high-risk countries from 2008 onward	Frequently hospitalized patients

NOTE. PACH, post–acute-care hospital; LTCF, long-term care facility.

While a staggered approach toward implementation may be undertaken,[1] a combination of early identification of asymptomatic CRE carriers followed by strict carrier and staff cohorting have been demonstrated to be particularly effective in controlling the horizontal transmission of CRE.[2]

Organizational characteristics, such as nursing staff levels and the presence of a safety culture, must also be considered in preparedness plans because these factors may influence the adherence of staff to required infection control practices. Strong and consistent inverse relationships have been reported between staffing levels and nosocomial infections.[89] More specifically, high levels of staff engagement have been shown to reduce CRE acquisition rates.[90] Active involvement of the hospital administration is therefore necessary in the development and support of programs to contain CRE.[91]

CRE DETECTION STRATEGIES

Screening

A proactive approach to screening is recommended. Screening includes both verification of continued carriage in those previously identified with CRE and detection of new asymptomatic carriage. Unidentified carriers with prior exposure to the healthcare system are a source for spread of CRE to other patients.[87] Clinical cultures obtained on suspicion of infection identify only approximately one-third of patients colonized with CRE.[92] It is therefore recommended that institutions develop the capacity both to verify continued carriage and to identify previously unrecognized colonized and infected patients on admission. Sweden, for example, boasts high levels of screening of patients for resistant *Enterobacteriaceae*. Patients screened on admission to Swedish hospitals include those who have received healthcare outside of Sweden during the past 6 months or within Sweden in areas with ongoing outbreaks.[93] National protocols regarding the detection of new, often asymptomatic carriers who require screening on admission or while in hospital are recommended. Such protocols should define which epidemiologically linked contacts of new CRE cases should be screened based on proximity to index cases, duration of exposure, and shared nursing staff,[87] and they should risk-stratify new patients to define those at risk for CRE (Table 4).[3,7,11,92,94]

The primary body site for screening is the rectum, sampled via swab or stool culture; these are the single most sensitive specimens for surveillance of CRE.[92,95] While routine sampling of additional sites has limited value,[78] the addition of inguinal or axillary skin swabs may improve yield.[92,96]

Notification

Rapid, real-time notification of culture results from the laboratory, enabling contact isolation to commence, is critical and requires close collaboration between microbiological laboratories and local and regional infection control teams.[78,97] Notification systems are recommended that function both to

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notify relevant infection control practitioners of new positive clinical or screening cultures and to alert staff when new admissions have a history of CRE infection or colonization. Such systems require that alerts be placed within the medical record (written and electronic) to enable repeat screening and contact isolation with future admissions, as appropriate.

CRE CONTAINMENT

Hand Hygiene

Patient-to-patient transmission in healthcare settings, usually via the hands of healthcare workers (HCWs), has been a major factor accounting for the increased incidence and prevalence of multidrug-resistant organisms (MDROs).[91] Hand hygiene within facilities must be promoted with an emphasis on HCW education. Hand-hygiene facilities must be accessible and conveniently located in all healthcare facilities.[91] Hand-hygiene guidelines (materials and methodology) are fully applicable in the setting of CRE, with no recommended alterations. In the Israeli intervention, alcohol-based handrub has been used as the predominant hand-hygiene agent, consistent with international guidelines.[98] Importantly, hand hygiene should be performed according to the WHO's 5 Moments model, including the measurement of performance and feedback to improve compliance.[99]

Contact Precautions

There is a direct relationship between colonization pressure and nosocomial CRE acquisition.[97] Effective national guidelines used in Israel incorporate physical separation of all hospitalized patients colonized or infected with CRE (in either isolation rooms or by creating carrier cohorts) and the use of dedicated nursing staff not assigned to care simultaneously for non-carriers. A significant inverse relationship between compliance with dedicated staffing guidelines and risk of CRE transmission was demonstrated. [97]

It is recommended that wherever possible, hospitals should dedicate rooms, equipment and staff for patients with CRE. Isolation on admission is recommended for patients known to be CRE carriers and for high-risk patients whose carriage status is not known.[85,87,91,92,100] The use of contact isolation in single rooms is dependent on single-room availability within institutions. Hospitals must determine, based on local epidemiology and risk factors among local populations, whether to isolate certain patients of unknown CRE carriage status preemptively pending culture results.

Discontinuation of Contact Precautions

There is no consensus guideline on discontinuation of contact isolation precautions among patients who were previously colonized or infected with CRE. MDR *Enterobacteriaceae* can persist for many months, especially in the presence of severe underlying disease, invasive devices, and recurrent courses of antimicrobial agents. In Israel, 35% of known carriers remained colonized when screened within 3 months of their initial identification as carriers,[101] and 30% of prior CRE carriers in LTCFs were CRE positive when cultured at least 90 days following their last positive culture.[102] Among patients with an initial positive rectal culture for CRE, even after 2 or more negative screening cultures, recurrence of CRE detection occurs in 15%–25% of patients.[103–105]

Careful risk assessment should be undertaken before removing previously culture-positive patients from isolation. More than 1 negative culture, from relevant body sites, is required to rule out continued CRE colonization. One approach is to require 2 negative surveillance rectal swabs and a negative carbapenemase gene polymerase chain reaction result on enrichment broth.[87,106,107] Uniform, evidence-based guidelines for revoking prior carrier status should be implemented at a regional or national level.

CRE Detection and Containment in LTCFs

Patients admitted from LTCFs can reintroduce CRE to acute-care hospitals, undermining containment efforts. Among LTCF patients, CRE risk factors include prolonged length of stay in acute care, sharing rooms with known carriers, and carrier prevalence on wards.[87]

Because the LTCF environment is different from that of acute-care hospitals, guidelines for the control of CRE must account for unhindered delivery of rehabilitation and socialization of residents. Point prevalence surveys in post-acute care hospitals (PACHs) and other epidemiologically relevant LTCFs are recommended in regions with CRE, both to measure CRE prevalence and to guide formulation of evidence-based recommendations for CRE surveillance and containment.[87,108]

Hand hygiene should be promoted in LTCFs, with guidelines adapted to these settings from the WHO hand-hygiene strategy.[109] Facilities should ensure access to adequate hand-hygiene stations that are well stocked with supplies.

The use of contact precautions for LTCF patients infected or colonized with CRE should not be routine, although targeted short-term interventions or even periodic ward closures may be required during outbreaks. In determining containment measures, CRE transmission risk should be considered, with contact precautions reserved for patients at highest risk of transmission based on such factors as incontinence of stool, ventilator dependence, and wounds with difficult-to-control drainage.[76] A successful approach employed in Israeli PACHs, codified in national guidelines, adapts recommendations to ward type and patient acuity. Recommendations for the highest-risk patients (eg, ventilated or skilled nursing patients) include CRE screening on admission, barrier precautions and cohorting for carriers, while for low-risk rehabilitation patients, modified contact precautions without cohorting or confinement of carriers to their rooms are sufficient.[87,102,108]

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Step 4: Enhance Existing Infection Control Requirements Education of HCWs

Education and training of HCWs regarding prevention of transmission, highlighting hand-hygiene and contact precautions, are prerequisites for ensuring that policies and procedures for standard and transmission-based precautions are understood and practiced correctly.[86] The CDC/HICPAC guidelines recommend targeting the following HCWs for education and training: medical and nursing staff, clinical technicians and laboratory staff, housekeeping staff, laundry, maintenance and dietary workers, students, contract staff, and volunteers. Training completion and competency assessment should be documented initially and repeatedly as appropriate for specific staff positions. It is important to ensure that HCWs employed by outside agencies also meet education and training requirements.[91]

Limitation of Patient Transfer

Patient transfer between healthcare facilities is a risk factor for the dissemination of resistant microorganisms. Cross-border transmission in European countries and inter-country transfer of multiresistant *K. pneumoniae* is well described and has led to the dissemination of CRE within hospitals.[27,35,71,110,111]

Facilities and regions should develop guidelines regarding patient transfers between facilities and countries, addressing issues such as the availability of screening results prior to patient transfer. In the context of rapid globalization, it is prudent to consider every patient transferred from foreign hospitals as at risk for CRE carriage.[24] Limiting patient transfers when feasible also can reduce the spread of CRE.[85] If transfer is unavoidable, communication with receiving facilities regarding CRE status is essential. Interfacility infection control transfer forms have been used successfully to communicate such information.[76,107]

Environmental Surface Decontamination

CRE can be eliminated from the environment by stringent application of normal standards of cleaning and decontamination, and no increased frequency of cleaning or special type of disinfectant is required.[107] Surface disinfectant cleaners have been found to be effective against gram-negative bacteria with multidrug resistance in the patient environment.[112]

Unlike *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which survive for long periods on environmental surfaces and may be transmitted to patients therefrom,[113–116] *Enterobacteriaceae* have not been associated with the same degree of risk for environmental transmission, likely due to their shorter environmental survival time.[116] CRE have been found infrequently in the environment of infected or colonized patients. In a recent study, only 8.4% of frequently touched surfaces in the rooms of patients colonized or infected with CRE were contaminated, with an average of only 5.1 colony-forming units per contaminated surface (120 cm^2). The surfaces that were most commonly culture positive were the toilet and the floor around the toilet. Poor organism survival (<15% at 24 hours, <5% at 48 hours, and no survival at 72 hours) was found when surfaces were inoculated with CRE, especially *E. coli*.[117] In another study, only 0.8% of 1160 environmental surfaces in French nursing homes that housed patients infected or colonized with extended spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae* were culture positive.[118]

We recommend that rooms occupied by CRE-positive patients be cleaned and disinfected at least once per day and that dedicated, single-patient or single-use equipment be used when possible. Following discharge or transfer of CRE-positive patients, terminal cleaning and disinfection of the room, its contents, and the bathroom should be performed, including laundering of privacy curtains and cleaning and disinfection of mattresses. Standard precautions apply for management of linen and waste from CRE-positive patients.[107,119] Hospitals must define responsibility for and frequency of cleaning and disinfection of equipment and surfaces and monitor compliance.[76]

Sanitary Measures in the Outpatient Setting

Few data exist on the risk of hospital-acquired infections in ambulatory care settings outside of hemodialysis centers.[85] Patient-to-patient transmission of ESBL-producing *K. pneumoniae* occurs in patients with hospital time overlap, and the incidence of transmission is higher for *K. pneumoniae* than for *E. coli*.[120,121] In addition, a Spanish study of ESBL-producing *E. coli* among non-hospitalized patients found no evidence of either horizontal transmission or clonal spread.[122] The rate of spread of *Enterobacteriaceae* is low and likely requires more than brief exposure.[123] Although further data specific to CRE are needed, existing data and data extrapolated from other MDROs[124] suggest that outpatients with CRE, especially those with draining wounds, incontinence, or other transmission risk factors should be seen after other patients, with full terminal cleaning of examination areas following visits.

Minimizing the Use of Devices

Indwelling devices, such as urinary catheters (IDC), central venous (CVC) and arterial catheters, endotracheal tubes, and synthetic implants facilitate the development of infection by providing surfaces for adherence of pathogens and the development of biofilms.[125] CRE have been implicated as a cause of device-associated infections, particularly catheter-associated urinary tract infections. In a recent outbreak of NDM-1–producing *Enterobacteriaceae* in South Africa, each additional day of exposure to an IDC or CVC was associated with 7% or 8% increased odds, respectively, of acquiring NDM-1 infection.[126] Therefore, limiting the use of invasive devices is another important intervention for CRE prevention. It is imperative that both vascular and urinary catheters be inserted only for

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appropriate indications, that aseptic technique be used for insertion, and that catheters be removed as soon as possible.[127]

Decolonization of Patients

Bathing with chlorhexidine has a role in bioburden containment and has been demonstrated to reduce the transmission of resistant organisms and the acquisition of hospital-acquired and line-associated bloodstream infections among patients in ICUs and LTACHs.[128–130] While some studies showed no effect on the incidence of colonization or hospital-acquired bloodstream infections with highly resistant *Enterobacteriaceae*,[129,131] bundled together with other measures, chlorhexidine has been shown to prevent KPC colonization and infection in LTACHs.[132]

Selective gut decontamination has been shown to reduce the incidence of ventilator-associated pneumonia,[133] but this strategy is known to increase ceftazidime resistance. In settings with high levels of endemic MDROs, it is associated with increased selection of such pathogens.[67,134] Although Zuckerman et al[135] achieved a 66% eradication of CRE using gentamicin, gut decontamination is not recommended for CRE control due to limited data on long-term eradication rates and the risk for emergence of pan-resistant strains.

Fecal microbiota transplantation (FMT), highly effective against *Clostridium difficile* infection, has emerged as a promising therapy for intestinal MDR bacterial decolonization. Several case reports have shown that FMT resulted in intestinal decolonization of ESBL-producers and CRE. Data from large trials currently underway will help determine whether FMT can be recommended for CRE decolonization.[136]

Step 5: Regional Strategy

We define the "regional" body as the public health authority with regulatory oversight over all healthcare institutions within a region, state, or country. Public health authorities are uniquely positioned to act because their activities span the full spectrum of health care, from community education to prevention efforts in all healthcare institutions. A regional strategy governing the following infection control measures is advised: screening protocols, surveillance data collection, measurements of laboratory capacity, a dedicated reference laboratory, recommendations regarding infection control measures, antimicrobial stewardship requirements, mandatory reporting, communication, and international considerations (Table 1).[10,11] Such strategies are reliant on political and financial commitment at the national level, ideally with international collaboration to respond to the global threat of CRE.

Local outbreaks of CRE have been shown to continue with accelerating incidence rates at multiple hospitals despite local infection control efforts.[13,87] National centers and strategies incorporating mandatory reporting of CRE cases with strict adherence to screening and contact isolation guidelines have been successfully employed in both Israel and France.[14,97,137] In many European countries, CRE are now included in mandatory reporting systems, and isolates are transported from clinical laboratories to national reference laboratories for characterization.[93,138] A national strategy including the addition of CRE infection/colonization to existing lists of reportable conditions is recommended.[11,139]

Central surveillance data collection at local and national levels is also necessary to detect temporal and geographical trends.[10] Without a national detection system for CRE, the nationwide character of a CRE outbreak may go unnoticed, delaying appropriate intervention. [97] The establishment of centralized surveillance for both antimicrobial resistance and antimicrobial use, as exists in many countries, is also recommended.[14,22,140,141] Apart from centralized data collection, a nationwide real-time network of communications is required to manage a large-scale countrywide CRE outbreak.[87] Unfortunately, in resource-limited settings, the capacity to perform surveillance and respond to the threat of MDROs is largely absent.

Local and National Antimicrobial Stewardship (AMS) programs

AMS is an important part of efforts to control MDROs,[91] and establishment of national AMS standards or guidelines is a core recommendation of the WHO Antimicrobial Resistance strategy.[142,143]

Guidelines for treatment of infections should be reviewed to ensure that alternatives to broad-spectrum agents are provided and that de-escalation of antibiotics and reductions in use of specific antimicrobial classes and total antibiotic burden are emphasized.[139,144] Antimicrobials such as carbapenems, fluoroquinolones, and metronidazole have been identified as possible risk factors for acquisition of CRE.[3,6,92,101] In the setting of CRE transmission, whether sporadic or epidemic, it is important to ensure minimization of unnecessary and unnecessarily broad-spectrum antibiotic use. Existing AMS interventions may need to be enhanced by stricter pre-prescription approval systems and timely postprescription review.[35] Antibiotic use should also be quantified by periodic audits. Ideally, detailed antimicrobial consumption trends should be available, as is the case in Europe and Canada.[1,140] Delivery of institution- or unit-specific antimicrobial consumption data can engage prescribers and improve compliance with guidelines.[145,146] Verbal and written feedback, ideally including explicit targets and action plans, are valuable.[147]

Local antibiotic treatment guidelines should include recommendations for treatment of proven and suspected infections caused by CRE.[85] Local guidelines should reflect the antibiotic susceptibility profiles of previous local CRE isolates. Selective reporting of susceptibilities of only the most appropriate agents is sensible, with extended susceptibilities available on request. Finally, clinical teams must be educated to ensure that they have good understanding of the

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implications of CRE colonization and infection for antimicrobial prescribing.

Local Laboratory Capacity

The contribution of diagnostic laboratories to both infection control and public health is often underappreciated and underfunded.[10] National strategies should ensure the capacity of local laboratories to perform susceptibility testing utilizing internationally recognized uniform break points and recognized methodologies. There must be agreement on the minimum test requirements for detection and data reporting of CRE with regular quality assurance.[78,97]

Uniform laboratory guidelines should be issued for screening of *Enterobacteriaceae* for carbapenem resistance and the phenotypic and molecular workups of CRE isolates for carbapenemase production, including carbapenem hydrolysis testing and carbapenemase gene detection.[76,78–82,87] Microbiology laboratories must be able to distinguish carbapenemase-producing isolates from CRE with other mechanisms of carbapenem resistance because of the differing epidemic potential of these organisms. Available data suggest that, in general, carbapenemase-producing (CP) *Enterobacteriaceae* (CPE) have a greater potential for nosocomial spread than non-CP CRE, as evidenced by the small number of reported outbreaks of non-CP CRE and by the reduced virulence of porin-mutant strains.[148] For example, among NDM-1–producing strains, some specific sequence types and successful clones are important for dissemination.[149] In addition, $bla_{\text{OXA-48}}$ can successfully spread horizontally and has strong epidemic potential.[66] Finally, carriage of a single CRE type does not confer immunity against infection with others; therefore, isolation measures to separate carriers of a single type from carriers of another are warranted.[87]

Reference Laboratories

Creation of reference laboratories to handle molecular diagnostics should be part of a coordinated regional control effort. Such reference laboratories are already in place in many European countries to identify the resistance mechanisms and to confirm carbapenemase production.[20,22,93,138]

International Considerations

In combating CRE, important international considerations include mechanisms to determine the scope of antimicrobial resistance in all countries, including those that are resource limited, and to inform neighboring countries about the prevailing epidemiology of resistant bacteria, so that safe policies for cross-border patient transfer can be established.[10] Importation of CRE may occur due to returned travelers, medical repatriation of patients, and medical tourism.[22]

The spread of KPC- and NDM-producing *Enterobacteriaceae* during the 2000s due to cross-border transfer of patients between healthcare facilities highlights the urgent need for both formalized CRE screening procedures by international and national health and travel insurance providers and global antimicrobial resistance surveillance systems.[22,27,68] Global surveillance systems incorporating molecular characterization can ensure early recognition of novel resistance mechanisms and the emergence of successful international CRE clones or sequence types.[68]

Global or regional networks for tracking antimicrobial resistance already exist. Examples include the SENTRY program developed in 1997, which incorporates North America, Latin America and Europe, and the National Healthcare Safety Network at the US Centers for Disease Control and Prevention.[150,151] Other networks include the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR), and EARS-Net, funded by the European Centers for Disease Control.[1,152] In addition, the Study for Monitoring Antimicrobial Resistance Trends (SMART) has been ongoing since 2002 in most regions of the world, with 192 hospitals currently participating.[36,49,70,153]

Step 6: Investigate for Community Spread of Carbapenemases

In developed countries, carbapenemase-producing bacteria are usually acquired in the healthcare setting. In developing countries, however, the spread of carbapenemases (primarily NDM-1 and OXA-48) occurs largely in the community via the fecal–oral route, by waterborne and foodborne transmission.[154] CRE have been identified in hospital sewage in China, Spain, and Brazil, in regular sewage on the island of Barbados, and in river water in Portugal.[14,155–157] CRE has recently been found in retail chicken meat in Egypt and in fresh vegetables and spices imported from Asia.[158,159] As with other enteric bacteria, waterborne outbreaks occur on a larger scale than foodborne outbreaks.[85]

In countries with a high burden of community CRE, strategies for CRE containment may differ. The remedy to community spread is complex and multifactorial and depends on improved sewage systems and their separation from potable water, adequate chlorination of drinking water and improved sanitation in food preparation. Countries in which CRE are not currently endemic need to be aware of the risks of importing CRE from countries where community spread occurs secondary to travel, medical tourism, immigration, and trade.

In conclusion, to prevent CRE from becoming widespread in nonendemic locations, collaboration is needed among healthcare providers, facilities, and public health authorities. Inadequate, delayed responses to the spread of resistant bacteria have been common and are associated with increased morbidity and mortality. The experience of countries with widespread CRE should serve to caution countries where CRE are still rare or absent to be alert and prepared for its emergence and preemptively to form centralized plans for detection and control of CRE. Countries currently

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without endemic CRE need to be in the preparation phase of multifaceted responses that should ideally be implemented before CRE have entered a region, or at the very least, immediately after its recognition.[160] Coordinated responses should come from policy makers and public health authorities, following a roadmap based on international experience.

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