Screening for carbapenem-resistant Enterobacteriaceae: Who, When, and How?

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ABSTRACT
The global spread of carbapenem-resistant Enterobacteriaceae (CRE) has been fostered by the lack of preemptive screening of patients in healthcare facilities that could prevent patient-to-patient transmission. Outbreaks of CRE infections have led some institutions to implement rigorous screening programs, although controlled comparative data are frequently lacking. Resource limitations and uncertainty regarding the optimal approach has kept many facilities from enacting more active routine surveillance policies that could reduce the prevalence of CRE. The ideal population to target for screening, the frequency of testing, and the preferred test method are components of surveillance programs that remain open to debate. This review discusses the rationale for different screening policies in use and the performance characteristics of laboratory methods available to detect CRE carriage.

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Introduction
In light of the limited therapeutic options and substantial mortality associated with infections caused by carbapenem-resistant Enterobacteriaceae (CRE), prevention is of the utmost importance.1,2 There are 2 primary modes of CRE acquisition thought to occur in the healthcare environment: 1) patient-to-patient transmission (i.e., from another patient, through healthcare staff, the proximal environment, or shared equipment); and 2) emergence of resistance, in which carbapenem susceptible isolates within a patient are genetically altered.3 The relative importance each mode plays is not known, but both must be considered to ensure a comprehensive infection prevention strategy. Measures to address patient-to-patient transmission include: 1) hand hygiene, 2) contact isolation precautions, 3) cohorting with dedicated staff, 4) environmental cleaning, 5) decolonization protocols, and 6) surveillance programs to identify asymptomatic carriage.4,5 In contrast, tackling the emergence of resistance requires enforcing antimicrobial stewardship policies to avoid unnecessary use of broad-spectrum agents (especially carbapenems).3 This review will focus on current practices and scientific evidence supporting CRE screening to identify asymptomatic carriers and implement patient-to-patient containment measures. Decisions regarding CRE screening are usually based on the local epidemiology and resources available in the institution. Because multiple measures have been simultaneously employed to control or prevent outbreaks and reduce the rate of CRE infections, the specific impact of active surveillance is unclear.6 Expert opinion rather than high quality scientific evidence guides most CRE screening policies.

Epidemiology of CRE
Carbapenemase-producing (CP) CRE harboring plasmid-encoded resistance genes that easily spread to different species emerged in the mid-1990s.7 The predominant carbapenemase produced by CP-CRE worldwide is the Klebsiella pneumoniae carbapenemase (KPC) family encoded by the blaKPC gene.8 Since its initial recognition, the KPC carbapenemase has been detected in organisms other than K. pneumoniae, including Klebsiella oxytoca, Enterobacter spp., Escherichia coli, Salmonella spp., Serratia spp., Citrobacter freundii, Proteus mirabilis, Acinetobacter baumannii, Pseudomonas aeruginosa, and Pseudomonas putida.7,9 Additional carbapenemases that have been associated with epidemics in Enterobacteriaceae include the Verona integron-encoded metallo-ß-lactamase (VIM), New Delhi metallo-ß-lactamase (NDM), Imipenemase (IMP) metallo-ß-lactamase, and Oxacillinase-48-type (OXA-48) enzymes.10 As of April 2016, in the United States, only 2 states have not reported KPC-producing CRE to the Center for Disease Control and Prevention (CDC).11 157 patients were reported with NDM, 61 patients with OXA-48, 17 patients with VIM, and 10 patients with IMP.11 These numbers are felt to
represent the proverbial tip of the iceberg. Plasmid-encoded carbapenemases of primary concern and areas of endemicity are summarized in Table 1.

The food supply is another potential reservoir of CP-CRE with detection reported in retail chicken meat in Egypt and in fresh vegetables and spices imported from Asia.12,13 A blanDM-1-carrying strain of Acinetobacter was detected in chickens from animal farms in China, and blaqOXA producing isolates were detected among cattle in France.14,15 Although it is difficult to quantify the impact of these findings on human CRE infections, emergent efforts to address antimicrobial use in agricultural industry are clearly needed.

In less than a decade, a transposon (Tn4401)-mediated outbreak of KPC-producing CRE has disseminated worldwide.8,13,16 While outbreaks were initially seen mainly in acute-care hospitals, the spread to non-acute care healthcare facilities rapidly followed.17-19 In less developed countries, CRE could also be isolated in community settings among patients with no recent healthcare exposure.12,13 Therefore, prevention of CRE should be targeted through the whole spectrum of the modern continuum of medical care.18 In the Israeli nationwide CRE epidemic for example, a stable decrease in new acquisitions was achieved only after broadening the prevention plan to long-term care facilities (LTCF).20,21 Therefore, this review will focus on screening for CRE among facilities from both acute-care and long-term care facilities.

The use of surveillance cultures has become an essential tool in infection control programs, not only during outbreaks but also as a routine measure in settings endemic for CRE.21 Screening patients to identify asymptomatic colonization, and instituting preemptive contact isolation measures reduces patient-to-patient transmissions and the colonization pressure, and improves patient outcomes by decreasing the delay in initiation of appropriate antimicrobial therapy.22 Active surveillance can estimate the colonization pressure better than cultures obtained from clinical samples alone.23 Moreover, delay in initiation of appropriate antimicrobial therapy is the strongest modifiable independent predictor for mortality in severe sepsis in general, and specifically in CRE infections as well.24,25

### Who should be screened and when?

Common risk factors reported for CRE acquisition in acute care hospitals include exposure to antimicrobials (not solely to carbapenems),3,26 high co-morbidity indexes, deteriorated functional status and/or cognition at baseline, recent LTCF stay, and recent invasive procedures or permanent foreign devices.13,26-30 Older age and immunosuppression are additional risk factors seldom reported, but are perceived mainly as confounders, and not as established independent predictors for CRE acquisition.26 Identifiable risk factors for acquisition of CRE in LTCF include prolonged length of stay in acute-care facilities, sharing rooms with known carriers, and a high degree of colonization pressure.21,29,30 Screening for CRE is a practice recommended by many national and international bodies,21,31 although controlled efficacy analyses are lacking. In Israel, the distribution of national guidelines in 2008 requiring all facilities to implement a CRE acquisition strategy,13,26,28 are patients admitted directly from long-term acute-care facilities (LTAC), other LTCFs with known endemicity, or patients who are transferred directly from another acute-care hospital. Recent hospital stay (in the previous 6 months),21 functional dependency,33 inter-ward transfers in the facility, prisoners, and patients from foreign countries with high endemic rates, are additional candidates for CRE screening.21,31 In Israeli LTCFs, screening is recommended for all new admissions that are transferred directly from an acute-care hospital or patients admitted from home with extensive healthcare exposure.18,29,34 Both the CDC and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) support additional periodic screening policies in the facility (e.g., weekly), for hospitalized patients in certain high-risk units (e.g., ICUs, LTACs).31 Populations that are candidates for screening are summarized in Fig. 1.
How to screen?

New laboratory methods have been introduced to improve detection of carbapenemase-producing organisms (CPOs). Determining whether a CRE is carbapenemase producing based on susceptibility testing results can be difficult since the presence of other mechanisms of carbapenem resistance (e.g., porin loss, cephalosporinases) can elevate the MIC. The changing epidemiology of carbapenemases further complicates the task since methods must be optimized to ensure all relevant circulating enzymes associated with CP-CRE are detected. In addition, the role of non-CP CRE, in terms of its epidemiological significance, and the impact of certain infection control measures on its rate of acquisition, is still a matter of ongoing debate.

CRE detection from cultures

Enterobacteriaceae isolates with KPC enzymes were not initially recognized because the carbapenem MICs were in the susceptible range when applying breakpoints to susceptibility test results. To address this problem with CP-CRE detection, the Clinical and Laboratory Standards Institute (CLSI) published recommendations in 2009 for Enterobacteriaceae with carbapenem MICs of 2 or 4 µg/ml and resistant to all third-generation cephalosporins to be tested further with the modified Hodge test which has good sensitivity for KPC. Problems with this approach included the modified Hodge test not reliably detecting non-KPC enzymes such as NDM and false positives with E. coli, C. freundii, and Enterobacter spp.

Another hindrance with the initial CLSI CP-CRE detection guidance was the more recent discovery that CRE producing OXA-48-type enzymes may be susceptible to third-generation cephalosporins and only resistant to eritapenem. In 2010, CLSI published lower carbapenem breakpoints (Table 2) based on review of clinical outcome, MIC distribution, and PK/PD data making performance of the modified Hodge test optional for epidemiologic purposes. Establishing a carbapenem breakpoint that would reliably distinguish all CP-CRE from those without carbapenemase production is hindered by overlapping susceptibility profiles. The PK/PD data suggest the small population of CP-CRE isolates with carbapenem MICs below the new breakpoint can be effectively treated with a carbapenem. However, this is not supported by prospective controlled trials.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) approach is similar, but breakpoints

| Table 2. CLSI and EUCAST carbapenem susceptibility testing breakpoints (µg/ml)40,45 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | CLSI            | EUCAST          |                  |                  | Screening for CPO |
|                  | S   | I   | R   |     | S   | I   | R   |     |                  |
| Doripenem        | ≤ 1  | 2   | ≥ 4  |     | ≤ 1  |     |     |     |                  |
| Imipenem         | ≤ 1  | 2   | ≥ 4  |     | ≤ 1  |     |     |     |                  |
| Meropenem        | ≤ 1  | 2   | ≥ 4  |     | ≤ 0.5|     |     |     |                  |
| Ertapenem        | 0.5  |     | 2    | ≥ 0.5|     |     |     |     |                  |

Notes.
* S, susceptible; I, intermediate, R, resistant.40,45
are higher than CLSI and they acknowledge that some CPO may test susceptible.43 This approach of encouraging laboratories to simply rely on the MIC for CPO detection has been met with criticism.44 In 2013, EUCAST responded by adding separate CPO screening cut-off values for infection control and public health purposes (Table 2) that are considerably lower than the clinical breakpoints.45

In 2015, the CDC CRE surveillance definition was revised to one of 2 criteria: 1) resistance to any carbapenem according to current CLSI breakpoints (MIC ≥2 for ertapenem or ≥4 for doripenem, meropenem, or imipenem) or 2) demonstration of carbapenemase production.32 For bacteria such as Proteus spp, Providencia spp., and Morganella morganii that naturally have elevated MICs to imipenem, a carbapenem other than imipenem must test resistant to meet the CRE surveillance definition. Besides the modified Hodge test, a number of other methods (Carba NP, molecular methods, metallo-β-lactamase testing) are considered acceptable to demonstrate carbapenemase production. Despite sensitivity and specificity issues with the modified Hodge test, it continues to be included as an acceptable method for carbapenemase production because it is widely used by laboratories. CLSI has endorsed the CarbaNP test, a colorimetric pH-based method for detecting carbapenem hydrolysis in isolates, but the sensitivity for OXA-48-type enzymes is poor (38.5%) and the reagents are only stable for 72 hours.46–48 A new carbapenem inactivation method (CIM) appears promising with initial reports of 96-100% sensitivity for KPC, metalloenzymes and OXA-48-like enzymes and results as quickly as 8 hours.49 To perform the CIM, an organism being evaluated for carbapenemase production is incubated in broth containing a carbapenem disk to the agar. Colonies growing around the disk on a lawn of carbapenem susceptible E. coli; no zone of inhibition indicates a positive test for CPO.

A significant advancement in CPO detection has occurred with the availability of FDA -cleared molecular methods to detect specific resistance genes (KPC, NDM, VIM, IMP, OXA) from positive blood cultures. Decreased length of stay and lower mortality has been demonstrated when rapid detection of resistance genes is provided in conjunction with antimicrobial stewardship interventions.50 As part of CRE prevention efforts, CDC encourages laboratories to screen CRE for specific carbapenemase enzymes (KPC, NDM, OXA-48-type) if they have the capacity.32 Some countries however, mandate that every CRE be subjected to specific carbapenemase determination by a molecular method, not relying solely on phenotypic determination of the presence of a carbapenemase.31 Although it is prudent to place all patients with CRE in contact isolation, only CP-CRE require more extensive interventions (e.g., screening patient contacts, cohorting patients with dedicated staff).

**CRE detection from rectal or perirectal swabs**

The Israeli ministry of health allows specimen collection for detection of CRE carriage using a rectal swab, but not a perirectal swab.51 The CDC includes the option of a perirectal swab because this site is preferred by patients and considered safer than an internal rectal swab collection for neutropenic patients. Equal sensitivity of rectal and perirectal swabs for detection of vancomycin-resistant enterococci colonization has been demonstrated,52 but similar data for CRE detection is lacking.

Screening patients for CPO using the CDC method from a rectal or perirectal swab is labor intensive and can take up to 4 days, but utilizes reagents, equipment and skills already available in the clinical laboratory. Commercial chromogenic agars have been developed, but none are FDA cleared, putting the burden on laboratories to perform an extensive validation prior to use. One limitation of studies evaluating performance of CP-CRE screening methods is that a convenience sample of pure cultures rather than rectal or perirectal swabs is often used. In addition, many studies only include KPC-producing strains. Evaluations of culture-based methods performed on rectal or perirectal swabs are summarized in Table 3.

The CDC broth enrichment method requires overnight incubation of a rectal swab in 5 ml of trypticase soy broth (TSB) containing a 10 µg carbapenem (meropenem or ertapenem) disk. Subculture of the broth onto MacConkey agar includes the option of adding a carbapenem disk to the agar. Colonies growing around the disk require identification and susceptibility testing or a phenotypic method for carbapenemase production which may lead to a turnaround time of 4 d. The CDC states the method was only validated for E. coli and Klebsiella spp. as reflected in the instruction to only look for lactose fermenting colonies on the MacConkey agar.53 However, detection of bacteria other than non-lactose fermenters can identify important reservoirs of carbapenemase-producing resistance genes.54 The reported sensitivities of the CDC method for KPC and VIM range from 65.6% to 98.8% with specificities of 49.6 to 100%.55–58 The sensitivity of the CDC method for detection of OXA-48 was only 57.6%.59

A screening method with 24–48 hours turnaround time involves direct inoculation on MacConkey agar with placement of carbapenem disks where the first quadrant meets the second quadrant and where the third quadrant meets the fourth.60 The reported sensitivities of MacConkey agar with carbapenem disks ranged from
75.8 to 96.9% with specificities of 73.8 to 100%. Evaluations of KPC carriage using MacConkey agar with imipenem demonstrated sensitivities of 78.3% to 89.5% and specificities of 31.9 to 99.4%.

Chromogenic agars can shorten turnaround time by eliminating the overnight incubation required for the enrichment step. Examples include Brilliance CRE (Thermo Diagnostics, USA), CHROMagar KPC (CHROMagar, France), chromID Carba (bioMerieux, France), chromID OXA-48 (bioMerieux, France), HardyChrom (Hardy Diagnostics, CA, USA), Supercarba (bioMerieux, France), and SpectraCRE (Thermo Diagnostics, USA).

The authors of an extensive review of surveillance methods to detect intestinal carriage of CPOs, favor chromID Carba for culture based screening unless OXA-48 incidence is high which then merits the addition of an OXA-48-specific medium (e.g., chromID OXA-48) or Supercarba. A recent evaluation demonstrated good performance of the direct MacConkey method in detecting carbapenem-resistant organisms, but the molecular Check-Direct CPE screen assay for BD MAXDirect and the chromID Carba were most sensitive for CPO detection and a broth enrichment step was not needed.

Advantages of using molecular assays to screen for carbapenemase genes include labor savings, faster turnaround time, and higher sensitivity than culture-based methods. Commercial molecular assays utilize multiplex PCR, microarray, or isothermal amplification technology to detect carbapenemase genes. The manufacturers include Check-Points Health (Check-Direct CPE), Amplex Biosystems (Eazyplex SuperBug complete A, Eazyplex Superbug complete B) and Cepheid (Xpert Carba-R).

A comparison of Xpert Carba-R, Eazyplex Superbug complete A and Check-Direct CPE kit for detection of carbapenemase genes in isolates demonstrated 100% sensitivity for KPC, NDM, and VIM, but only the CHECK-Direct CPE detected all OXA-48 genes. Suboptimal detection of OXA-48-like genes by Xpert Carba-R has also been noted by other investigators. A multicenter study of the Xpert Carba-R performance on rectal swabs (383 clinical and 250 contrived samples) with comparison to culture and sequencing reported 96.6% sensitivity and 98.6% specificity for detection of IMP-1, VIM, NDM, KPC, and OXA-48.

The projected annual reagent and labor cost of PCR to screen 6,860 specimens at an academic medical center with CRE-CRE prevalence of 2.7% was approximately 10 times higher than the CDC-recommended phenotypic method ($224,596 vs. $22,818 US dollars). However, the longer turnaround time of the culture-based method means a patient may be unnecessarily placed in preemptive isolation for 3 d longer which has been estimated to cost $925 in Canada. The cost of CPO transmission that may occur
with a less sensitive culture-based screening test must also be considered since CPO isolates with low level resistance (MIC < 2 μg/ml) or low inocula at risk for overgrowth by competing organisms may not be detected.67

Conclusions

Preventing the transmission of CP-CRE is a high priority for all institutions. Screening contacts of CP-CRE infected patients is essential to curb transmissions and control outbreaks. However, approaches to routine screening for CRE carriage vary depending on institutional epidemiology, resources and policies. Baseline surveillance is recommended to determine the prevalence and types of carbapenemase enzymes circulating in an institution. Although molecular assays are the most expensive method for CP-CRE screening, the fast turnaround time, high sensitivity, specific genetic information, and availability of FDA-approved or CE-marked assays are appealing. Culture-based methods are not approved by regulatory agencies, less sensitive than molecular methods, labor intensive and slow (up to 4 d to generate results), but have a lower reagent cost. Public health initiatives that focus on the community setting to better understand the factors leading to colonization with CP-CRE are needed. Strategies to reduce the presence of CP-CREs in the environment, animals, and our food supply must be more aggressively pursued.

Disclosure of potential conflicts of interest

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