Antimicrobial Stewardship News

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Updates in Carbapenem-Resistant Enterobacteriaceae Testing

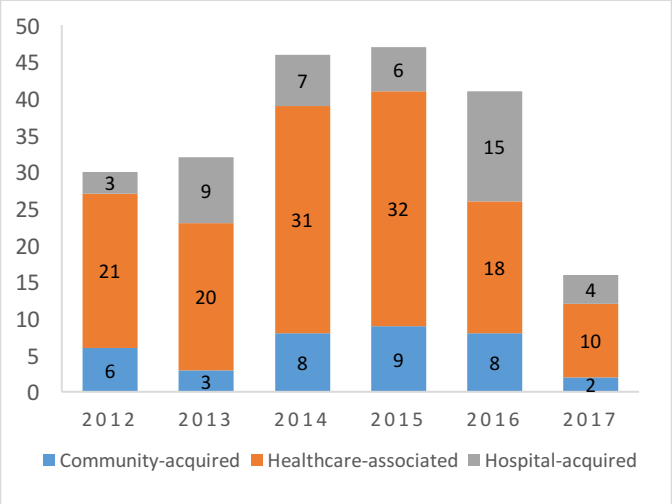
Introduction

The North Carolina Department of Public Health (DPH) recently sent a memo to North Carolina clinicians and laboratories regarding an increase in infections caused by carbapenem-resistant Enterobacteriaceae (CRE) in North Carolina. Specifically, the NC DPH recommended that providers communicate with their laboratories to 1) ensure that labs are using appropriate methods to detect CRE and 2) assess their lab's capacity to detect carbapenemase producing CRE (CP-CRE). Finally, the NC DPH recommended hospitals perform surveillance for CRE and assess for increasing trends over time. In this newsletter, we review DICON surveillance data regarding CRE in member hospitals, explain the difference between CP-CRE and non-CP-CRE and why this distinction is important, and provide recommendations for DICON hospitals regarding laboratory identification of CRE.

Epidemiology of CRE in DICON

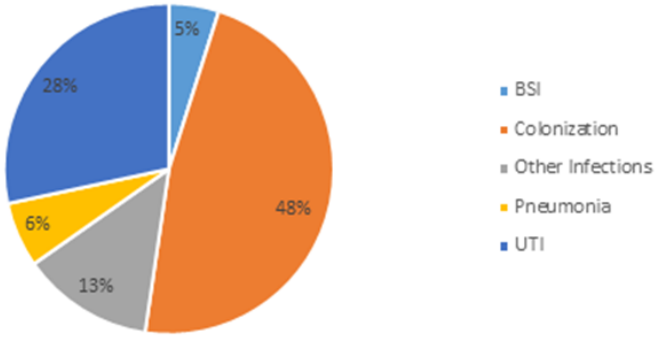
We reviewed CRE surveillance data from DICON hospitals to assess trends from 2012 to 2017. To avoid bias related to hospitals joining DICON during this time period, we limited the analysis to 19 hospitals that participated in DICON continuously from 1/2012 through 7/2017. We found 212 distinct patients with one or more positive CRE cultures. The median number of isolates reported per facility was 5 (range 1, 37). Infection preventionists (IPs) categorized 98 (46 %) CRE isolates as colonizers and the remaining 54% as sources of infection. 37 (17%) of events were community acquired, whereas 44 (21%) were hospital acquired and 131 (62%) were community-onset healthcare associated infections. Overall, the number of isolates has increased from 2012 through present (Figure 1). However, we suspect that DICON surveillance data underestimate the true burden of CRE in our hospitals due to under-reporting and the challenges of laboratory identification of CRE, which we discuss below.

Figure 1. Incidence of CRE in 19 DICON Hospitals



*2017 year-to-date

Figure 2. Types of CRE Infections



Understanding the Difference Between CP-CRE and non-CP-CRE and Why It's Important

CRE are generally defined as *Enterobacteriaceae* that are resistant to carbapenem antibiotics, as determined by phenotypic antibiotic susceptibility tests such as broth dilution, disk diffusion, or automated, MIC-based, systems. What is important to understand is that *Enterobacteriaceae* acquire resistance via different

mechanisms. CRE are sub-categorized as CP-CRE or non-CP-CRE depending on the mechanism of resistance (See Table 1).

Carbapenemases are enzymes that inactivate carbapenem antibiotics. Carbapenemase enzymes are encoded by specific genes that are easily transmitted back and forth between bacteria. Examples of carbapenemases include: *Klebsiella pneumoniae* carbapenemase (KPC), Verona Integron-encoded metallob-β-lactamase (VIM), Oxacillinase-48-type carbapenemases (OXA-48), imipenemase metallo-β-lactamase (IMP), and New Delhi metallo-β-lactamase (NDM-1).

Table 1. Description of CRE, CP-CRE, and Non-CP-CRE

Acronyms	Definition	Laboratory Identification
CRE	Enterobacteriaceae that are carbapenem resistant regardless of the mechanism.	"R" result from a carbapenem disk diffusion or MIC test interpreted with current (2013) breakpoints.
CP-CRE	CRE that produce carbapenemase enzymes.	Positive result from a carbapenemase test, which can be phenotypic (e.g., Modified Hodge Test, Carba NP, mCIM) or genotypic (e.g., Carba-R).
Non-CP-CRE	CRE that are resistant to carbapenems by mechanisms other than carbapenemase production.	"R" result from a carbapenem disk diffusion or MIC test interpreted with current CLSI breakpoints AND negative result for carbapenemase.

Some CRE do not contain carbapenemases, but have decreased susceptibility to carbapenem antibiotics by other means, such as changes in the bacteria's cell wall that decrease permeability to the antibiotic. Typically, this resistance mechanism develops in individual bacteria over time after prolonged exposure to broad-spectrum antibiotics.

Distinguishing CP-CRE from non-CP-CRE can be important, particularly when there is concern about intra-facility transmission of CRE. As stated above, carbapenemase genes are easily spread from one bacteria to another, and can even cross species of bacteria (e.g., spread from *E. coli* to *Klebsiella spp.*), resulting in very rapid spread of resistant bacteria. Without proper infection prevention controls, CP-CRE can quickly spread between patients through direct and indirect transmission. In contrast, non-CP-CRE are less often associated with institutional outbreaks.

Laboratory Detection of CP-CRE

Laboratories may test for carbapenemase production using phenotypic or molecular tests. In general, phenotypic tests are cheaper than molecular tests, but have some downsides shown below in Table 2. Molecular tests (e.g., Biofire, Nanosphere, Cepheid Carba-R, BD Max, Verigene) accurately detect the presence of carbapenemase genes, but are more expensive and not available in many community hospital laboratories.

Table 2. Comparison of Phenotypic Tests for Detection of Carbapenemases

	Modified Hodge	Carba NP	mCIM*
Cost Per Test	< 1$	$2-10	< 1$
Result Time	24 hrs, requires overnight incubation	2 hrs	24 hrs, requires overnight incubation
Interpret	Subjective	Subjective	Subjective, but less problematic
Strengths	Simple to perform	Rapid results. Also detects in *P. aeruginosa* and *Acinetobacter.*	Good sensitivity for detection of class A, B, and D carbapenemases.
Limitations	False positives with some *Enterobacter spp.* with AmpC and porin alterations. False negatives with NDM-1.	Poor sensitivity for detection of OXA-48 carbapenemases.	Poor sensitivity and specificity for carbapenemases in *Acinetobacter.*

*modified carbapenem inactivation method

While the CDC continues to endorse the Modified Hodge test, we discourage its use based on its weaknesses outlined above (false positive results with ESBL/AMP-C producing organisms and false negative results with NDM) and the commercial availability of other more reliable tests.

Laboratory Detection of CRE

In 2010 the Clinical and Laboratory Standards Institute (CLSI) updated the MIC and disk diffuse breakpoints for *Enterobacteriaceae* when it was discovered that many

clinical isolates classified as susceptible to carbapenem antibiotics were, in fact, resistant to carbapenem treatment. The new MIC breakpoints are one to three doubling dilutions lower than the prior breakpoints and the disk diffusion criteria includes larger zone diameters than the previous guidelines. Therefore, some organisms that would be categorized as susceptible by old breakpoints are categorized as resistant based on the new breakpoints (See Table 3).

Table 3. CLSI Clinical Breakpoints (mcg/mL) for *Enterobacteriaceae*[1]

	Ertapenem		Doripenem*, Imipenem, Meropenem	
	2010	**2013**	**2010**	**2013**
Susceptible	≤ 2	≤ 0.5	≤ 4	≤ 1
Intermediate	4	1	8	2
Resistant	≥ 8	≥ 2	≥ 16	≥ 4

*No criteria published by the CLSI in 2010

We recently surveyed DICON hospitals to understand how many are implementing the current 2013 CLSI breakpoints. Of 19 hospitals that responded, only 8 reported using the 2013 CLSI guidelines.

Recommendations for Hospitals

- Identify your state's definition of CRE as these definitions vary slightly. If your state does not have a required definition, we recommend using the CDC's 2015 definition:
  - Enterobacteriaceae resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possesses a carbapenemase
- Document patients with CRE colonization or infection in the DICON database. Review trends at least annually, or more frequently depending on your local epidemiology.
- Hospital labs that are using outdated CLSI breakpoints must perform additional testing to confirm that isolates that test sensitive to carbapenems by old breakpoints are not, in fact, resistant. Additional tests include disk-diffusion or E test OR confirmation of carbapenemase production by phenotypic or molecular tests. The recommended workflow is discussed in our prior Position Statement: Recommended Laboratory Methods to Detect CRE in Community Hospitals.
- Hospital labs that are using current CLSI breakpoints should still confirm unexpected or unusual susceptibility patterns by disk diffusion or E test, but do not need to perform additional testing for carbapenemase production for the purpose of antibiotic treatment decisions.
- Hospitals that identify hospital-onset cases of CRE or experience an outbreak of CRE should test isolates for carbapenemase production to assist with the epidemiologic investigation.
- Hospital laboratories should assess their capacity for performing carbapenemase testing in-house.
  - We no longer recommend the Modified Hodge test for the reasons stated above.
  - Hospital laboratories with low prevalence of CRE isolates may choose to first perform phenotypic testing (e.g., Carba-NP, mCIM) for carbapenemase production, followed by molecular testing (e.g., Carba-R) on isolates that screen positive by phenotypic testing.
  - Hospital labs without capability to test for carbapenemase production should identify a suitable reference lab that performs molecular testing for carbapenemase-production.

References

1. Clinical and Laboratory Standards Institute. 2015. Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement. CLSI document M100-S25. Clinical and Laboratory Standards Institute, Wayne, PA.