

# North Carolina CRE Laboratory Task Force

## Carbapenem-Resistant Enterobacteriaceae (CRE) Screening and Confirmatory Testing for Infection Control Purposes in North Carolina

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# TABLE OF CONTENTS

|  |    |
|--|----|
| Introduction .....   | 4  |
| Statement of Purpose and Definitions .....   | 5  |
| Breakpoints for Carbapenems and Cephalosporins .....   | 5  |
| Modified Hodge Test .....  | 6  |
| Specific Guidance According to Methodology .....   | 8  |
| ▪ Disk diffusion.....  | 8  |
| ▪ Etest® .....   | 9  |
| ▪ Automated Systems .....  | 9  |
| ○ MicroScan® WalkAway® (Siemens Healthcare Diagnostics, Inc.) .....  | 10 |
| ○ VITEK® 2 ( bioMérieux Diagnostics) or Phoenix™ (BD Diagnostics) .....  | 12 |
| <br>   |    |
| <b>Appendices</b>  |    |
| 1. Table 1. Zone diameter interpretive criteria (mm) for 3rd generation cephalosporins and carbapenems for Enterobacteriaceae..... | 14 |
| 2. Table 2. MIC interpretive criteria (µg/ml) for 3rd generation cephalosporins and carbapenems for Enterobacteriaceae .....       | 15 |
| 3. Flow chart for MicroScan® WalkAway® (Siemens Healthcare Diagnostics, Inc.) .....  | 16 |
| 4. Flow chart for VITEK® 2 ( bioMérieux Diagnostics) or Phoenix™ (BD Diagnostics) .....  | 17 |
| <br>   |    |
| Abbreviations .....  | 18 |
| References.....  | 19 |

# INTRODUCTION

Antibiotic management of Gram-negative bacterial infections is an ongoing challenge faced by physicians. One of the most common mechanisms of resistance to beta-lactam drugs is the production of beta-lactamases. In the past, these beta-lactamases were limited in their specificity, but mutations in the genes encoding the beta-lactamases have led to enzymes with a wider spectrum, such as the extended spectrum beta-lactamases (ESBLs). Emergence of ESBLs limited the antibiotic armamentarium available to physicians, but carbapenems remained effective against most organisms until recently. With the increased use of carbapenems, it was only a matter of time before organisms expressing beta-lactamases active against carbapenems (known as carbapenemases) emerged.

Carbapenemases have been detected in a wide variety of bacteria and are given various designations, such as OXA, GES, FAR, SME and CTX-M. Those abbreviations may or may not have any biological relevance to the activity of the specific carbapenemase. Carbapenemase genes may reside on chromosomes or on plasmids. Additionally, expression of carbapenemases may be continuous at low or high levels or may be inducible. Some carbapenemases, as well as additional drug resistance genes, may be located within integrons and transposons, allowing the genes to be inserted into plasmids and chromosomes.

Within the United States, the most common plasmid mediated carbapenemase is the *Klebsiella pneumoniae* carbapenemase (KPC), encoded by the *bla<sub>KPC</sub>* gene. Interestingly, KPC was first described in an isolate of *Klebsiella pneumoniae* collected in 1996 from a patient in North Carolina. KPC-producing bacteria have now been detected across the United States and are increasingly identified as a cause of healthcare-associated infections. While originally described in *K. pneumoniae*, *bla<sub>KPC</sub>* has been detected in other species of *Klebsiella* as well in other genera of the Enterobacteriaceae and in *Pseudomonas*.

It is well demonstrated that infections with carbapenem-resistant Enterobacteriaceae (CRE) are associated with a higher attributable mortality than infections with Enterobacteriaceae that are susceptible to carbapenems. Additionally, once CRE are established within the hospital, eradication becomes challenging. For these reasons, it is important for microbiology laboratories in concert with infection control programs to be vigilant in their efforts to detect these organisms before they become established within the health care institution.

In 2012, the Centers for Disease Control and Prevention (CDC) published a CRE prevention toolkit. Critical to this effort is the contribution of the clinical laboratories. In 2013, the North Carolina Division of Public Health convened a task force of experts in clinical microbiology and infection prevention to develop guidelines for detection of CRE by clinical laboratories within the state. These guidelines consider variations in available resources, experience and instrumentation at those laboratories.

## STATEMENT OF DEFINITIONS AND PURPOSE

This document contains recommendations for the detection of carbapenem resistance among *E. coli*, *Klebsiella* species and *Enterobacter* species according to methodology and breakpoints used for testing and interpreting antimicrobial susceptibility results. These recommendations are for infection control and public health purposes.

**DEFINITION:** For the purpose of this document, CRE are defined as *E. coli* and *Klebsiella* or *Enterobacter* species from any site that are:

- Non-susceptible (intermediate [I] or resistant [R]) to imipenem, meropenem or doripenem **AND** resistant to one or more third-generation cephalosporin (ceftriaxone, cefotaxime or ceftazidime)

**OR**

- Positive for carbapenemase production by a phenotypic test (e.g., the Modified Hodge Test (MHT))

**OR**

- Positive for carbapenemase gene sequence by molecular methods

## BREAKPOINTS FOR CARBAPENEMS AND CEPHALOSPORINS

The Clinical Laboratory Standard Institute (CLSI) lowered the breakpoints for the cephalosporins and the carbapenems in Enterobacteriaceae in 2010 (1). Table 1 lists the current CLSI disk diffusion breakpoints for cephalosporins and carbapenems. Table 2 lists the previous and current minimum inhibitory concentration (MIC) breakpoints for cephalosporins and carbapenems (2).

Laboratories can implement these new (current) CLSI susceptibility breakpoints immediately through one of two ways:

- Use of the disk diffusion method

**OR**

- Conducting an appropriate in-house validation study if using automated antimicrobial susceptibility test (AST) systems

Contact the manufacturer to determine how your commercial AST system's software will be able to accommodate the revised breakpoints.

Before implementation of the current CLSI breakpoints for cephalosporins and carbapenems, the laboratory MUST perform verification as required by Clinical Laboratory Improvement Amendments (CLIA). The Infectious Diseases Society of America (IDSA) has published guidance for performing validation (verification). This guidance is included as a separate document. This document can be also accessed at: [http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient Care/Guideline Methodology and Other Resources/Educational Resources/Appendix%20A%20Brief%20Validation%20Protocol%20FINAL.pdf](http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient%20Care/Guideline%20Methodology%20and%20Other%20Resources/Educational%20Resources/Appendix%20A%20Brief%20Validation%20Protocol%20FINAL.pdf). This IDSA guidance recommends testing a minimum of 30 isolates including carbapenem susceptible as well as ESBL and KPC-producing Enterobacteriaceae.

Additionally, the College of American Pathologists (CAP) with the support of CDC developed a Breakpoint Implementation Toolkit for laboratories to use for updating the breakpoints for cephalosporins and carbapenems. This toolkit includes appropriate resistant and susceptible organisms. For assistance regarding this toolkit, visit the CAP website ([www.cap.org](http://www.cap.org)) or contact the CAP by email ([contactcenter@cap.org](mailto:contactcenter@cap.org)).

### **SCREENING AND CONFIRMATORY TESTING FOR CARBAPENEMASE PRODUCTION**

Flagging suspecting organisms: Isolates that have an MIC >1 µg/ml to doripenem, imipenem, meropenem or ertapenem and that are resistant to one or more 3<sup>rd</sup> generation cephalosporins should be flagged as possible CRE.

Ertapenem Nonsusceptibility (I or R): This is a commonly used initial screening test to flag suspected CRE organisms by automated systems. Although ertapenem nonsusceptibility is the most sensitive indicator of carbapenemase production, its specificity can vary. Therefore, production of carbapenemase should be confirmed by other phenotypic or molecular methods (2) as many organisms that test nonsusceptible to ertapenem **only** but susceptible to other carbapenems are not confirmed as carbapenemase producers.

### **CONFIRMATORY TESTS FOR CARBAPENEMASE PRODUCTION**

A confirmatory test should be done when the screening test is positive (e.g., MIC >1 µg/ml to ertapenem) and resistance to one or more 3<sup>rd</sup> generation cephalosporins is present. Confirmatory tests include phenotypic tests, such as the MHT, as well as molecular methods. **It is not necessary to test an isolate by the MHT when all carbapenems that are reported by a laboratory test as either I or R.**

## **MODIFIED HODGE TEST (MHT)**

This is a phenotypic test that detects the presence of KPC-type of carbapenemase in Enterobacteriaceae and can be used to confirm carbapenemase production in *E. coli* and *Klebsiella* isolates that have an MIC >1 µg/ml to doripenem, imipenem, meropenem or ertapenem and are resistant to one or more 3<sup>rd</sup> generation cephalosporins (2,3). **It is not necessary to test an isolate by MHT when all of the carbapenems tested by a laboratory test as either intermediate or resistant. These isolates can be considered as CRE for reporting purposes.**

The MHT provides high level of sensitivity and specificity for detection of KPC-type carbapenemases in *E. coli* and *Klebsiella* spp. However, the sensitivity and specificity of MHT for detecting KPC-producing *Enterobacter* spp. can vary. A positive MHT in *Enterobacter* spp. may not indicate carbapenemase production. See below for interpretation of MHT results.

**NOTE:** The procedure for performing the MHT is included as a separate document. This procedure can be also accessed at: [www.cdc.gov/HAI/pdfs/labSettings/HodgeTest\\_Carbapenemase\\_Enterobacteriaceae.pdf](http://www.cdc.gov/HAI/pdfs/labSettings/HodgeTest_Carbapenemase_Enterobacteriaceae.pdf).

### **INTERPRETATION OF MHT IN *E. coli* and *Klebsiella* SPECIES**

- If MHT is positive, the isolate is a KPC-producing organism and **should be considered carbapenem resistant** independent of MIC result
- If MHT is negative, interpret the carbapenem MIC using CLSI interpretive criteria

### **INTERPRETATION OF MHT IN *Enterobacter* SPECIES**

As stated above, the MHT has been found to be sensitive and specific for detection of KPC- carbapenemase in *E. coli* and *Klebsiella* species, but it lacks specificity for detection of KPC-producing *Enterobacter* spp. If you suspect that *Enterobacter* species in your institution may harbor *bla*<sub>KPC</sub>, please consider alternative methods, such as the Indirect Carbapenemase Test (4) for detection, or send those suspicious isolates to a reference laboratory for molecular testing.

#### **NOTE:**

Although the recommendations and definitions in this document are for infection control and public health purposes, laboratories may consider the following CLSI recommendations for reporting patients' results:

- Laboratories using automated systems may want to use Etest<sup>®</sup> or disk diffusion to test isolates that were flagged as possible CRE but tested negative by MHT to confirm that these isolates are carbapenem nonsusceptible (I or R).
- For isolates that are MHT positive and have a MIC >1µg/ml to one or more of the carbapenems tested, **report all carbapenems as resistant** (2).

## SPECIFIC GUIDANCE ACCORDING TO METHODOLOGY

Guidance for CRE screening in *E. coli*, *Enterobacter* and *Klebsiella* species will be described for the following susceptibility testing methods:

- Disk diffusion
- Etest®
- Automated Systems (e.g., MicroScan®, VITEK® 2, Phoenix™)

### **DISK DIFFUSION**

The recommendations below are for laboratories using disk diffusion for routine testing of cephalosporins and carbapenems in *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. Disk diffusion is considered a reference method for susceptibility testing and therefore current (new) CLSI breakpoints for cephalosporins and carbapenems can be implemented immediately (See Table 1).

Test ertapenem (10µg), plus meropenem (10µg) or doripenem (10µg) or imipenem (10µg). Note: The imipenem disk performs poorly as a screen for CRE (2) so at least one other carbapenem should be tested. Interpret zone diameter results according to current disk diffusion breakpoints described in Table 1 of this document. Follow procedure for disk diffusion described in CLSI document M02-A11 (5).

- If an isolate (*E. coli*, *Enterobacter* or *Klebsiella* species) tests I or R to ertapenem AND meropenem or doripenem or imipenem by current breakpoints  
**AND**
- Resistant to one or more of 3<sup>rd</sup> generation cephalosporins (e.g., cefotaxime, ceftriaxone, or ceftazidime)

**Then the organism should be considered a CRE**

#### **Note:**

- If an *E. coli* or *Klebsiella* isolate is I or R to ertapenem only → Perform MHT.
  - If MHT is positive, **the organism should be considered CRE.**
    - For *Enterobacter* species, additional testing may be performed for confirmation of carbapenemase production. It is not necessary to test an isolate by the MHT when all carbapenems that are reported by a laboratory test as either I or R. However, the MHT may be performed for infection control or epidemiological investigation to confirm the production of KPC.

### **Etest®**

The screening recommendations below are for laboratories using Etest® for routine testing of 3<sup>rd</sup> generation cephalosporins and carbapenems and for those that use Etest® in addition to their automated systems to expand the dilution range to allow for application of the current (lower) breakpoints.

Test one or more of the carbapenems according to your protocol. Follow the recommendations of the manufacturer, bioMérieux Diagnostics, for performing the Etest® procedure

- If an isolate (*E. coli*, *Enterobacter* or *Klebsiella* species) tests I or R to ertapenem AND meropenem, or doripenem, or imipenem by current MIC breakpoints

**AND**

- Resistant to one or more of 3<sup>rd</sup> generation cephalosporins (e.g., cefotaxime, ceftriaxone, or ceftazidime)

**Then the organism should be considered a CRE**

#### **Note:**

- If an isolate is I or R to ertapenem only, and resistant to 3<sup>rd</sup> generation cephalosporins → Perform MHT or test by a different method to confirm resistance
- **If MHT is positive, the organism should be considered CRE.** For *Enterobacter* species, additional testing may be performed for confirmation of carbapenemase production. It is not necessary to test an isolate by the MHT when all carbapenems that are reported by a laboratory produce either I or R results. However, the MHT may be performed for infection control or epidemiological investigation to confirm the production of KPC.

### **AUTOMATED SYSTEMS**

The screening recommendations below are for laboratories using automated systems for routine testing of cephalosporins and carbapenems. All automated systems have alert rules for CRE based upon pre-defined conditions set up in the system software. These conditions are determined based on the card type selected and the antimicrobials and MIC concentration range tested. Therefore, isolates exhibiting the pre-defined resistance patterns will be flagged as possible CREs. For more specific information about the pre-defined criteria for CRE flagging on your system, please contact your manufacturer representative.

Follow the criteria defined in this document to report an organism as CRE for infection control and public health reporting purposes.

If an *E. coli*, *Enterobacter* or *Klebsiella* species tests intermediate or resistant to imipenem, meropenem or doripenem) **AND** resistant to 3<sup>rd</sup> generation cephalosporins, **the organism should be considered a CRE** according to the criteria defined in this document and no further testing is necessary.

This guidance below describes the CRE criteria for each automated antimicrobial testing system and is based on CLSI recommendations described on Table 2A of M100-S23 document (2).

# MicroScan<sup>®</sup> WalkAway<sup>®</sup> (Siemens Healthcare Diagnostics Inc.)

## Criteria for CRE Detection in *E. coli*, *Klebsiella* and *Enterobacter* Isolates

- If I or R to imipenem, meropenem or doripenem by old breakpoints

**AND**

- I or R to one or more 3<sup>rd</sup> generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)

**Then the organism should be considered a CRE**

- If I or R to imipenem, meropenem or doripenem by old breakpoints

**AND**

- All 3<sup>rd</sup> generation cephalosporins are susceptible by old breakpoints - look at MIC value(s):

- ❖ If MIC >1 µg/ml for ceftriaxone on panels with lowest range beginning at 1 (e.g., Panel 60 or 61)

**OR**

- ❖ If MIC > than the lowest dilution on your panel for cefotaxime, ceftriaxone, or ceftazidime (e.g., Panels 31, 32, 35, 44)

Examples: Cefotaxime or ceftriaxone MIC= 2, 4, or 8 or ceftazidime MIC= 4 or 8

**Then the organism should be considered a CRE**

- **If all carbapenem tested are sensitive by old breakpoints, assess the MIC value(s):**

- ❖ If MIC >1 µg/ml for ertapenem or imipenem or meropenem or doripenem on panels with imipenem / meropenem range of 1–8, doripenem range of 0.5–2 and ertapenem range of 1–4 (e.g., Panels 38, 47, 50, 51, 55, 60, 61, 62)

**OR**

- ❖ If MIC > than the lowest dilution on your panel for ertapenem, imipenem, or meropenem (e.g., Panels 30, 31, 32, 34, 41, 44, 35, 51)

Examples: ertapenem, imipenem, or meropenem MIC= 2, 4, or 8 µg/ml

**AND**

- ❖ I or R to one or more 3<sup>rd</sup> generation cephalosporins

**Then Confirm carbapenem nonsusceptibility by:**

- Testing by a different method (disk diffusion or Etest®).

**OR**

- Perform MHT or indirect carbapenemase test to confirm carbapenemase production

- For newer WalkAway<sup>®</sup> panels (carbapenem MIC values all within current CLSI interpretive ranges (e.g., Panels 67, 68, 73, 42, or 43):

- ❖ If I or R to imipenem, meropenem or doripenem

**AND**

- ❖ Intermediate or Resistant to one or more 3<sup>rd</sup> generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)

**Then the organism should be considered a CRE**

**Note:**

- If an isolate is I or R to ertapenem only, but
- Also resistant to 3<sup>rd</sup> generation cephalosporins

**Perform MHT or test by a different method to confirm resistance.**

- If an *E coli* or *Klebsiella* species MHT is positive

**Then the organism should be considered a CRE**

- For *Enterobacter* species, additional testing may be performed for confirmation of carbapenemase production.

It is not necessary to test an isolate by the MHT when all carbapenem agents that are reported by a laboratory produce either I or R results. The MHT may be performed for infection control or epidemiological investigation to confirm the production of KPC.

## VITEK® 2 (bioMérieux Diagnostics) or Phoenix™ (BD Diagnostics)

### Criteria for CRE Detection in *E. coli*, *Klebsiella* and *Enterobacter* Isolates

- If I or R to imipenem, meropenem or doripenem by old breakpoints

**AND**

- I or R to one or more 3<sup>rd</sup> generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)

**Then the organism should be considered a CRE**

- If I or R to imipenem, meropenem or doripenem by old breakpoints

**AND**

- All 3<sup>rd</sup> generation cephalosporins Sensitive (S) by old breakpoints, but

- ❖ MIC >1 µg/ml for Cefotaxime or ceftriaxone

**OR**

- ❖ MIC >4 µg/ml for Ceftazidime

**Then the organism should be considered a CRE**

- If all carbapenem results are sensitive by old breakpoints, but

MIC >1 µg/ml for ertapenem or imipenem or meropenem or doripenem

**AND**

Intermediate or Resistant to one or more 3<sup>rd</sup> generation cephalosporins (or MIC >1 µg/ml for ceftriaxone or MIC>4 for ceftazidime)

**Then Confirm carbapenem nonsusceptibility by:**

- Testing by a different method (Disk diffusion or Etest®).

**OR**

- Perform MHT or indirect carbapenemase test to confirm carbapenemase production

- If I or R Imipenem, meropenem or doripenem by current CLSI breakpoints\* (MIC >1 µg/ml for imipenem or meropenem or doripenem)

**AND**

- I or R to one or more 3<sup>rd</sup> generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)

**Then the organism should be considered a CRE**

**Note:**

- If an isolate is I or R to ertapenem only
- But also resistant to 3<sup>rd</sup> generation cephalosporins

Perform MHT or test by a different method to confirm resistance

**If MHT is positive, the organism should be considered a CRE**

For *Enterobacter* species, additional testing may be performed for confirmation of carbapenemase production.

It is not necessary to test an isolate by the MHT when all carbapenem agents that are reported are either I or R. However, the MHT may be performed for infection control or epidemiological investigation to confirm the production of KPC.

# APPENDICES

**Table 1**

## Zone Diameter Interpretive Criteria (mm) for 3<sup>rd</sup> Generation Cephalosporins and Carbapenems for Enterobacteriaceae

|             | Current CLSI Breakpoints *               |       |     |
|-------------|--|-------|-----|
|             | Zone Diameter Interpretive Criteria (mm) |       |     |
| Drug        | S  | I     | R   |
| Cefotaxime  | ≥ 26                                     | 23-25 | ≤22 |
| Ceftizoxime | ≥ 25                                     | 22-24 | ≤21 |
| Ceftriaxone | ≥ 23                                     | 20-22 | ≤19 |
| Ceftazidime | ≥ 21                                     | 18-20 | ≤17 |
|             |  |       |     |
| Doripenem   | ≥23                                      | 20-22 | ≤19 |
| Ertapenem   | ≥22                                      | 19-21 | ≤18 |
| Imipenem    | ≥23                                      | 20-22 | ≤19 |
| Meropenem   | ≥23                                      | 20-22 | ≤19 |

**\*NOTE:** Laboratories using disk diffusion can implement the current breakpoints immediately.

**Table 2**

**MIC Interpretive Criteria ( $\mu\text{g/ml}$ ) for  
3<sup>rd</sup> Generation Cephalosporins and Carbapenems  
for Enterobacteriaceae**

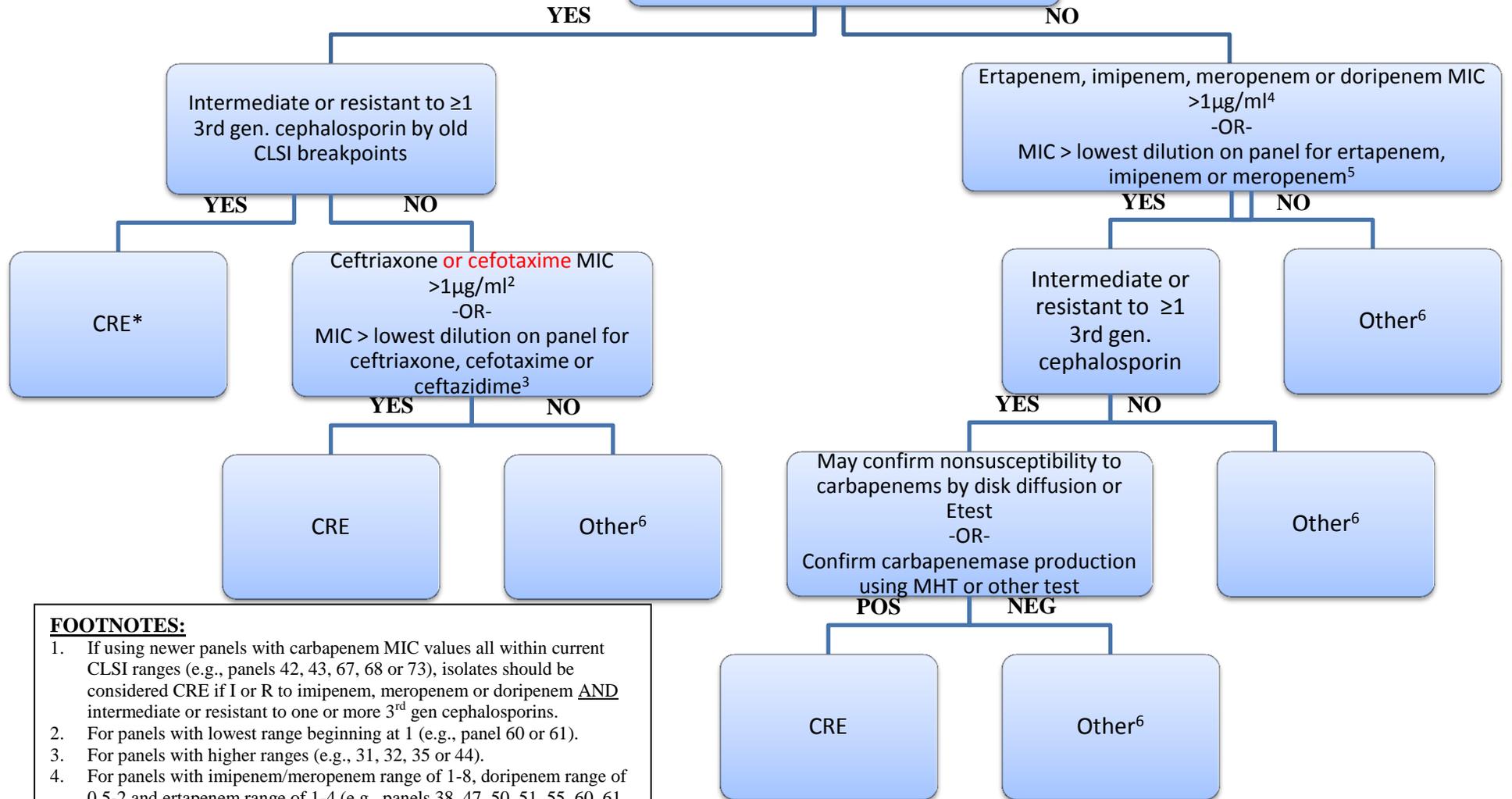
|             | Old CLSI Breakpoints                           |          |           | Current CLSI Breakpoints*                      |          |           |
|-------------|--|----------|-----------|--|----------|-----------|
|             | MIC Interpretive Criteria ( $\mu\text{g/ml}$ ) |          |           | MIC Interpretive Criteria ( $\mu\text{g/ml}$ ) |          |           |
| <b>Drug</b> | <b>S</b>                                       | <b>I</b> | <b>R</b>  | <b>S</b>                                       | <b>I</b> | <b>R</b>  |
| Cefotaxime  | $\leq 8$                                       | 16-32    | $\geq 64$ | $\leq 1$                                       | 2        | $\geq 4$  |
| Ceftizoxime | $\leq 8$                                       | 16       | $\geq 32$ | $\leq 1$                                       | 2        | $\geq 4$  |
| Ceftriaxone | $\leq 8$                                       | 16-32    | $\geq 64$ | $\leq 1$                                       | 2        | $\geq 4$  |
| Ceftazidime | $\leq 8$                                       | 16       | $\geq 32$ | $\leq 4$                                       | 8        | $\geq 16$ |
|             |  |          |           |  |          |           |
| Doripenem   | -  | -        | -         | $\leq 1$                                       | 2        | $\geq 4$  |
| Ertapenem   | $\leq 2$                                       | 4        | $\geq 8$  | $\leq 0.5$                                     | 1        | $\geq 2$  |
| Imipenem    | $\leq 4$                                       | 8        | $\geq 16$ | $\leq 1$                                       | 2        | $\geq 4$  |
| Meropenem   | $\leq 4$                                       | 8        | $\geq 16$ | $\leq 1$                                       | 2        | $\geq 4$  |

**\*NOTE:** Laboratories using automated systems must have completed the validation before implementing the current CLSI breakpoints.

# Flow Chart for MicroScan® WalkAway® (Siemens Healthcare Diagnostics, Inc.)\*

*E. coli, Klebsiella or Enterobacter*  
intermediate or resistant to imipenem,  
meropenem or doripenem by old CLSI  
breakpoints<sup>1</sup>

\*These recommendations are for  
infection control and public health  
purposes.



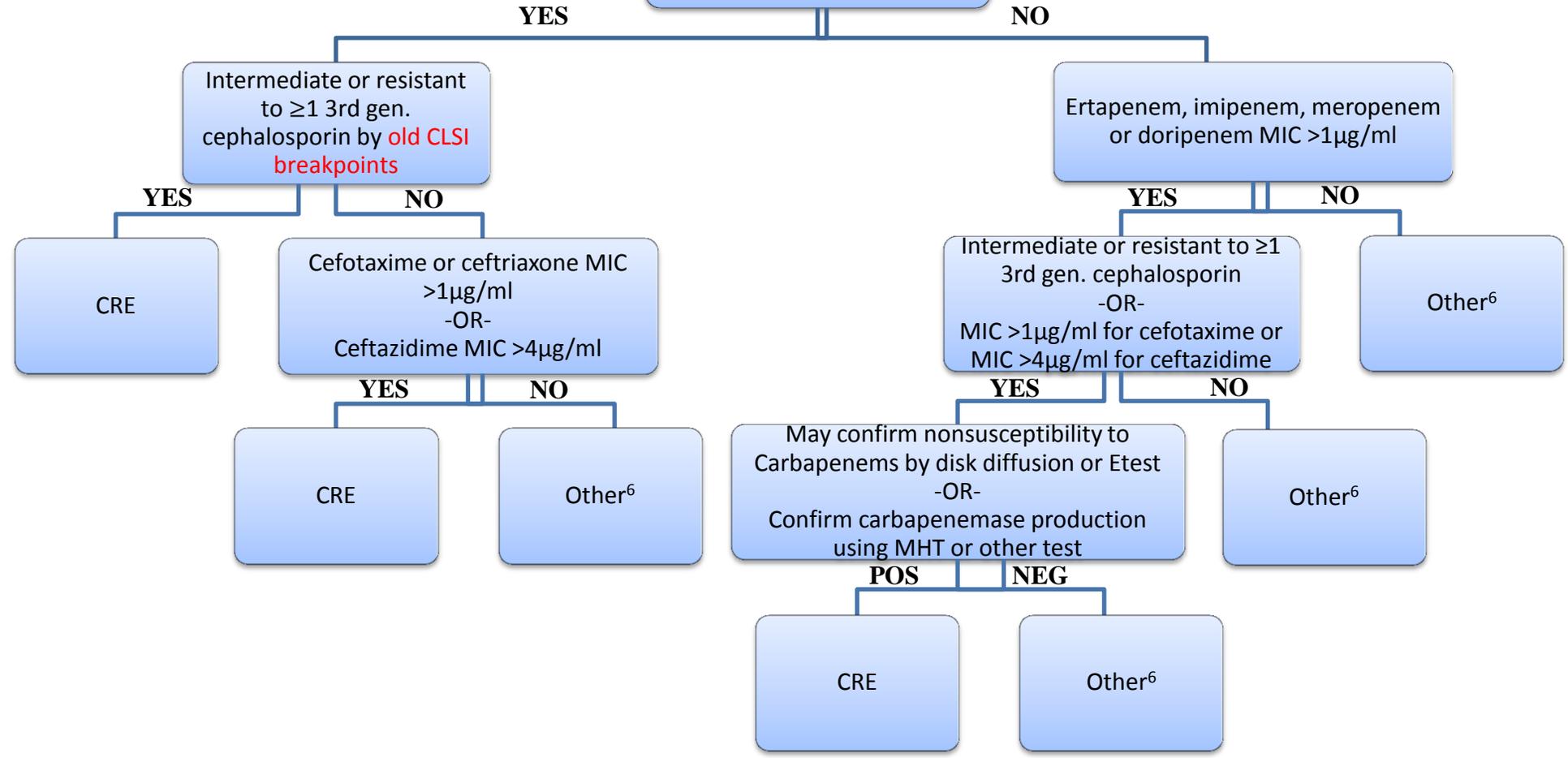
## FOOTNOTES:

1. If using newer panels with carbapenem MIC values all within current CLSI ranges (e.g., panels 42, 43, 67, 68 or 73), isolates should be considered CRE if I or R to imipenem, meropenem or doripenem AND intermediate or resistant to one or more 3<sup>rd</sup> gen cephalosporins.
2. For panels with lowest range beginning at 1 (e.g., panel 60 or 61).
3. For panels with higher ranges (e.g., 31, 32, 35 or 44).
4. For panels with imipenem/meropenem range of 1-8, doripenem range of 0.5-2 and ertapenem range of 1-4 (e.g., panels 38, 47, 50, 51, 55, 60, 61 or 62).
5. For panels with higher ranges (e.g., panels 30, 31, 32, 34, 41, 35 or 51).
6. Organisms in this category do not meet the definition in this guidance for public health and infection control purposes.

# Flow Chart for VITEK<sup>®</sup>2 (bioMérieux Diagnostics) or Phoenix<sup>™</sup> (BD Diagnostics)\*

\*These recommendations are for infection control and public health purposes.

*E. coli*, *Klebsiella* or *Enterobacter* intermediate or resistant to imipenem, meropenem or doripenem by **old CLSI breakpoints**



## ABBREVIATIONS

|         |   |
|---------|---|
| AST     | Antimicrobial susceptibility test                               |
| CAP     | College of American Pathologists                                |
| CDC     | Centers for Disease Control and Prevention                      |
| CLIA    | Clinical Laboratory Improvement Amendments                      |
| CLSI    | Clinical Laboratory Standard Institute                          |
| CRE     | Carbapenem-Resistant Enterobacteriaceae                         |
| CTX-M   | Type of Carbapenemase (Class A $\beta$ -lactamase)              |
| ESBL    | Extended Spectrum Beta-Lactamases                               |
| FAR     | Type of Carbapenemase (associated with fusidic acid resistance) |
| FDA     | Food and Drug Administration                                    |
| GES     | Type of Carbapenemase (Class A $\beta$ -lactamase)              |
| I       | Intermediate  |
| IDSA    | Infectious Diseases Society of America                          |
| KPC     | <i>Klebsiella pneumoniae</i> carbapenemase                      |
| $\mu$ g | Microgram   |
| MHT     | Modified Hodge Test   |
| MIC     | Minimum Inhibitory Concentration                                |
| ml      | Milliliter  |
| mm      | Millimeters   |
| NC DPH  | North Carolina Division of Public Health                        |
| NC HAI  | North Carolina Healthcare-Associated Infection Task Force       |
| NCSLPH  | North Carolina State Laboratory                                 |
| OXA     | Type of Carbapenemase (Class D $\beta$ -lactamase)              |
| R       | Resistant   |
| SME     | Type of Carbapenemase (Class A $\beta$ -lactamase)              |
| spp.    | Species   |

## REFERENCES

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