Title

Carbapenems and Enterobacteriaceae

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Review of laboratory methodology for antimicrobial susceptibility testing

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Carbapenems and Enterobacteriaceae

Background

- Carbapenem-resistant Enterobacteriaceae
  - (CRE) are usually resistant to all β-lactam agents as well as most other classes of antimicrobial agents.
- cause severe infections among residents of long-term-care facilities .
  - The treatment options for patients infected with CRE are very limited.
    - Tigecycline and polymyxins including colistin have been used with variable success.
  - Healthcare-associated outbreaks of CRE have been reported
    - CRE are increasingly recognized as the cause of sporadic and outbreak infections in the U.S.
    - Aggressive infection-control practices are required in aborting these outbreaks .

Carbapenems and Enterobacteriaceae

- Carbapenems Resistance Enterobacteriaceae
  - The treatment options
  - Public Health Problem.
    - Epidemiology record .
  - Aggressive Infection control

Carbapenems

- Ertapenem
- Doripenem
- Imipenem
- Meropenem

Carbapenem-Resistance in Enterobacteriaceae

- Mechanisms of resistance
  - Carbapenemase
    - (β-lactamase that can hydrolyze carbapenems)
  - Cephalosporinase combined with porin loss
    - Some cephalosporinases (e.g., AmpC-type β- lactamses or certain ESBLs i.e. CTX-M) have a low-level carbapenemase activity
    - Porin loss limits entry of the carbapenem into the periplasmic space

Carbapenemases in the U.S.

Enzyme	Bacteria
KPC	Enterobacteriaceae
SME	*Serratia marcesens*
Metallo-β-Lactamase	*P. aeruginosa* & *Acinetobacter* spp.
OXA	*Acinetobacter* spp.

Class A Carbapenemases

- **Rare** – Enterobacteriaceae
- ***K. pneumoniae* carbapenemase** *(*KPC-type) possess carbapenem-hydrolyzing enzymes most common on East Coast of U.S.
- Enzymes are capable of efficiently hydrolyzing penicillins, cephalosporins, aztreonam, and carbapenems and are inhibited by clavulanic acid and tazobactam (low-level carbapenemase activity)

  (ESBL that hydrolyzes carbapenems)

Carbapenemase-Producing Klebsiella pneumonia (KPC)

- "KPC-1" reported in 2001
- Now KPC-2 to KPC-8
  - Recovered from isolates of *K. pneumoniae*, other Enterobacteriaceae, *P. aeruginosa*.

Carbapenemase-Producing *Klebsiella pneumoniae* (KPC)

- The presence of KPC in *K. pneumoniae* may increase the MIC of imipenem, but not to the level of frank resistance.
- Identifying isolates possessing KPC type resistance may be difficult using current methods of susceptibility testing.
- **Therefore, strains carrying this enzyme may only be recognized as ESBL-producing isolates**

KPC Enzymes

- **NB; not easily detected in the clinical microbiology laboratory routinely.**
- Located on plasmids
- Active against all β-lactam agents,but may test susceptible to imipenem
  - *bla*$_{KPC}$ reported on plasmids with:
    - Normal spectrum β-lactamases
    - Extended spectrum β-lactamases
    - Aminoglycoside resistance [AAC(6')-Ib]
    - Plasmid-mediated fluorquinolone resistance

Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Carbapenemase Isolate likely to be **resistant to all carbapenems and other β-lactam agents**
  - May need to change susceptible reports to resistant for β-lactam drugs
  - Need to implement infection control measures such as contact precautions and possibly active surveillance testing
  - **These are an Infection Control Emergency**
- Healthcare institutions may reserve more aggressive measures for carbapenemase-producing isolates

Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Cephalosporins combined with porin-loss
  - Class A ESBL's(CTX-M) + reduced permeability
  - Class C High AmpC+ reduced permeability
- These hydrolyze ertapenem more than meropenem or imipenem
  - Not necessarily resistant to all carbapenems(i.e., would not need to change susceptible results to resistant reports for β-lactam drugs
- These isolates are clearly MDR and infection control measures are recommended.

Strategy for Laboratory Detection of Carbapenemases

- Establish screening criteria and a confirmatory test
  - Necessary when isolates test susceptible to carbapenems, but a carbapenemase is suspected
    - When should a carbapenemase be suspected?
    - What screening criteria should be used?

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Ref : 2011 Jan CLSI

- Revised interpretative criteria for carbapenems
  - Published in June 2010 (M100-S20-U)
    - Evaluation of PK-PD properties, limited clinical data, and MIC distributions(including carbapenemase production strains .
  - (C- MIC & Zone –Intermediate range)
    - Limited treatment options
      - Design Dosage regimens(maximum recommended doses, prolong iv infusion regimen- reported
      - Consultation with infectious diseases practitioner – recommended

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- Until labs can implement the new interpretive criteria
  - MHT – s/b performed (updated supp table 2A-S3.)
- After implementation of the new interpretive criteria
  - MHT – NOT need (other than for epidemiological or infection control purposes(refer table 2A-S2)
  - Clinical effectiveness (C-MIC-I range in the new interpretive criteria)– uncertain
    - Lack of controlled clinical studies
  - Imi MICs for Proteus/Providencia/Morganella higher than mero or doripenem MICs.
    - By mechanisms other than production of carbapenemases.

MIC breakpoints for carbapenems (µg/mL):

Table1 ; MIC breakpoints for carbapenems (µg/mL):

Agent	Old (M100-S19)			Revised (M100-S20 June 2010)		
	S	I	R	S	I	R
Doripenem (10µg)	NA	NA	NA	≤ 1	2	≥ 4
				500mg-8hly		
Ertapenem	≤ 2	4	≥ 8	≤ 0.25	0.5	≥ 1
				1g 24hly		
Imipenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
				500mg6hly or 1g 8hly		
Meropenem	≤ 4	8	≥ 16	≤ 1	2	≥ 4
				1g 8hly		

Zone diameter breakpoints for carbapenems (mm)

Table2 ; Zone diameter breakpoints for carbapenems (µg/mL):

Agent	Old (M100-S19)			Revised (M100-S20 June 2010)		
	S	I	R	S	I	R
Doripenem (10µg)	NA	NA	NA	≥23	20-22	≤19
				500mg-8hly		
Ertapenem	≥19	16-18	≤15	≥23	20-22	≤19
				1g 24hly		
Imipenem	≥ 16	14-15	≤ 13	≥23	20-22	≤19
				500mg6hly or 1g 8hly		
Meropenem	≥ 16	14-15	≤ 13	≥23	20-22	≤19
				1g 8hly		

Strategy for Laboratory Detection of Carbapenemases

- **CLSI Screening Criteria for KPCs (M100-S-19 Jan 2009)**
  - Disk zone of **<22 mm** for ertapenem or meropenem
  - MIC of **>1 µg/ml** for imipenem, ertapenem or meropenem

  - CLSI Confirmatory Test (M100-S19, Jan 2009)Modified Hodge Test

- Procedure Notes
  - Imipenem disk test is **not a good screen**
  - Imipenem **MIC does not work as a screen** for Proteus/Providencia/Morganelladue to slightly elevated MICs in this group
- carbapenems(CLSI recommendation in the Jan 2009 M100-S19)
  - Report MIC with “I”interpretation if MIC 2, 4, 8 ug/mL
  - Report MIC with “R”interpretation if MIC ≥16 ug/mL

Strategy for Laboratory Detection of Carbapenemases

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CLSI Screening Criteria for KPCs (M100-S-20 Jan 2010)- table 2A-S3

- USING Old interpretative criteria (table 2A in M100-S20 (Jan -2010)
  - Initial screen test (applies only when using IC for carbapenem – in M100-S20 (Jan -2010)
    - Test method
      - Disc diffusion
        - Ert (16 - 21mm)
        - Mero (14 - 21mm)
        - Imipenem disk test is not a good screen
      - Broth microdilution
        - Ert (2-4 *µg/mL*)
        - Mero (2-8 *µg/mL*)
        - Imipenem (2-8 *µg/mL*)
  - Indicate carbapenemase production, despite the fact that they are in current sus interpretative categories.
    - Confirmed with MHT.

Strategy for Laboratory Detection of Carbapenemases[M100-S20 (Jan -2010)]

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- Phenotypic confirmatory test

  [Positive screen test and resistant to ≥ 1 cephalosporins III (Eg CTX,CRO,CAZ, etc)]

  - Test method
    - MHT (applies only when using IC for carbapenem – in M100-S20 (Jan -2010)]>90% sensitive and >90% specific for detecting KPC –type C
      - Isolate ;
        - MHT + and Ert (MIC 2-4µg/ml), imi (2-8µg/ml) or mero(2-8 µg/ml)
        - report as all carbapenems resistance

Strategy for Laboratory Detection of Carbapenemases(new IC for carbapenems)

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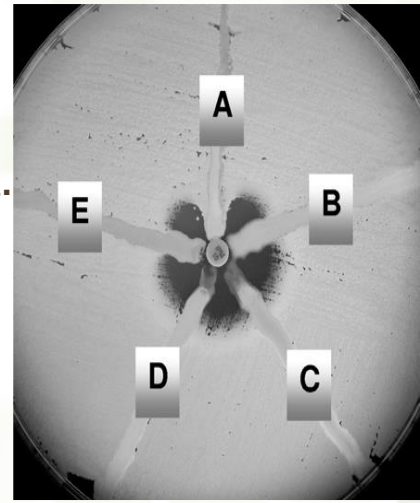
Confirmatory test FOR Suspected Carbapenemase Production in Enterobacteriaceae (M100-S20 –U June 2010)- table 2A-S2

- Only when using the new interpretative criteria for carbapenems first published in June 2010 (M100-S20-U)
- Initial screen test (Table 2A-S3) and CT (MHT)
  - No longer necessary for routine patient testing
- MHT (when to do this test)
  - Epidemiological
  - Infection control purposes
  - I or R to ≥1 carbapenems (ert)
  - R to ≥1 cephalosporin III (CTX,CRO,CAZ etc)

  Pos MHT – do MIC test before reporting results.
- No change in the interpretation of carbapenems susp test results is required for MHT – POSITIVE isolates

Modified Hodge Test

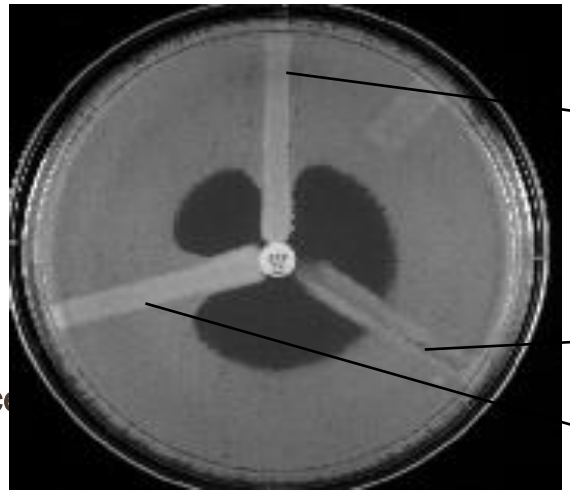
- Inoculate MH agar with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streak for confluent growth using a swab.
- Place 10-µg ertapenem or **meropenem (best)** disk in center
- Streak each test isolate from disk to edge of plate
- Isolate A is a KPC producer and positive by the modified Hodge test.



Anderson KF et al. JCM 2007 Aug;45(8):312

QC recommendation

- *E. coli* ATCC 25922
- Test positive and negative QC organisms
  - *K.pneumoniae* ATCC –BAA-1705- MHT Positive
  - *K.pneumoniae* ATCC –BAA-1706- MHT negative



2723-5. Figure 1: *photo courtesy of CDC*

Figure 1. The MHT performed on a 100 mm MHA plate. (1) *K. pneumoniae*ATCC BAA 1705, positive result (2) *K. pneumoniae*ATCC BAA 1706, negative result; and (3) a clinical isolate, positive result

Reference

SUMMARY

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Why is Carbapenem Resistance a Public Health Problem?

- Significantly **limits treatment** options for life- threatening infections
- **No new drugs** for gram-negative bacilli
- Emerging resistance mechanisms, carbapenemases are **mobile /Spreading ,**
  - Suboptimal detection
  - Molecular factors
  - Antibiotic selection pressure
- Detection of carbapenemases and implementation of infection control practices are necessary to limit spread

Extent of Problem

- Highly endemic in greater NY area Endemic in ICUs at Columbia, Cornell, St. Vincent's, Mount Sinai, SUNY Downstate (Brooklyn), ...
  - Officially a reportable disease in New York State

- Still relatively uncommon, now being reported from multiple other regions of U.S.: AZ, NJ, DE, NC, NM, FL, PA, DE, GA, MD, MI, MO, MA, CA, AK, OH, VA..... *and now Illinois*
- Reports from other parts of world: Scotland, Israel, Colombia, China, Brazil, France, Turkey, Greece, Singapore, Korea, Puerto Rico.....

AAC. 2005; 49(10): 4423-4; *AAC.* 2006; 50(8): 2880-2; *AAC.* 2007; 5(2): 763-5; 47th ICAAC. Abstract C2-1929.2007; 47th ICAAC. Abstract C2-2063. 2007; 47th ICAAC. Abstract C2-1933. 2007

Who is Infected with Carbapenemase- Producing Enterobacteriaceae?

- Hospitalized patients with:
  - Increased number of co-morbid conditions
  - Frequent or prolonged hospitalization
  - Invasive devices
  - Antimicrobial exposure (vancomycin, fluoroquinolones, penicillins, and extended-spectrum cephalosporins)
  - Carbapenemase-producers are most frequently isolated from urine or blood

- **Esther T. Tan, et al. CID. Submitted**

Active Surveillance Cultures to Detect Colonization with KPC in ICUs

- Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant Klebsiella pneumoniae in intensive care unit patients Infect Control Hosp Epidemiol. 2008 Oct;*29*(*10*):*966-8*

- Laboratory Protocol for Detection of KPC from Rectal Swabs

  19 Jan 2009 ***Carbapenem Resistance in Enterobacteriaceae - An Infection Control Emergency****"Paul C. Schreckenberger, Ph.D., D(ABMM)Professor of PathologyDirector, Clinical Microbiology LaboratoryLoyola University Medical Centerpschrecken@lumc.edu*

MMWR Morb Mortal Wkly Rep. 2009 Mar 20;58(10):256-60.

Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities.

Centers for Disease Control and Prevention (CDC).

Abstract

Infection with carbapenem-resistant Enterobacteriaceae (CRE) or carbapenemase-producing Enterobacteriaceae is emerging as an important challenge in health-care settings. Currently, carbapenem-resistant Klebsiella pneumoniae (CRKP) is the species of CRE most commonly encountered in the United States. CRKP is resistant to almost all available antimicrobial agents, and infections with CRKP have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices (e.g., ventilators or central venous catheters). This report provides updated recommendations from CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) for the control of CRE or carbapenemase-producing Enterobacteriaceae in acute care (inpatient) facilities. For all acute care facilities, CDC and HICPAC recommend an **aggressive infection control strategy, including managing all patients with CRE using contact precautions and implementing Clinical and Laboratory Standards Institute (CLSI) guidelines for detection of carbapenemase production.** In areas where CRE are not endemic, acute care facilities should 1) review microbiology records for the preceding 6-12 months to determine whether CRE have been recovered at the facility, 2) if the review finds previously unrecognized CRE, perform a **point prevalence culture survey in high-risk units** to look for other cases of CRE, and 3) perform active surveillance cultures of patients with epidemiologic links to persons from whom CRE have been recovered. In areas where CRE are **endemic,** an increased likelihood exists for imporation of CRE, and facilities should consider **additional strategies to reduce rates of CRE. Acute care facilities should review these recommendations and implement appropriate strategies to limit the spread of these pathogens.**

Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts

Euroroundups

www.eurosurveillance.org

Article published on 18 November 2010

QUESTIONS

- Would you change new break point?
  - Vitek – old break points (? New card available)
  - Would you use new zone diameter break point ?
  - Dose of mero
    - If 500mg 8hr for (skin and soft tissue infections), which break point would you use?
- Would you do MHT?
- Would you also do molecular method for MHT positive isolate (epidemiology record)

References

- Calfee, D., and S. G. Jenkins. 2008. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant *Klebsiella pneumoniae* in intensive care unit patients. Infect. Control Hosp. Epidemiol. 29:966-8.
- CLSI 2009, 2010, 2011
- Anderson KF et al. JCM 2007 Aug;45(8):2723-5.
- Paul C. Schreckenberger.2009 . Carbapenem Resistance in Enterobacteriaceae - An Infection Control Emergency
- Esther T. Tan, et al. CID. Submitted
- Kenneth S. Thomson;Extended-Spectrum--Lactamase, AmpC, and Carbapenemase Issues; JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2010, p. 1019–1025
- H Grundmann (Hajo.Grundmann@rivm.nl)1,2, D M Livermore3, C G Giske4, R Canton5,6, G M Rossolini7, J Campos8, A Vatopoulos9,; Carbapenem-non-susceptible Enterobacteriaceae in
- Europe: conclusions from a meeting of national experts; www.eurosurveillance.org;Article published on 18 November 2010

THANKS