
Testing for Carbapenemase Production Among Carbapenem-Resistant Organisms: When and How?

October 27, 2022

Presented via Webinar

Healthcare-Associated Infections (HAI) Program
Center for Health Care Quality
California Department of Public Health

Healthcare Outreach Unit
Acute Communicable Disease Control Program
Los Angeles County Department of Public Health



Presenters

Romney M. Humphries, PhD, D(ABMM)
**Division Director, Laboratory Medicine and Clinical
Microbiology**
Vanderbilt University Medical Center

Lucas J. Osborn, PhD, MLS(ASCP)^{CM}
Clinical Microbiology Fellow
Children's Hospital Los Angeles

June L. Chan, PhD
Medical and Public Health Microbiology Fellow
University of California Los Angeles

Objectives

- Discuss when carbapenemase testing can be useful in a healthcare facility for clinical care and infection prevention and control activities.
 - List practical methods for detecting and reporting carbapenemases in Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.
 - Using case studies presented by microbiology subject matter experts, explain how to manage various CPO and non-carbapenemase-producing CRO results.
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CRO Versus CPO!

CRO, Carbapenem-Resistant Organism

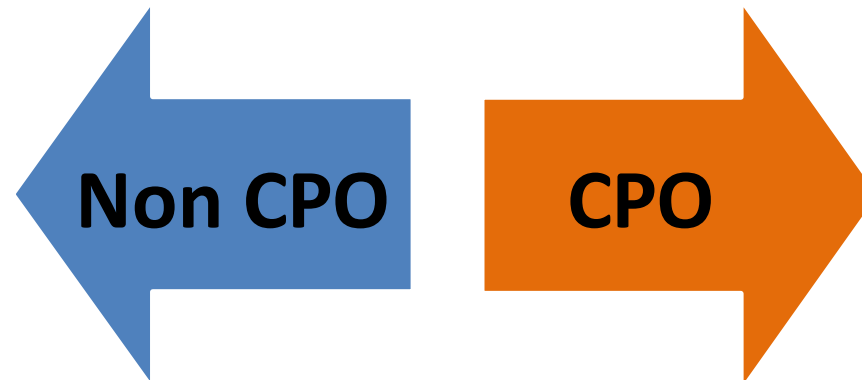
CPO, Carbapenemase-Producing Organism

**Must do a CARBAPENEMASE TEST to
determine if a CRO is a CPO!**

Both CRO and CPO are considered Multidrug-Resistant Organisms (MDRO)
Labs should consider performing confirmatory testing for CPO!

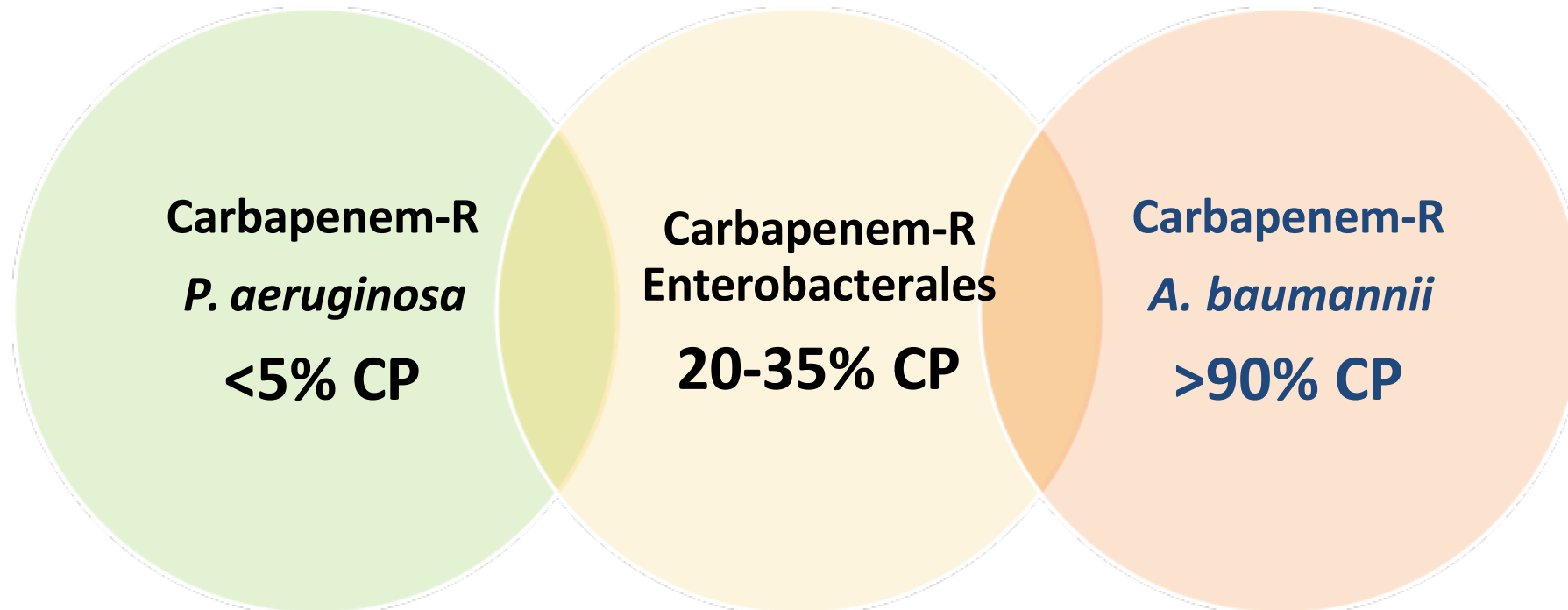
Flavors of Carbapenem Resistance in Gram-negative Bacteria

- Resistant by mechanisms other than carbapenemase, usually acting in concert
 - Porin loss
 - Efflux
 - Other beta-lactamases
- May have borderline carbapenem MICs
- Random mutations
- Less of a concern for public health as not as transmissible



- Possess carbapenemase enzyme that degrades the carbapenem
- Many types of carbapenemases
- Carbapenemase genes often on plasmids
 - Carry other AR genes
 - Can be transmitted among different isolates and species
- Most concerning for public health, as these are increasing!

Carbapenemase (CP) Prevalence in Carbapenem-Resistant Isolates Varies by Organism



Additional [CDC Antibiotic Resistance Data](https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=ar-lab-network)

(arpsp.cdc.gov/profile/antibiotic-resistance?tab=ar-lab-network)

Carbapenemase Types



“Serine” Carbapenemases

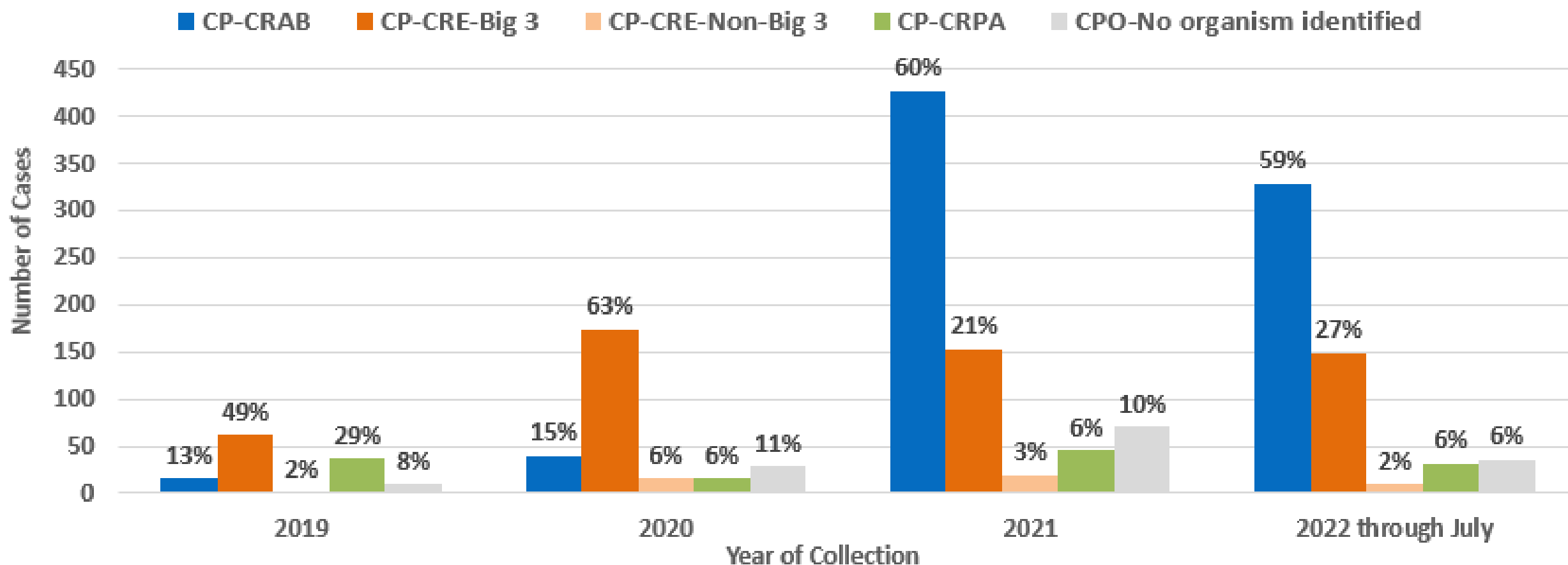
- Serine in active site
- Two primary types:
 - “Class A” – KPC
 - “Class D” – OXAs
- Destroy all beta-lactams, some exceptions
- Newer beta-lactamase inhibitors active against these enzymes



“Metallo” Carbapenemases

- Zinc ions in active site
- Examples:
 - NDM, VIM, IMP
- Destroy all beta-lactams EXCEPT aztreonam
- No currently available beta-lactamase inhibitors active against these enzymes

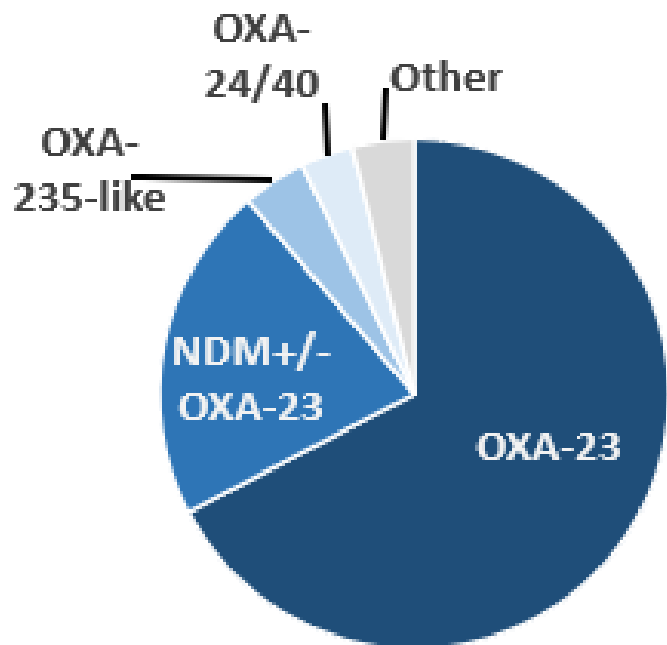
CPO Cases Reported in California, January 2019–July 2022



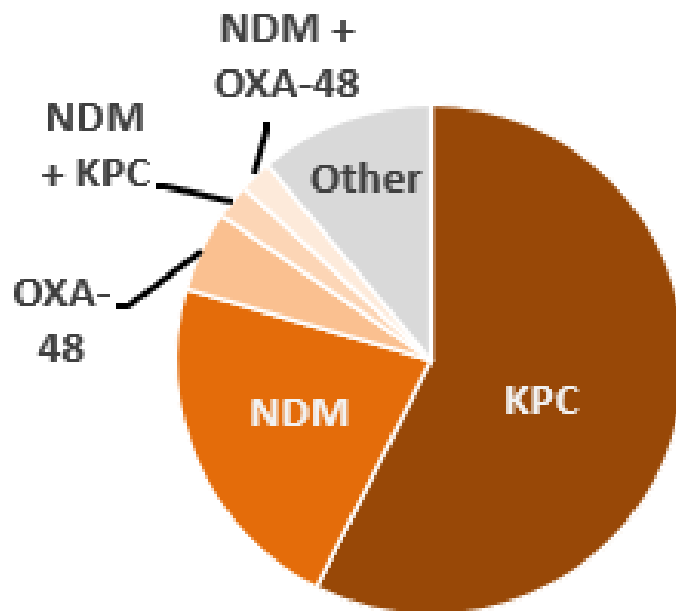
CP=carbapenemase-producing; CRAB=carbapenem-resistant *Acinetobacter baumannii*; CRE=carbapenem-resistant Enterobacterales; CRPA=carbapenem-resistant *Pseudomonas aeruginosa*; Big 3=*E. coli*, *Enterobacter* and *Klebsiella* species

Most Common Carbapenemases Among CPO Cases Reported in California

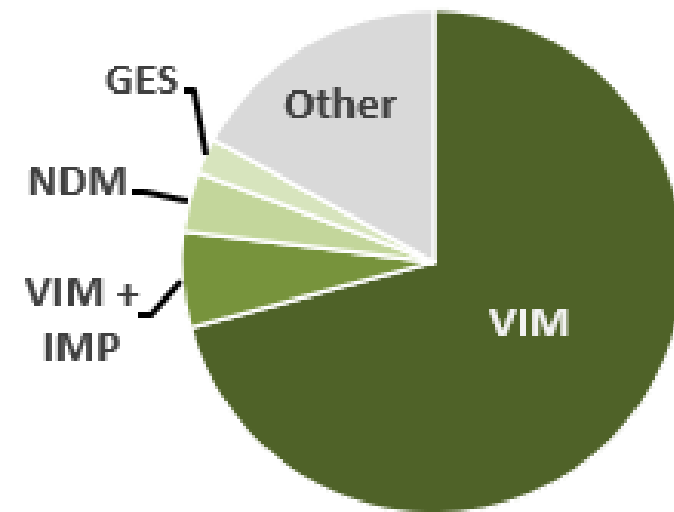
Big 5!
 KPC
 NDM
 VIM
 IMP
 OXA-48



CP-CRAB



CP-CRE



CP-CRPA

GES=Guiana extended-spectrum β -lactamase; IMP=imipenemase; KPC=*Klebsiella pneumoniae* carbapenemase; NDM=New Delhi metallo- β -lactamase; OXA=oxacillinase; VIM=Verona integron metallo- β -lactamase

Case #1A

In Burn ICU!

Unexpected CP-CRE

- 30-year-old with **no previous medical history**
- Sustained friction burns following flash diesel explosion at industrial plant
- 65% total body surface area **burn wounds**
- Multiple operations and allografts
- 2 weeks after admission:
 - ***Klebsiella pneumoniae*** in blood cultures (direct molecular test)

Report Comment:

Molecular results (positive blood culture):

***bla*_{VIM}** carbapenemase gene detected.

This isolate is resistant to ceftazidime-avibactam.

ID consult required.

Notify
IP

Klebsiella pneumoniae

Antimicrobial	MIC (µg/mL)	Interp
Amikacin	≤8	S
Cefazolin	>16	R
Cefepime	>16	R
Ceftazidime-avibactam	>8/4	R
Ceftriaxone	>32	R
Ciprofloxacin	>2	R
Ertapenem	>2	R
Gentamicin	>8	R
Levofloxacin	>4	R
Meropenem	>8	R
Meropenem-vaborbactam	>8	R
Piperacillin-tazobactam	>64/4	R
Tobramycin	>8	R
Trimeth-sulfamethoxazole	>2/38	R

Case #1A

- Supplemental AST (Sensititre):
 - Cefiderocol MIC: 0.5 µg/mL (S)
 - Colistin MIC: 2 µg/mL (I)
- Patient placed on cefiderocol for 10 days
- Remains intermittently febrile

Case #1A Unexpected CP-CRE

- Wound cultures, day 10:
 - *K. pneumoniae* VIM positive
 - Cefiderocol MIC >32 µg/mL
 - Confirmed at reference laboratory
- Patient started on **ceftazidime-avibactam + aztreonam**



Hardy NG-Test®
Carba 5

Carbapenem-resistant Enterobacterales (CRE)*

Treatment Guidelines - IDSA

Carbapenemase Test	Ertapenem	Meropenem	Recommended Therapy	
			1 st line	2 nd line
Negative or not done	R	S	Extended infusion meropenem	Ceftazidime-avibactam
Negative or not done	R	R	Ceftazidime-avibactam Imipenem-relebactam Meropenem-vaborbactam	Cefiderocol Tigecycline Eravacycline
KPC	-	-	Ceftazidime-avibactam Imipenem-relebactam Meropenem-vaborbactam	Cefiderocol Tigecycline Eravacycline
NDM, VIM, IMP	-	-	Ceftazidime-avibactam + Aztreonam Cefiderocol	Tigecycline Eravacycline
OXA-48-like	-	-	Ceftazidime-avibactam	Cefiderocol Tigecycline Eravacycline

*CRE = "R" to at least one carbapenem or "+" for carbapenemase. For infections outside the urinary tract.
[Tamma et al. 2022. CID. 75:187-212 \(www.idsociety.org/practice-guideline/amr-guidance-2.0/\)](https://www.idsociety.org/practice-guideline/amr-guidance-2.0/)

Activity of Newer Beta-lactam Combination Agents and Cefiderocol Against 5 Common Carbapenemases

Carbapenemase Type	Example	Ceftazidime-avibactam	Meropenem-vaborbactam	Imipenem-relebactam	Ceftolozane-tazobactam	Cefiderocol
Serine, Class A	KPC	Yes	Yes	Yes	N	Yes
Metallo, Class B	NDM	N	N	N	N	Yes
	VIM	N	N	N	N	Yes
	IMP	N	N	N	N	Yes
Serine, Class D	OXA-48-like	Some	N	N	N	Yes

Available Cefiderocol (Fetroja) Test Methods (10/25/22)

Available susceptibility testing methods for Fetroja

HardyDisk™ (AST):

- Disk-diffusion method for cefiderocol is standardized to be performed on regular Mueller-Hinton agar plates

Thermo Scientific™ Sensititre™ AST Plates:

Not currently available!

- These plates do not require specialty media; standard Sensititre Mueller-Hinton broth is used for inoculation

Laboratory Specialists, Inc. (LSI)

- Panel of clinical isolates for verification and validation

Refer to [Fetroja Diagnostic Testing \(www.fetroja.com/diagnostic-testing\)](http://www.fetroja.com/diagnostic-testing) for additional information

How can we find carbapenemase-producing organisms in the laboratory?

First step! Use current CLSI/FDA breakpoints for MIC and disk diffusion tests!

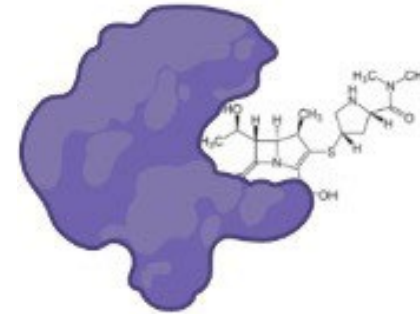
Organism Group	MIC Breakpoints ($\mu\text{g/mL}$)		
	Susc	Int	Res
Enterobacterales			
Ertapenem	≤ 0.5	1	≥ 2
Imipenem	≤ 1	2	≥ 4
Meropenem	≤ 1	2	≥ 4
<i>Pseudomonas aeruginosa</i>			
<i>Acinetobacter</i> sp.			
Imipenem	≤ 2	4	≥ 8
Meropenem	≤ 2	4	≥ 8

CLSI M100, 32nd ed. (also lists current disk diffusion breakpoints)

[FDA Susceptibility Test Interpretive Criteria](#)

(www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria)

How can we confirm the presence of a carbapenemase in the laboratory?



Molecular Test for Gene

Detects presence of carbapenemase *gene*

Examples: PCR or hybridization

Identify enzyme present

Risk of **FP**: inactive/mutated genes (rare)

Risk of **FN**: unusual or novel carbapenemase that is not targeted by PCR

Phenotypic Test for Enzyme

Detects activity of the *carbapenemase* enzyme

Examples: Carba-NP, mCIM

Does not identify enzyme present

Risk of **FP**: other enzymes with weak carbapenemase activity (e.g., AmpC)

Risk of **FN**: carbapenemase does not have good affinity for carbapenem used (e.g., OXA-48 and imipenem)

FP, false positive; FN, false negative

Carbapenemase Testing for Carbapenem-Resistant Organisms (CRO) A Primer for Clinical and Public Health Laboratories

Contents:

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Table 2. Features of Various Tests for Carbapenemases

Table 3. Current CLSI and FDA-recognized Carbapenem Breakpoints

Table 4. Activities of Newer Agents for Common Carbapenemases

Table 5. Strategies for Testing Isolated Colonies for Carbapenemase Production and/or Carbapenemase Genes and Results Reporting

Table 6. CRO Examples

References

Introduction

The intent of this primer is to provide clinical and public health laboratorians with information about tests available for detection of carbapenemases among gram-negative bacteria. It does not describe when carbapenemase testing should be performed. Each facility should work with their antimicrobial stewardship team to implement a plan to detect carbapenemase-producing organisms that is appropriate for the facility and stakeholders served. Recommendations and requirements from local public health departments should be taken into consideration when developing this plan.

Acronyms

AST, Antimicrobial susceptibility test

CRO, carbapenem-resistant organism

CRAB, carbapenem-resistant *Acinetobacter baumannii*

CRE, carbapenem-resistant *Enterobacterales*

CRPA, carbapenem-resistant *Pseudomonas aeruginosa*

CPO, carbapenemase-producing or carbapenemase gene-positive organism

CP-CRAB or CPAB, carbapenemase-producing *Acinetobacter baumannii*

CP-CRE or CPE, carbapenemase-producing *Enterobacterales*

CP-CRPA or CPPA, carbapenemase-producing *Pseudomonas aeruginosa*

Non-CP-CRO, non carbapenemase-producing, carbapenem-resistant organism

To be distributed with slides from this webinar.

Tests to Detect Carbapenemase Genes

TEST	Specimen	Enterobacterales	<i>P. aeruginosa</i>	<i>Acinetobacter</i> spp.
Cepheid Xpert® Carba-R	Isolates Rectal Sw.	KPC, NDM, VIM, IMP, OXA-48-like	KPC, NDM, VIM, IMP, OXA-48-like	KPC, NDM, VIM, IMP, OXA-48-like
Hardy NG-Test® CARBA 5 ¹	Isolates	KPC, NDM, VIM, IMP, OXA-48-like	KPC, NDM, VIM, IMP, OXA-48-like	No
OpGen Acuitas AMR Gene Panel	Isolates	KPC, NDM, VIM, IMP, OXA-48, OXA-1, OXA-9	KPC, NDM, VIM, OXA-1	No
Biofire® FilmArray® BCID Panel	Blood	KPC, NDM, VIM, IMP, OXA-48-like	KPC, NDM, VIM, IMP, OXA-48-like	KPC, NDM, VIM, IMP, OXA-48-like
GenMark® ePlex BCID	Blood	KPC, NDM, VIM, IMP, OXA (23 & 48)	KPC, NDM, VIM, IMP, OXA (23 & 48)	KPC, NDM, VIM, IMP, OXA (23 & 48)
Luminex® VERIGENE gene detection	Blood	KPC, NDM, VIM, IMP, OXA (23, 40, 48 and 58)	KPC, NDM, VIM, IMP, OXA (23, 40, 48 and 58)	KPC, NDM, VIM, IMP, OXA (23, 40, 48 and 58)
Check-Points CPO for BD MAX™	Rectal sw.	KPC, NDM, VIM/IMP, OXA-48	KPC, NDM, VIM/IMP, OXA-48	KPC, NDM, VIM/IMP, OXA-48

¹ Phenotypic immunological assay that detects specific antigens associated with the 5 main carbapenemases

Phenotypic Tests for Carbapenemases

Phenotypic (for isolates)	Enterobacterales	<i>P. aeruginosa</i>	<i>Acinetobacter</i> spp.
Modified Carbapenem Inactivation Method (mCIM) with or without EDTA Carbapenem Inactivation Method (eCIM)	yes	yes (mCIM only)	no
CarbaNP	yes	yes	no
BioMerieux Rapidec® Carba NP	yes	yes	no
BD Phoenix™ CPO Detect	yes	yes	yes

Additional information on carbapenemase tests and reporting results in CPO Primer....

Table 2. Features of Various Tests for Carbapenemases

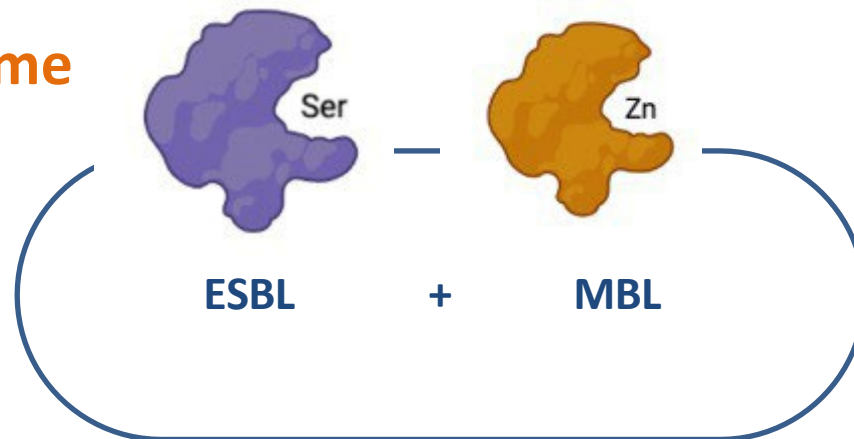
Feature	Phenotypic				Genotypic						
	mCIM / eCIM	CarbaNP	bioMerieux Rapidec® Carba NP	BD Phoenix™ CPO Detect	Cepheid Xpert® Carba-R	Hardy NG-Test® CARBA 5 ¹	OpGen Acuitas® AMR Gene Panel	Biofire® FilmArray® BCID Panel	GenMark® ePlex BCID	Luminex® VERIGENE	Check-Points Check-Direct CPO for BD MAX™
Test system											
Special equipment needed	No	Yes (pH meter)	No	Yes (BD Phoenix)	Yes	No	Yes	Yes	Yes	Yes	Yes
Kit storage temperature	NA	NA	2-8°C	≈20°C (RT)	2-28°C	4-30°C	15-25°C; 2-8°C	15-25°C	2-8°C	2-30°C; -20°C	2-25°C
Relative Cost / test	\$	\$ - \$\$\$	\$\$	\$\$\$	\$\$\$	\$\$	\$\$\$	\$\$\$\$	\$\$\$\$	\$\$\$\$	\$\$\$

Table 5A. Optional Report Comments for Carbapenemase Testing

	Phenotypic Test mCIM ¹	Genotypic Test KPC, NDM, VIM, IMP, OXA-48 ²	Optional Report Comment (s)
No carbapenemase testing			
1A	Not done	Not done	Carbapenem-resistant [ORGANISM] isolated. Contact laboratory if carbapenemase testing desired.
Phenotypic testing only (e.g., mCIM)			
2A	Negative	Not done	Carbapenem-resistant [ORGANISM] isolated. Carbapenem resistance NOT due to carbapenemase production.
2B	Positive	Not done	Carbapenemase-producing [ORGANISM] isolated. Contact laboratory if carbapenemase characterization desired.

Why ceftazidime-avibactam + aztreonam for Case #1?

ESBL hydrolyzes **ceftazidime**
& **aztreonam**
Inhibited by **avibactam**



MBL hydrolyzes **ceftazidime**,
NOT aztreonam
NOT inhibited by avibactam

Given together, **avibactam** protects **aztreonam** from ESBL = activity
Formulation not currently available, so administer **aztreonam plus**
ceftazidime-avibactam in combination

Expanded Antimicrobial Susceptibility Testing for Hard-to-Treat Infections



Antimicrobial susceptibility testing for Enterobacteriales producing a metallo-beta-lactamase (MBL)

Clinicians and clinical and public health laboratories can request expanded antimicrobial susceptibility testing (**ExAST**) from CDC's Antibiotic Resistance Lab Network (AR Lab Network) to find potentially effective treatment options for their patients' most resistant infections.

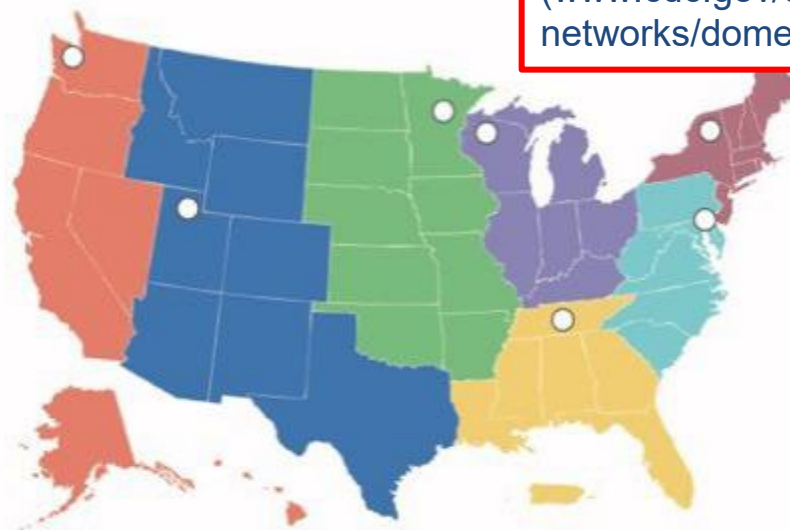
- Testing of aztreonam-avibactam for MBLs
- Turn-around, 3 business days
- Email local ARLN lab for more information!

Antimicrobial Resistance (AR) Lab Network

Work with healthcare facilities to detect AR and prevent spread.

[CDC AR Lab Network](http://www.cdc.gov/drugresistance/ar-lab-networks/domestic.html)

(www.cdc.gov/drugresistance/ar-lab-networks/domestic.html)



- **Southeast:** Tennessee Public Health Laboratory | ARLN.health@tn.gov
- **Mid-Atlantic:** Maryland Public Health Laboratory | MDPHL.arln@maryland.gov
- **Northeast:** Wadsworth Center Labs | ARLNcoreNY@health.ny.gov
- **Midwest:** Wisconsin State Lab of Hygiene | wjARLN@slh.wisc.edu
- **West:** Washington State Public Health Labs | ARLN@doh.wa.gov
- **Central:** Minnesota Dept. of Health Public Health Lab | ARLNMN@state.mn.us
- **Mountain:** Utah Public Health Lab | ARLNUtah@utah.gov

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

- >90% are CPO (produce carbapenemase)
 - OXA most common; many OXA variants
 - OXA-23, OXA-24 most common in *A. baumannii*
 - OXA-48-like (OXA variant included in commercial kits) not common in *A. baumannii*
- Phenotypic carbapenemase tests not reliable
- Few treatment options
 - Newer beta-lactam combinations ineffective
 - Agents that might be tested:
 - Cefiderocol
 - Eravacycline*
 - Omadacycline*
 - Plazomicin*
- Outbreak of **NDM-CRAB** in California (May 2020 – present)



Urgent Threats

These germs are public health threats that require urgent and aggressive action:



CARBAPENEM-RESISTANT
ACINETOBACTER

[CDC Antibiotic Resistance Threats 2019](https://www.cdc.gov/drugresistance/biggest-threats.html)

(www.cdc.gov/drugresistance/biggest-threats.html)

Acinetobacter baumannii - CA NDM Outbreak

Antimicrobial	MIC (µg/mL)	Inter
Amikacin	>32	R
Cefepime	>16	R
Ceftazidime	>16	R
Cefotaxime	>32	R
Ceftriaxone	>32	R
Ciprofloxacin	>2	R
Colistin	≤0.25	Int
Doxycycline	>16	R
Gentamicin	>8	R
Imipenem	>8	R
Meropenem	>4	R
Minocycline	8	Int
Piperacillin-tazobactam	>128/4	R
Tigecycline	0.5	No BPs
Tobramycin	>8	R
Trimeth-sulfamethoxazole	>2/38	R

- Detected via targeted surveillance
- Previously rare in US
- Majority NDM + OXA-23
- Outbreaks in hospitals and skilled nursing facilities (SNF)

June 2022
223 Cases



[CDPH NDM CRAB CAHAN](http://www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CAHAN.aspx)

(www.cdph.ca.gov/Programs/CHCQ/HAI/Pages/CAHAN.aspx)

[LACDPH MDRO Update 6](https://publichealth.lacounty.gov/acd/docs/LA_CDPH_MDRO_Update6.pdf) (PDF)

(publichealth.lacounty.gov/acd/docs/LA_CDPH_MDRO_Update6.pdf)

Case #2

- 67 year old male with neurogenic bladder
- Gulf War Veteran
- Self-catheterizes routinely, but frequent UTIs
- Presents to the ED with concern for UTI
 - Urine is cloudy, smelly
 - Febrile to 38.5°C and WBC of 10K in urine
 - Urine culture - >100K *Acinetobacter baumannii*
- Laboratory uses Hardy Carba-5 for testing, but NOT FDA-cleared for *A. baumannii*
- Tested off-line, detects IMP carbapenemase
- Send for WGS

Notify
IP

Acinetobacter baumannii

Antimicrobial	MIC (µg/mL)	Inter
Amikacin	>32	R
Cefepime	>16	R
Ceftazidime	>16	R
Cefotaxime	>32	R
Ceftriaxone	>32	R
Ciprofloxacin	>2	R
Gentamicin	>8	R
Imipenem	>8	R
Meropenem	>4	R
Minocycline	8	Int
Piperacillin-tazobactam	>128/4	R
Tigecycline	4	No BPs
Tobramycin	>8	R
Trimeth-sulfamethoxazole	>2/38	R

Case #2

- Ran isolate on ePlex off-line, which detects IMP and OXA-23-like carbapenemases
- Carba-5 repeated, positive for IMP only
- Whole genome sequencing: OXA-23 and IMP detected
- Remember...
 - A. baumannii* often harbor OXA, but OXA-23, NOT OXA-48

Carbapenemase Methods and OXA Detection

Carbapenemase	Hardy Carba-5	Cepheid Carba-R	Luminex Verigene	bioMerieux BCID (Biofire)	Roche ePlex
OXA-48-like	Y	Y	Y	Y	Y
OXA-23 group	N	N	Y	N	Y

Case #1B, 1C, 1D

Back in Burn ICU!

Subsequent Carbapenem-R Cases

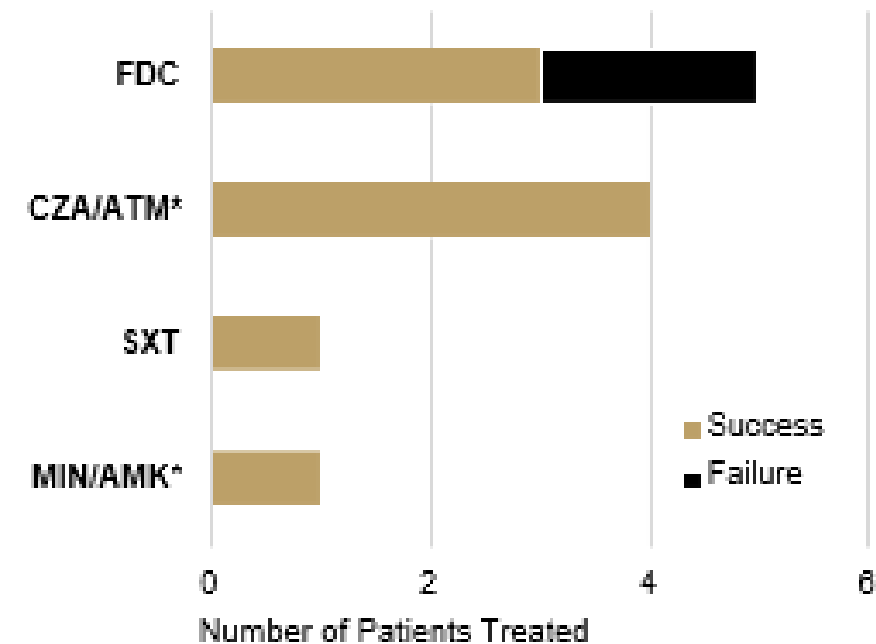
Case #	Weeks After Case #1A	Organism	Carbapenemase Detected
1B	1	<i>P. aeruginosa</i>	VIM
1C	2	<i>Serratia marcescens</i>	VIM
		<i>Enterobacter cloacae</i>	VIM
1D	2	<i>K. pneumoniae</i>	VIM
Original Case			
1A	-	<i>K. pneumoniae</i>	VIM

Antimicrobial	<i>P. aeruginosa</i>	Enterobacterales
Amikacin	R	R
Cefazolin	NA	R
Cefepime	R	R
Ceftazidime	R	R
Ceftazidime-avibactam	R	R
Ceftolozane-tazobactam	R	R
Ceftriaxone	NA	R
Ciprofloxacin	R	R
Ertapenem	NA	R
Gentamicin	R	R
Meropenem	R	R
Meropenem-vaborbactam	NA	R
Piperacillin-tazobactam	R	R
Tobramycin	R	R
Trimeth-sulfamethoxazole	NA	R

NA, not applicable

Surveillance Testing

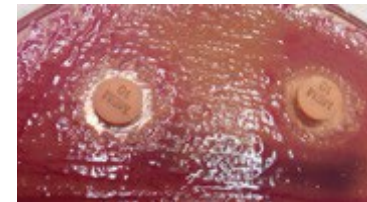
- Patients (N=25) in the burn unit, environment all screened in a point prevalence study for CP-CRE (VIM) by testing rectal swabs
- Outbreak summary:
 - 9 infected patients
 - 5 species (*P. aeruginosa*, *E. cloacae*, *S. marcescens*, *K. pneumoniae*, *A. baumannii*)
 - All harbor same large, 150 kb plasmid with VIM



FDC, cefiderocol; CZA-ATM, ceftazidime-avibactam+aztreonam, SXT, trimethoprim-sulfa, MIN/AMK, minocycline plus amikacin

Freiberg et al. IDWeek 2022, Poster 672, Washington DC, October 2022

How can we perform surveillance testing?



Culture-independent

Test detects presence of carbapenemase gene

Examples: Cepheid Carba-R, CPO for BD Max

Advantage:

- Sensitive, quick, easy

Disadvantages:

- Does not detect all genes or variants
- Cannot determine species gene “belongs” to
- Unable to detect common carbapenemases in *A. baumannii*
- Expensive

Culture

Use of selective media / methods to recover carbapenem-resistant isolates

Examples: Chromagar, use of meropenem disks, etc.

Advantages:

- (theoretically) detect any carbapenemase mechanism
- Inexpensive
- Isolates available for further study

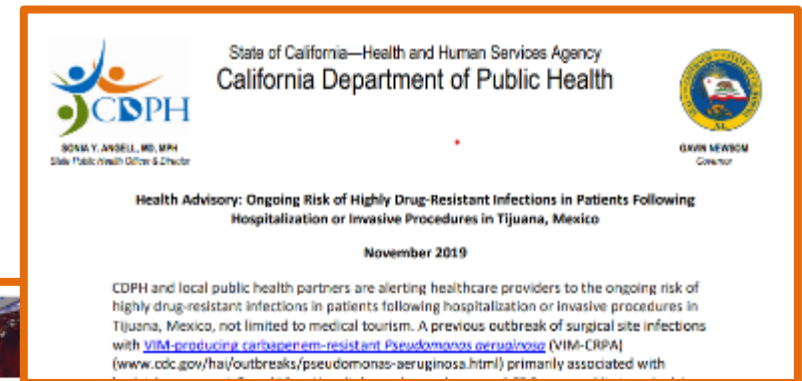
Disadvantages:

- Time consuming!
- Sensitivity unknown

Pseudomonas aeruginosa - VIM

Antimicrobial	MIC (µg/mL)	Inter
Amikacin	>32	R
Aztreonam	>16	R
Cefepime	>16	R
Ceftazidime	>16	R
Ciprofloxacin	>2	R
Gentamicin	>8	R
Imipenem	8	R
Meropenem	8	R
Piperacillin-tazobactam	32	Int
Tobramycin	>8	R

- Several recent cases (eye specimens) in California (see Epi-X)
- WGS suggests link among these cases
- Other *P. aeruginosa*-VIM cases linked to medical tourism in Mexico



EMERGING INFECTIOUS DISEASES

Extensively Drug-Resistant Carbapenemase-Producing *Pseudomonas aeruginosa* and Medical Tourism from the United States to Mexico, 2018–2019

Ian Kracalik, D. Cal Ham, [...], and for the Verona Integron-Encoded Metallo- β -Lactamase-Producing

Emerg Infect Dis. 2022 Jan; 28(1): 51–61.
doi: [10.3201/eid2801.211880](https://doi.org/10.3201/eid2801.211880)

Sensitivity and Specificity for Identifying Carbapenemase Producers among CRPA (resistant to Imipenem and/or Meropenem)

Definition	Sensitivity	Specificity
NS [^] to cefepime	83	53
NS to ceftazidime	94	61
NS to cefepime OR ceftazidime	91	50
NS to ceftolozane-tazobactam	100	86

[^]NS, not susceptible (e.g., I or R)

Conclusion:

- High suspicion for carbapenemases in CRPA isolates that are NS to ceftazidime and/or cefepime
- Very high suspicion for CRPA that are NS to ceftolozane-tazobactam
- These isolates should be targeted for carbapenemase testing and infection control interventions

Extracted from Vallabhaneni, Huang, Grass et al. 2021. J Clin Microbiol. 59:e02874-20

CDC Investigating a Multistate Cluster of VIM-*P. aeruginosa* Announced **TODAY** 10/27/22!

- Isolates:
 - ST 1203, harbor *bla*_{VIM-80} and *bla*_{GES-9}
 - Combination not previously seen in the US)
 - Closely related by WGS
 - R to cefepime, ceftazidime, ceftolozane-tazobactam
- 34 isolates from 32 patients in 6 jurisdictions
 - CA, CT, NM, NY, UT, WA
 - 28 isolates are part of 4 facility clusters
- May 2022-present
- Many specimen types, facility settings

Epi-X The Epidemic Information Exchange

Call for Cases: Multistate Cluster of Verona Integron-mediated Metallo- β -lactamase (VIM)-producing Carbapenem-resistant *Pseudomonas aeruginosa* -- October 27, 2022

Access and Notification: [Click to see who has viewed this report.](#)

Distribution: **Release outside of Epi-X as needed**
Contributor's instructions for distributing this report.

Brief Summary of Report: The Centers for Disease Control and Prevention (CDC) is investigating a multistate cluster of VIM-producing carbapenem-resistant *Pseudomonas aeruginosa* (VIM-CRPA).

Description: The Centers for Disease Control and Prevention (CDC) is investigating a multistate cluster of VIM-producing carbapenem-resistant *Pseudomonas aeruginosa* (VIM-CRPA). In addition to demonstrating carbapenem resistance, isolates in this cluster are not susceptible to ceftazidime or cefepime; the subset of isolates that underwent antimicrobial susceptibility testing for ceftolozane-tazobactam were also not susceptible to this agent. Isolates in this cluster are ST 1203, harbor *bla*_{VIM-80} and *bla*_{GES-9} (a combination not previously observed in the United States) and are closely related by whole genome sequencing (WGS) analysis.

- CDPH requesting CRPA isolates VIM-positive with collection date from 1/1/22
- CAHAN forthcoming
- For more information, email: HAIProgram@cdph.ca.gov

Laboratory Requirements for Reporting CPO in California

- **CDPH - Title 17, California Code of Regulations (CCR), Section 2505 REPORTABLE CONDITIONS: NOTIFICATION BY LABORATORIES TO PUBLIC HEALTH (August 2022)**
 - [Carbapenemase-producing organism, colonization or infection \(PDF\)](#)
(www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/LabReportableDiseases.pdf)
- **LACDPH – Title 17 REPORTABLE CONDITIONS: NOTIFICATION BY LABORATORIES, California Code of Regulations (CCR), § 2505 and § 2643.10; Title 17, California Code of Regulations (CCR), § 2612; California Health and Safety Code (HSC), §124130 and specific Los Angeles County Requirements This list is specific to Los Angeles County and includes state and federal reporting requirements. (June 2022)**
 - [Carbapenemase-producing Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter* sp. \(PDF\)](#)
(publichealth.lacounty.gov/acd/docs/LabList.pdf)

And...

**Inform your facility's Infection Preventionists of CPO
(and CRO) ASAP so actions can be taken to prevent
spread of these MDRO!**

Lucas J. Osborn, PhD, MLS(ASCP)^{CM}
Clinical Microbiology Fellow
Children's Hospital Los Angeles

Healthcare-Associated Infections (HAI) Program
Center for Health Care Quality
California Department of Public Health

Healthcare Outreach Unit
Acute Communicable Disease Control Program
Los Angeles County Department of Public Health



Case #3

KPC – *Citrobacter freundii*

Extremely premature infant boy born at 26 week, 5 days by spontaneous vaginal delivery, due to PTL

Birth weight, 1110 grams

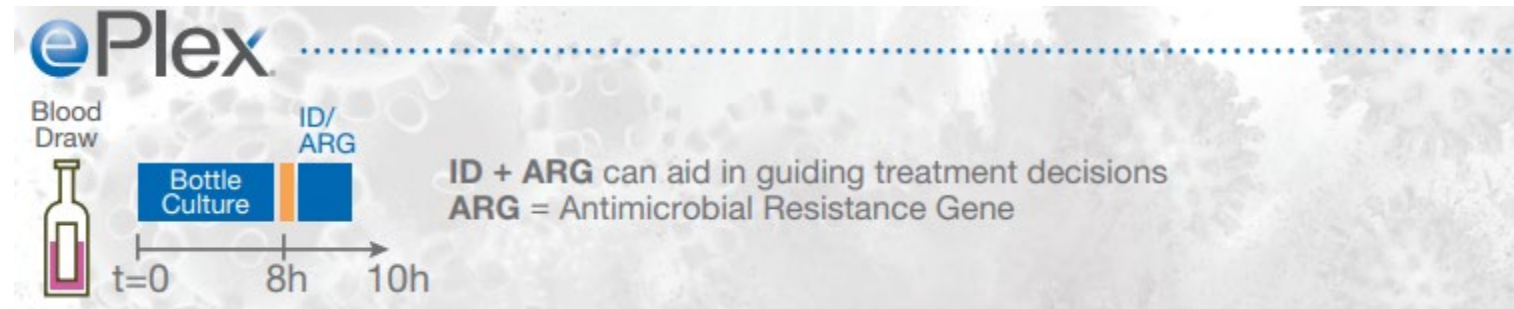
Apgar scores of 1 at 1 minute and 7 at 5 minutes

Transferred to NICU for extreme prematurity

Mom is a 34-year-old from Guatemala, with history of 2 C-section deliveries

Intubated, started on empiric ampicillin and gentamicin due to mom's untreated GBS

Blood cultures collected, which grow *Citrobacter freundii*, KPC + by ePlex



Resistance Genes

CTX-M

NDM

IMP

OXA (groups 23 and 48)

KPC

VIM

Case #3

Citrobacter freundii

Blood culture susceptibility results

Antimicrobial	MIC	Result	Final Report
Amikacin	≤8	S	S
Cefepime	2	S	S
Ciprofloxacin	0.5	I	I
Ertapenem	1	I*	R
Gentamicin	>8	R	R
Levofloxacin	≤0.5	S	S
Meropenem	≤0.5	S*	R
Piperacillin-tazobactam	>64/4	R	R
SXT	≤0.5	R	R

Laboratory Results

- ePlex: *Citrobacter* spp. → KPC detected.

Additional Testing

- Repeated ePlex and AST, subcultured again from bottle.
- Dropped meropenem disk to screen for mixed *Citrobacter* culture.
- Communicate with ID team!*

Clinical Outcome

- Treated w/ empiric ampicillin and gentamicin.
- Infant clinically decompensated two days later with abdominal distension, hypoxia, metabolic acidosis, and passed away.

*Caution is advised. Current clinical evidence is insufficient to conclude whether carbapenem monotherapy of carbapenemase-carrying strains with an MIC in the susceptible range will be effective. – CLSI M100 Table H3

Troubleshooting Carbapenemase Tests

Appendix H. (Continued)

Table H3. (Continued)

Indication	Targets	Methods	Specimen Types	Results		Suggestions for Resolution	Report as:	Comments ^a
				Molecular Target Results	Observed Phenotype (if tested)			
Detection of carbapenem resistance in Enterobacterales (Continued)	KPC, OXA-48-like, VIM, NDM, or IMP Or Phenotypic evidence of a carbapenemase (eg, mCIM or CarbaNP positive)	NAAT, microarray	Colonies, blood culture	Detection of any tested carbapenemase target or phenotypic detection of carbapenemase production	Susceptibility (S or SDD) to 3rd- and/or 4th-generation cephalosporins but intermediate or resistant to at least one carbapenem tested	Repeat molecular and phenotypic tests.	If the discrepancy is not resolved, repeat AST should be performed using a reference method, and the conflicting genotypic and phenotypic testing results should both be reported along with a comment advising caution: "Current clinical and laboratory evidence is insufficient to conclude whether cephalosporin therapy of carbapenemase-carrying strains with an MIC in the S/SDD range will be effective."	1-4, 12-14

Troubleshooting Reporting



[CLSI M100 32nd ed. Appendix H3. 2022](https://em100.edaptivedocs.net/dashboard.aspx)
(em100.edaptivedocs.net/dashboard.aspx)

CHLA Criteria for performing Cepheid Xpert Carba-R

Organisms	Criteria for performing CRE PCR
<i>Enterobacter</i> spp; <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i>	Resistant to Meropenem
<i>Proteus</i> spp., <i>Morganella</i> spp., <i>Providencia</i> spp.	Resistant to Ertapenem or Meropenem
Enterobacterales (all other not listed above)	Resistant to Ertapenem, Imipenem, or Meropenem

***Do not perform CRE PCR if test has been performed in last 3 months**

“This organism is resistant to carbapenem and is positive for carbapenemase production by detection of a carbapenemase gene. Enhanced precautions are recommended”

Selected Limitations of Xpert Carba-R

The Xpert Carba-R Assay will generate a negative IMP result when testing samples containing IMP-7, IMP-13, or IMP-14 gene sequences.

The performance of the Xpert Carba-R Assay has not been evaluated with rectal or perirectal swab specimens from pediatric patients.

The detection of blaKPC, blaNDM, blaVIM, blaOXA-48, and blaIMP gene sequences is dependent on the number of organisms present in the sample.

Case #4

IMP – *Pseudomonas aeruginosa*

- 15 y/o with cerebral palsy, chronic lung disease, chronic respiratory failure, tracheostomy/home ventilator dependence
- Long ICU-stays since age of 2 in Middle East, extended ICU-stay in US for pneumonia
- Recurring admissions for fever, increased trach secretions, and/or hypoxia
- Tracheal aspirate sent for culture upon each admission → *P. aeruginosa* w/ IMP gene detected



CP-CRO Alert

- o This patient is infected or colonized with a Carbapenemase-Producing Carbapenem Resistant Organism (CP-CRO).
- o Place patient on ENHANCED Contact Precautions.
- o Refer to policy IC.301 for ENHANCED precautions isolation guidance.

IC 301

OK

1

Insert swab into Sample Reagent vial and vortex



2

Transfer the Sample Reagent to the cartridge



3

Insert cartridge and start test



Resistance Genes

KPC NDM
 VIM IMP-1
 OXA-48 OXA-181
 OXA-232

Case #4

Pseudomonas aeruginosa

Tracheal aspirate susceptibility results

Drug	MIC	Result
Amikacin	>32	R
Aztreonam	16	I
Cefepime	>16	R
Ceftazidime	>16	R
Ciprofloxacin	>2	R
Colistin	1	S
Gentamicin	>8	R
Imipenem	>8	R
Levofloxacin	>8	R
Meropenem	>8	R
Piperacillin/Tazobactam	>64/4	R
Tobramycin	>8	R

“Carbapenemase IMP gene detected”

Laboratory Results

Tracheal aspirate respiratory culture

- Few normal respiratory flora
- Moderate MRSA
- Moderate *Pseudomonas aeruginosa*

Additional Testing

- Confirm ID *and* carbapenems (AST w/ 2nd method)
- Cepheid Xpert Carba-R
 - IMP gene detected

Clinical Outcome

- IMP-containing *P. aeruginosa* with same resistance pattern **treated x3 over 3 years w/ nebulized colistin**
- No new infection for 1+ year

Multiple drug resistant organism isolated. Carbapenem resistant organism isolated. Contact isolation is recommended.

CHLA MDRO (including CRO and CPO) Reporting Guidelines

Both of the following criteria must be met:

1. Any Gram-negative organism that is intermediate or resistant to at least 1 antibiotic within 2 drug classes*
2. Resistant to at least one 3rd or 4th generation cephalosporin*

*Excludes intrinsic resistance

Purpose of MDRO reporting:

Generates code in EMR and Infection Prevention and Control (IPC) surveillance tool: “Multiple drug resistant organism isolated. Contact isolation is recommended”.

Antimicrobial Stewardship Program (ASP) performs daily audit of antimicrobial therapy.

IPC and ASP receive real time alerts for MDRO and CPO → coordinate with clinical care team to ensure appropriate antimicrobial therapy and appropriate contact isolation, cleaning, etc.

IPC and ASP track and report antibiotic use and resistance data to outside agencies/collaborators to create benchmark outcomes for CHLA.

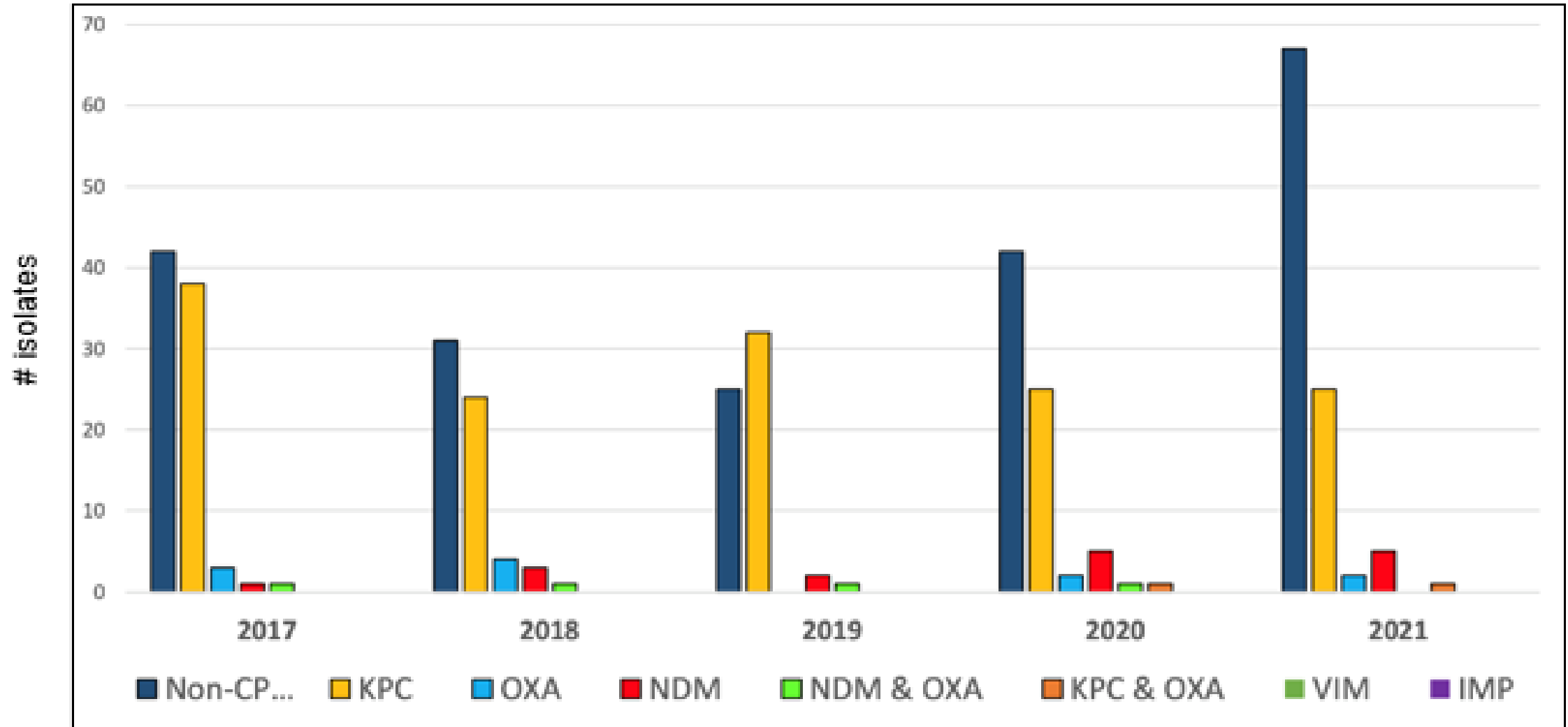
June L. Chan, PhD
Medical and Public Health Microbiology Fellow
University of California Los Angeles

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Center for Health Care Quality
California Department of Public Health

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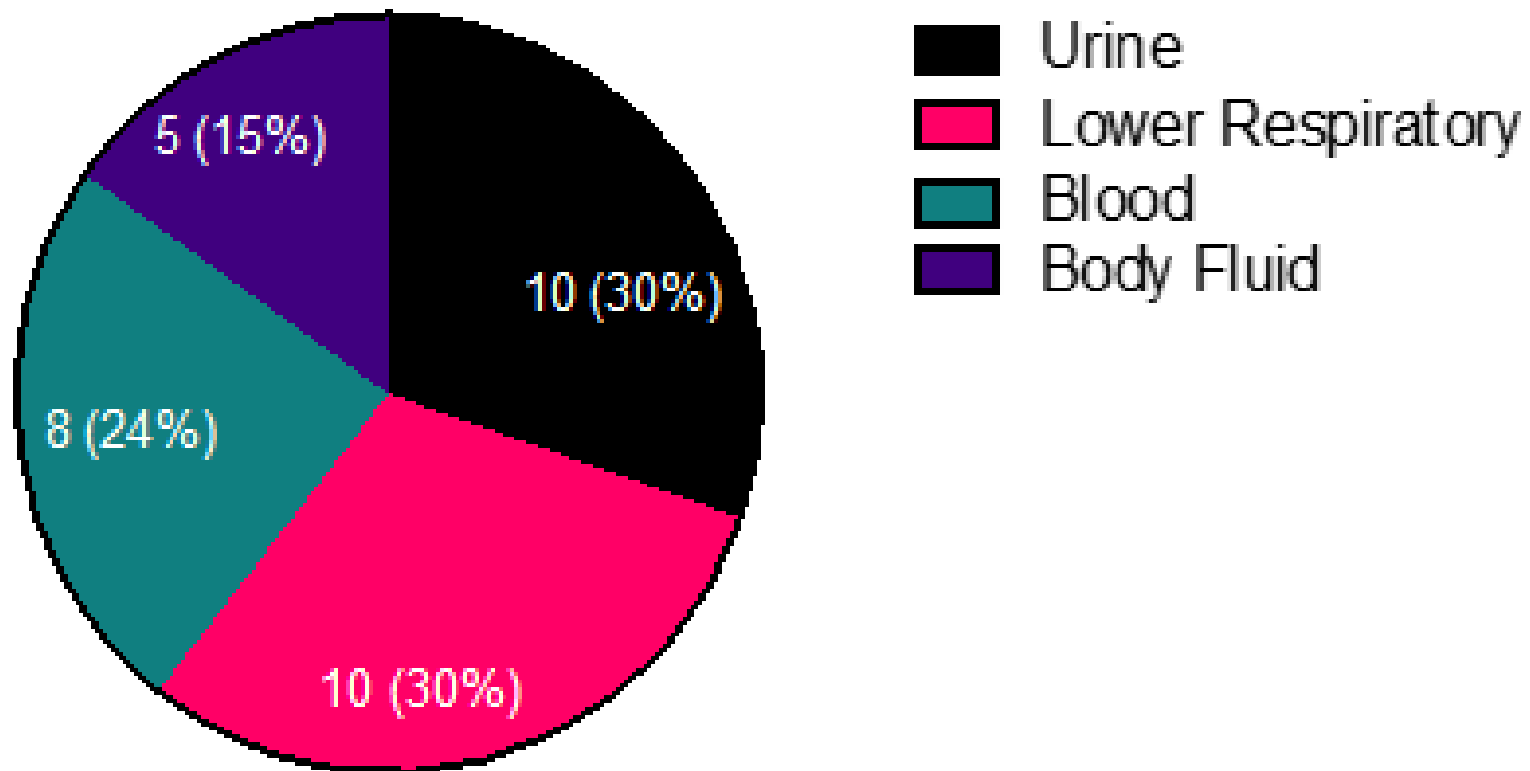


UCLA Health: Carbapenem-resistant Enterobacterales (CRE): 2017-2021



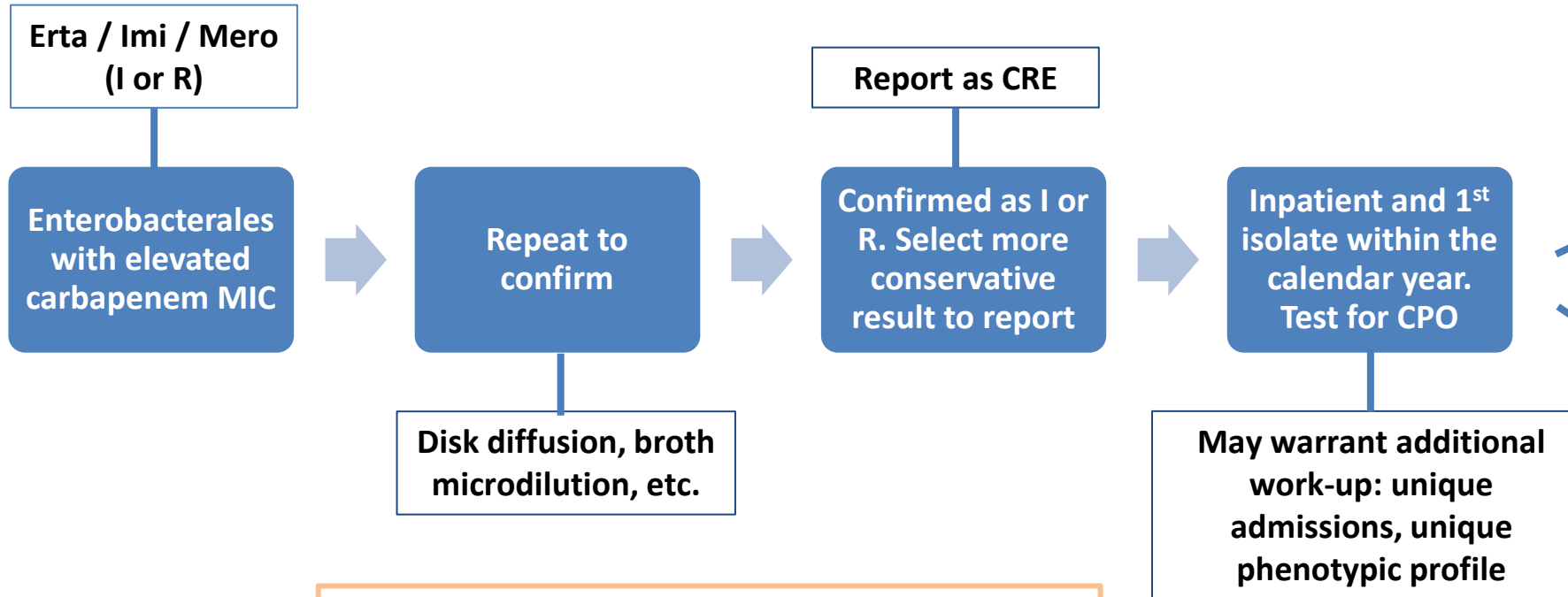
UCLA Health: Carbapenem-Resistant Enterobacterales (CRE): 2021

2021 CP-CRE Specimens



Total = 33

Unusual Susceptibility - CRE Confirmation Workflow



Positive CPO Report to LAC



LAC Public Health

NG-Test® CARBA 5



Cepheid Xpert Carba-R®



UCLA Clinical Case

Case #5

- 57 yo female presents with COVID-19 pneumonia
 - Status post Remdesivir, convalescent plasma, steroids
 - Acute hypoxic respiratory failure (ARDS)
 - Proned and intubated 3 days
 - 4 hours venous-venous ECMO
- Tracheostomy performed ~17 days after admission
- Skin breakdown at stoma noted 11 days after tracheostomy
 - Serosanguinous drainage
 - Neck wound cultures sent



Case #5

Klebsiella pneumoniae Neck Wound Culture

Original treatment:
minocycline, meropenem

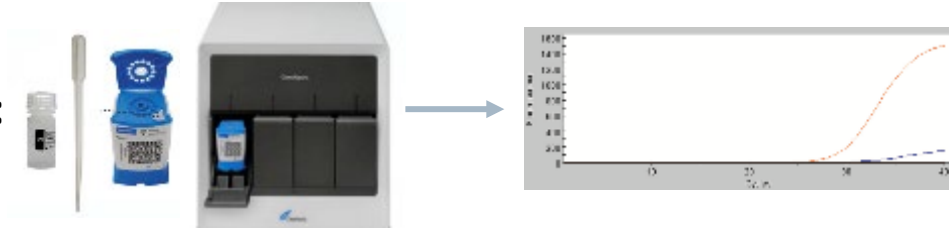
Revised treatment:
ceftazidime-avibactam

Antimicrobial	MIC (µg/mL)	Interp
Amikacin	>64	R
Aztreonam	>32	R
Cefazolin	>32	R
Cefepime	>32	R
Ceftazidime	>32	R
Ceftazidime/Avibactam	<2	S
Ceftolozane/Tazobactam	>32	R
Ceftriaxone	>64	R
Ciprofloxacin	>4	R
Ertapenem	>4	R
Gentamicin	>16	R
Imipenem	>16	R
Levofloxacin	>8	R
Meropenem	>16	R
Piperacillin + Tazobactam	>128	R
Tigecycline	2	S
Tobramycin	>16	R
Trimethoprim/Sulfamethoxazole	>4/80	R

Case #5

Carbapenemase Testing and Reporting Comments

CARBA-R Testing on the *K. pneumoniae* isolate:



KPC + OXA-48

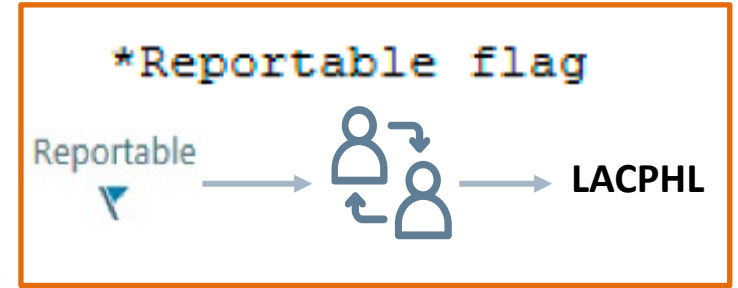
Specimen Information: Neck; Wound

Bacterial Aerobic Culture

Few Klebsiella pneumoniae !

Repeat Susceptibility Testing:

Carbapenem Resistant Enterobacteriaceae (CRE).



This organism is positive for the KPC and OXA-48 Carbapenemases. Infectious diseases consult strongly suggested. This patient requires contact precautions, consult HSIC 002.

Few Probable candida albicans !

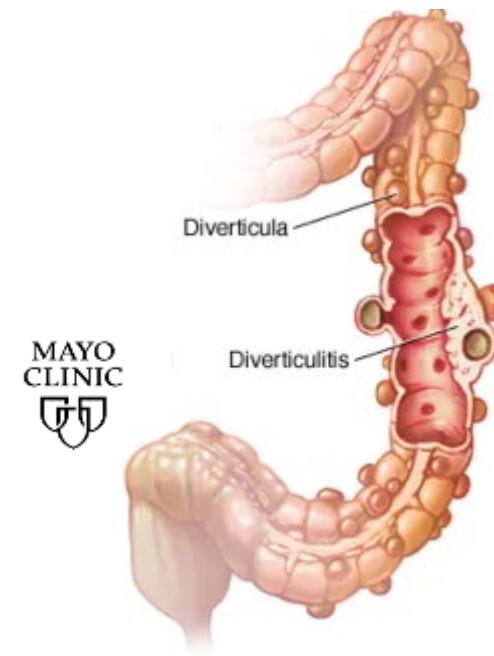
Gram Stain

No bacteria seen.
Moderate WBC

UCLA Clinical Case

Case #6

- 51 yo male presents to ED: referred from general surgery clinic with concern for drain malfunction
- Past medical history: anemia, **perforated diverticulitis**, gastritis
- Percutaneous drainage for diverticular abscess (4 weeks ago) with surgical drain in place
 - CT concerning for persistent fluid collection
 - Worsening pain with difficulty urinating
 - Multiple recent visits for purulent/feculent discharge around drain
- *Enterobacter cloacae* complex recovered on prior occasions
- Aspirate of abdominal abscess sent for culture



Case #6

Enterobacter cloacae complex Abdominal Fluid Culture

Original treatment:

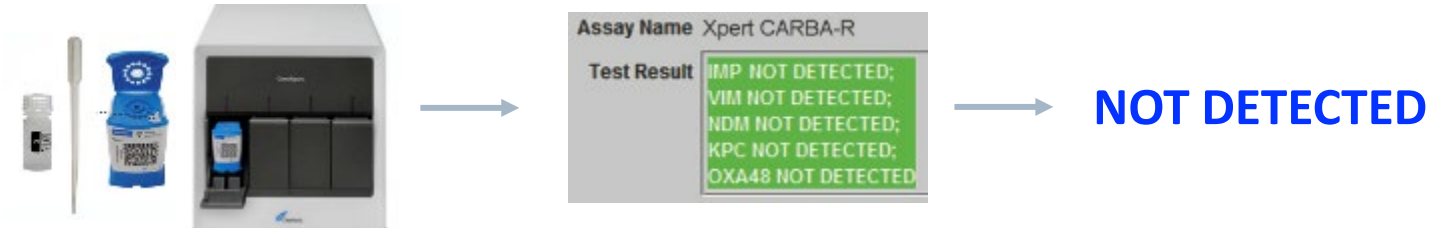
ciprofloxacin, metronidazole

Revised treatment: meropenem
(while addressing source control
& drainage issues)

Antimicrobial	MIC ($\mu\text{g/mL}$)	Interp
Amikacin	32	I
Aztreonam	>32	R
Cefazolin	>32	R
Cefepime	16	R
Ceftazidime	>32	R
Ceftazidime/Avibactam	≤ 2	S
Ceftolozane/Tazobactam	≤ 0.5	S
Ceftriaxone	>64	R
Ciprofloxacin	>4	R
Ertapenem	4	R
Gentamicin	>16	R
Imipenem	≤ 1	S
Levofloxacin	>8	R
Meropenem	0.5	S
Piperacillin + Tazobactam	>128	R
Tigecycline	≤ 0.25	S
Tobramycin	>16	R
Trimethoprim-sulfmethoxazole	>4/80	R

Carbapenemase Testing and Reporting Comments

CARBA-R Testing on the *E. cloacae* isolate:



Specimen Information: Abdomen; Body Fluid

Bacterial Aerobic Culture

Rare *Enterobacter cloacae* complex !
Repeat Susceptibility Testing:

Carbapenem Resistant Enterobacteriaceae (CRE).

Negative for Carbapenemase, resistant to ertapenem by another resistance mechanism (e.g., porin mutation).

Rare *Haemophilus parainfluenzae* !

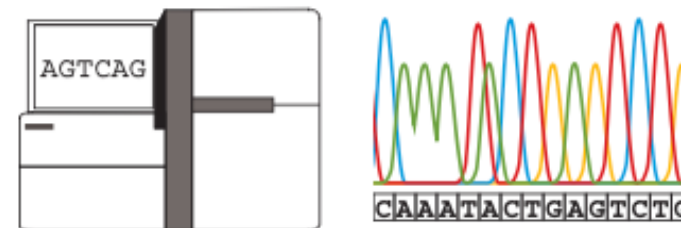
Rare *Enterococcus*-like colonies !

Gram Stain

No bacteria seen.
Many WBC

Case #6

NGS AMR Assessment: presence of *ampC* beta-lactamase and porin mutations



UCLA CRO Protocols

- Infection Prevention and Antimicrobial Stewardship teams recommend when to test for carbapenemases

Contact Precautions for Inpatients – Isolation

- CRO: resistant to any carbapenem
- Duration of hospitalization and for each readmission with no clearance process
 - Clean hands upon entering and leaving room
 - PPE: gown and gloves on entry (single use)
 - Private room (patient cohorting, curtain separation)
 - Post contact precautions sign outside the room, clearly visible

Select CDC/CDPH/LACDPH Resources with Laboratory-Related Content for CPO*

- [CDC Antibiotic Resistance Laboratory Network \(AR Lab Network\)](https://www.cdc.gov/drugresistance/ar-lab-networks/domestic/testing-details.html)
(www.cdc.gov/drugresistance/ar-lab-networks/domestic/testing-details.html)
- [CDC Antibiotic Resistance & Patient Safety Portal](https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance) (contains CPO data)
(arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance)
- [Washington State Regional AR Lab Network Test Menu](https://doh.wa.gov/public-health-healthcare-providers/public-health-laboratories/arIn-lab-test-menu)
(doh.wa.gov/public-health-healthcare-providers/public-health-laboratories/arIn-lab-test-menu)
- [CDPH CPO Reporting Requirements FAQ – NEW September 2022](https://www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPOReportingFAQ.pdf) (PDF)
(www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPOReportingFAQ.pdf)
- [CDPH Algorithm for Carbapenemase Testing](https://www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CPTestingPrioritizationAlgorithm.pdf) (PDF)
(www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH Document Library/CPTestingPrioritizationAlgorithm.pdf)
- [LACDPH Monthly \(now quarterly\) MDRO Lab Newsletters \(click on #10 link to see topics covered in all 10 publications\)](https://publichealth.lacounty.gov/acd/Diseases/NMDRO.htm)
(publichealth.lacounty.gov/acd/Diseases/NMDRO.htm)
- [LACDPH Multifacility Antibiogram and Antibiogram Dashboard](https://publichealth.lacounty.gov/acd/AntibiogramData.htm)
(publichealth.lacounty.gov/acd/AntibiogramData.htm)

* The other webinars in this 2022 3-part CPO series list other resources for management of patients with CPO



Q & A



Thank you!

Questions?

Contact us at,

HAIProgram@cdph.ca.gov

hai@ph.lacounty.gov