UCLA David Geffen School of Medicine

SCASM 2023 Case Study 3

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Objectives

- Describe the genes associated with carbapenemase production
- Identify how relatedness is determined using sequencing
- Understand clinical and public health implications of CRPA infections

CASE 1

Male in 50s presents with cardiogenic shock of unknow etiology

History
Weeks

t=0
Travel to Hawaii

t=1
Diarrhea, chest pain, dyspnea, cold-like symptoms

t=4
ECMO and impella support

t=6
Heart and kidney transplant

Culture results

Blood cx + for *Bacillus cereus*

Urine cx + for *Pseudomonas aeruginosa*

Susceptibility Testing

Antibiotic	Interpretation
Amikacin	Intermediate
Cefepime	Resistant
Cefiderocol	Susceptible
Ceftazidime	Resistant
Ceftazidime/Avibactam	Resistant
Ceftolozane/Tazobactam	Resistant
Ciprofloxacin	Resistant
Colistin	Intermediate
Gentamicin	Resistant
Imipenem	Resistant
Imipenem/relebactam	Resistant
Meropenem	Resistant
Piperacillin + Tazobactam	Resistant
Tobramycin	Resistant

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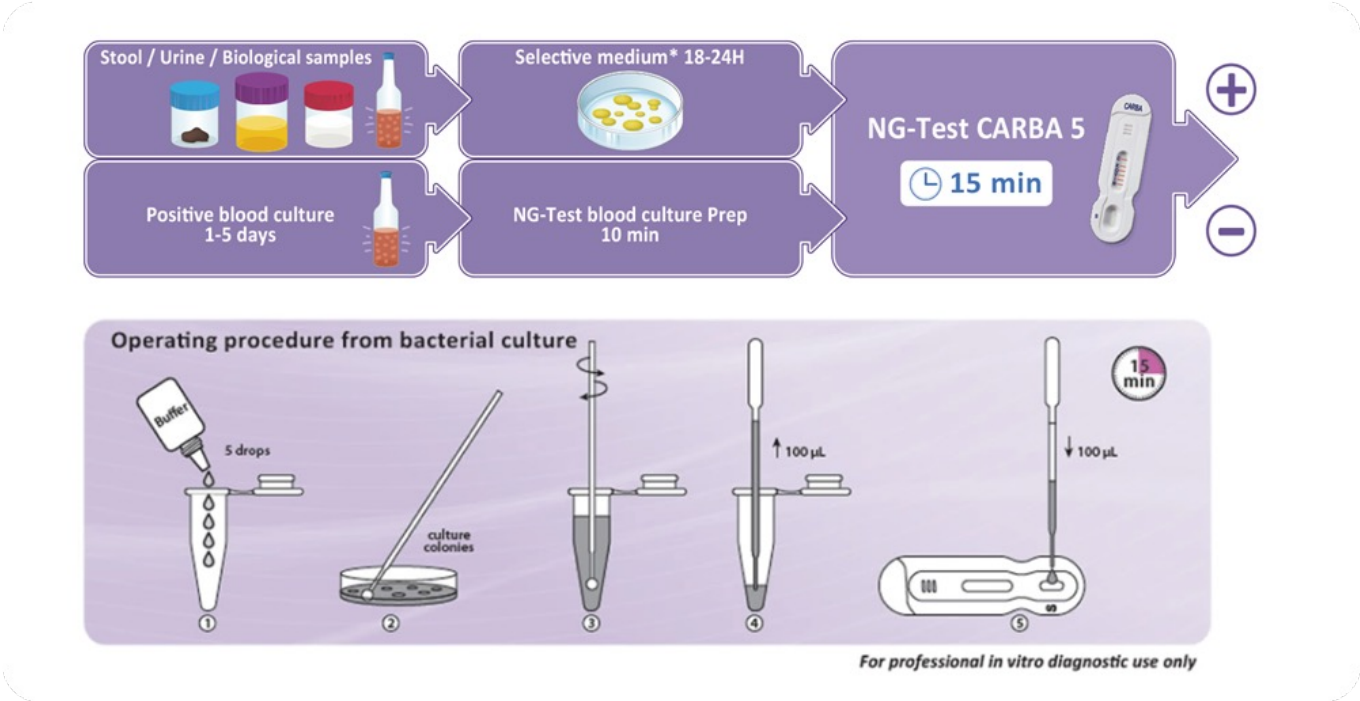
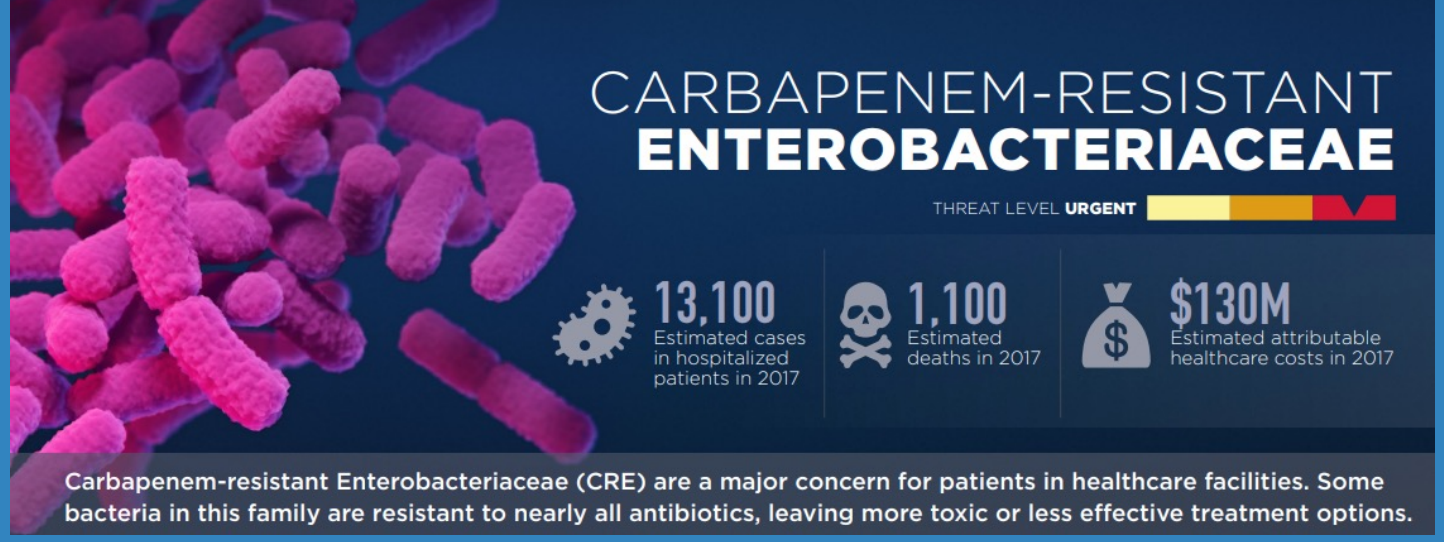
Carbapenemase production

CARBA-5 NDM+





The Big 5 Carbapenemases

- Acquired and mobilizable genes encoding for enzyme production
- Hydrolysis of penicillins, cephalosporins, monobactams, and carbapenems
- Class A – *Kleb. pneumo* carbapenemase (**KPC**)
- Class B – Imipenemase (**IMP**), New Dehli Metallo-β-lactamase (**NDM**), Verona integron-encoded metallo-β-bactamase (**VIM**)
- Class D – Oxacillinase-48 (**OXA-48**)

CASE 2

Male in 80s presented with inability to walk following international travel

History and Clinical Course

Parkison's disease
Hip fracture surgical repair in Iran
Chronic foley catheter

Culture results

Urine cx + for Pseudomonas aeruginosa

CASE 3

Male in 70s presents with urinary and fecal retention, colitis and enteritis

History and Clinical Course

Prostate cancer
Acute kidney injury
Respiratory failure

Culture results

Blood cx + for Pseudomonas aeruginosa

CASE 4

Female in 70s presents with hyponatremia and progressive dyspnea

History and Clinical Course

Recurrent papillary thyroid cancer
G-tube dependent
MSSA pneumonia
Worsening secretions, hypoxia

Culture results

Resp cx + for Pseudomonas aeruginosa

CASE 5

Male in 60s presents with cardiogenic shock

History and Clinical Course

Vascular disease, cardiomyopathy
Intubated
Heart tx
UTI

Culture results

Urine cx + for Pseudomonas aeruginosa

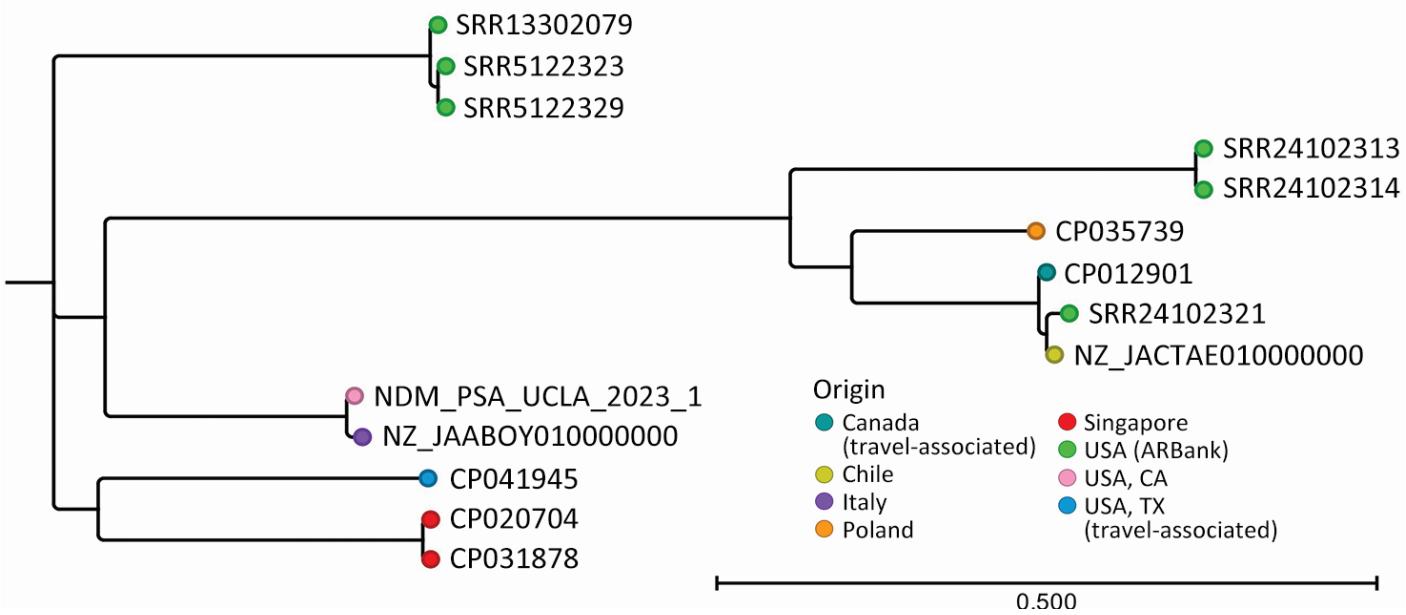
All 5 isolates NDM producers… Are they related?

Next-generation sequencing used to determine:

1) Relatedness of isolates to each other
2) Genes associated with resistance
3) Relatedness of isolates to other previously identified NDM-CRPA

NGS – Case 1

Mechanism	Genes (Case 1)
Aminoglycoside	aac(6')-Ib9, ant(3")-IIa, aph(3')-IIb, aph(3')-VIa
Beta-Lactamases	bla_{NDM-1}, bla_{OXA-10}, $bla_{OXA-488}$, bla_{PDC-35}, bla_{PME}
Fluoroquinolone	gyrA (T83I) + parE (S457R)
Chloramphenicol	catB3, catB7, cmlA9
Fosfomycin	fosA
Tetracycline	tet(D)
Sulfonamide	sul1



Possibly a local strain circulating in community prior to detection

ARGs and core genome SNPs

Case 1	Case 2	Case 3	Case 4	Case 4	Case 5
aac(6')-Ib3	aph(3')-IIb	aadA6	aadA6	aadA6	aadA6
aadA1	aph(3')-VI	aph(3')-IIb	aph(3')-IIb	aph(3')-IIb	aph(3')-IIb
aph(3')-IIb	blaNDM-1	aph(3')-VIa	aph(3')-VIa	aph(3')-VIa	aph(3')-VIa
aph(3')-VIa	blaOXA-488	blaNDM-1	blaNDM-1	blaNDM-1	blaNDM-1
blaNDM-1	blaPAO	blaOXA-488	blaOXA-488	blaOXA-488	blaOXA-488
blaOXA-10	blaPME-1	blaPAO	blaPAO	blaPAO	blaPAO
blaOXA-488	catB7	blaPME-1	blaPME-1		
blaPAO	fosA	catB7	catB7	catB7	catB7
blaPME-1	sul1	crpP	crpP	crpP	crpP
catB3	tet(G)	fosA	fosA	fosA	fosA
catB7		qacE	qacE	qacE	qacE
crpP		Sul1	sul1	sul1	sul1
fosA		tet(G)	tet(G)	tet(G)	tet(G)
qacE					
sul1					
tet(G)					

Sequence Type: *235*

	Case 1	Case 4	Case 4	Case 5	Case 3	Case 2
Case 1	0	1	1	1	5	282
Case 4	1	0	0	2	4	281
Case 4	1	0	0	2	4	281
Case 5	1	2	2	0	6	283
Case 3	5	4	4	6	0	281
Case 2	282	281	281	283	281	0

Collaboration with LACPHL

Long-read sequencing integrated with Illumina NGS:

- Isolates from cases 1,3,4,5 closely related
- Changes in ARGs between initial case and Case 3 (2 mos)

Updated policies, including:

Inpatients with a culture positive for an MDRO including CRE on the current admission will remain on contact precautions indefinitely, including during readmissions.

Epidemiological investigation did not determine a source

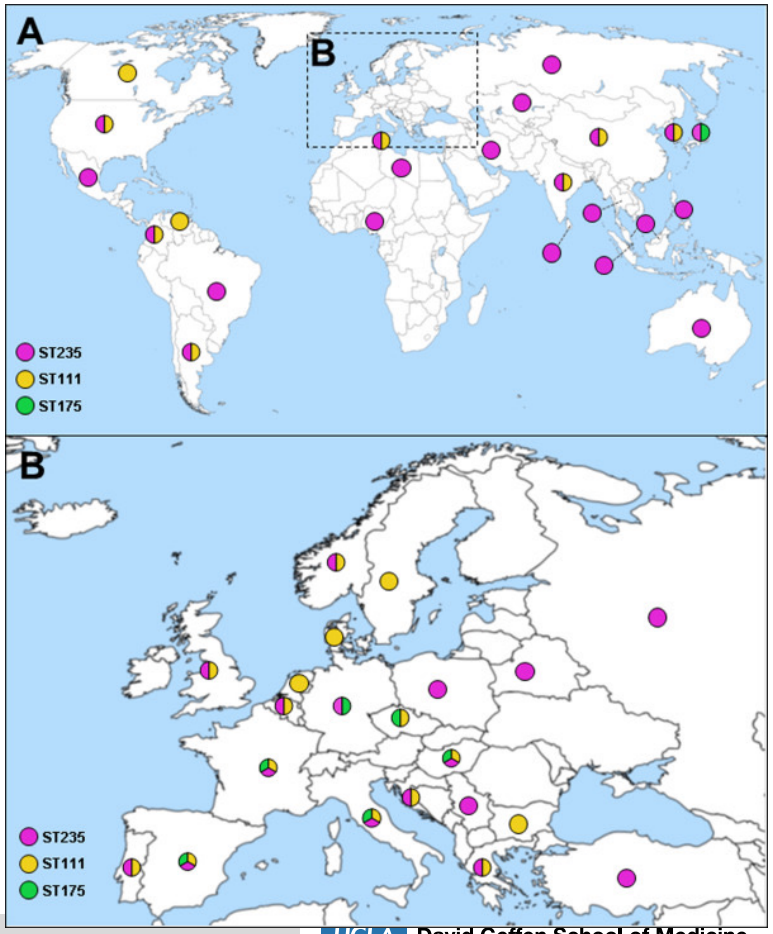
Sequence Type: *235*

Review Article
Infection & Chemotherapy 2015; 47(2): 81-97.
Published online: 30 June 2015
DOI: https://doi.org/10.3947/ic.2015.47.2.81

Epidemiology and Characteristics of Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa*

MBL enzymes	Frequently identified sequence type	Country of isolation	Reported gene location	Reference(s) or GenBank accession No.
NDM-1	235	Serbia	Chromosome	[20]
		France	Chromosome	[54, 55]
		India	Plasmid	[56]
		Italy	Chromosome	[57]
		Egypt	Unknown	[58]
		Slovakia	Unknown	[59]
SPM-1	NR	Brazil	IS*CR4*	[160]
		Switzerland	IS*CR4*	[48]
GIM-1	NR	Germany	Class 1 Integron, Plasmid	[51, 52]
FIM-1	235	Italy	Chromosome	[60]

MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; SPM, Sao Paulo metallo-β-lactamase; NR, not reported; IS*CR4*, insertion sequence common region 4; GIM, Germany imipenemase; FIM, Florence imipenemase.

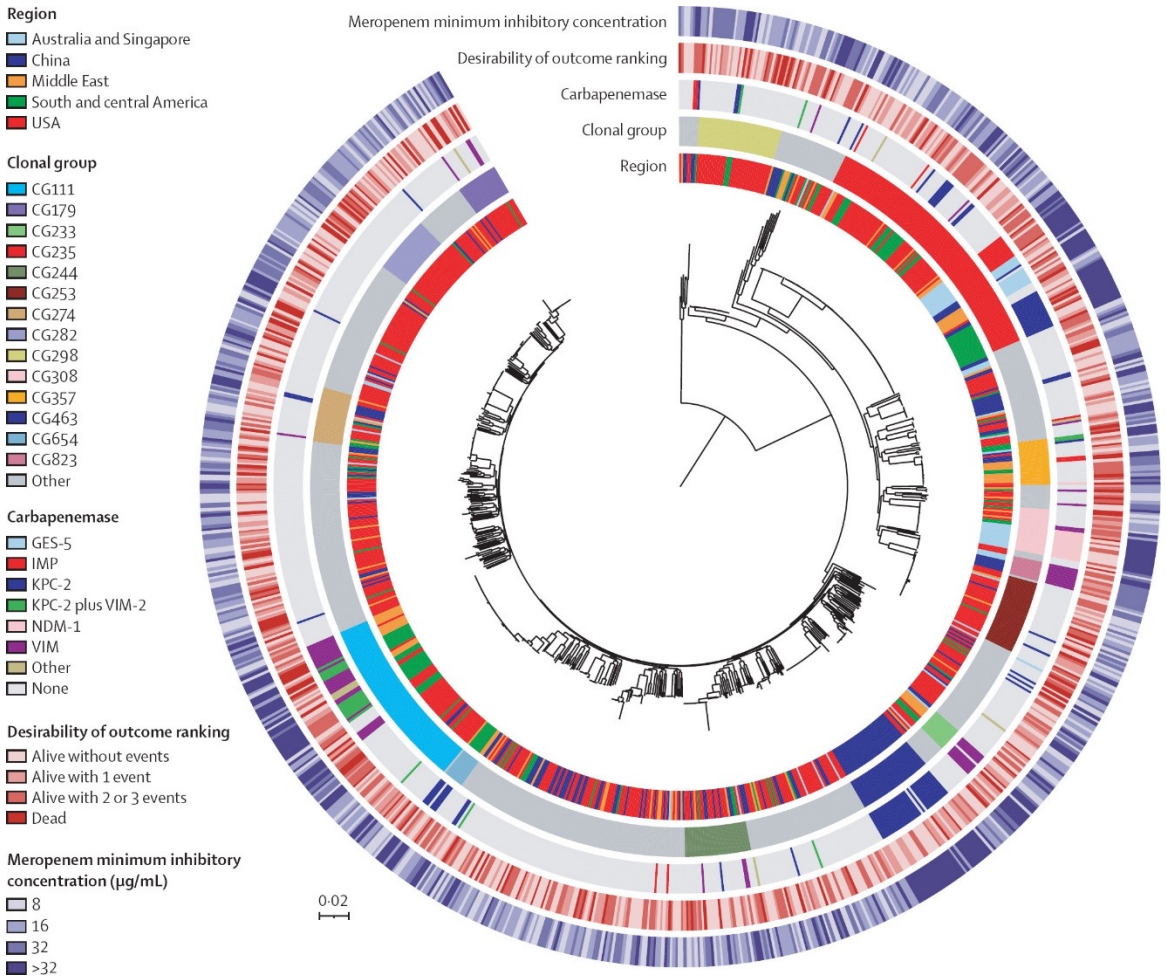


CP-CRPA vs. CRPA→ >900 patients with carbapenem-resistant *Pseudomonas aeruginosa*

CP-CRPA associated with increased mortality (30 and 90 day)

Elevated MICs to: meropenem, cefepime, ceftazidime, pip-tazo, amikacin in CP-CRPA

ST235 most prevalent



Global epidemiology and clinical outcomes of carbapenem-resistant *Pseudomonas aeruginosa* and associated carbapenemases (POP): a prospective cohort study
Reyes, Jinnethe et al.,The Lancet Microbe, Volume 4, Issue 3, e159 - e170

CP-CRPA

Clinical and Public Health

Risk factors

- Ventilation
- Indwelling devices
- Wound
- Long term acute care or skilled nursing facilities
- Healthcare outside of the US

Transmission routes

Sinks, drains, shared equipment, contaminated water, person-to-person, etc.

Stopping the spread of CRPA

- Timely identification of CRPA
- Identification of source
- Hand hygiene and PPE
- Precautions with colonized patients
- Antibiotic stewardship

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