Carbapenemase-Resistant Enterobacteriaceae (CRE): Can We Define a Universal Treatment Strategy?

David P. Nicolau, PharmD, FCCP, FIDSA
Director,
Center for Anti-Infective Research and Development
Hartford Hospital
Hartford, CT

Disclosures

I am a consultant, speakers bureau member or have received research funding from:

Achaogen, Bayer, Cepheid, Merck,

Melinta, Pfizer, Shionogi, VenatoRx, Wockhardt

Advisory Member: Clinical Laboratory Standards Institute (CLSI)

The Resistance Vocabulary

	Common Resistance Phenotypes	Major Mechanisms of Resistance
Enterobacteriaceae	Third- ± fourth-generation cephalosporins	ESBL, AmpC β-lactamases
	Carbapenem resistance	Carbapenemases
	Fluoroquinolones	DNA gyrase and topoisomerase mutations
	Aminog	
Pseudomonas aeruginosa	Carbapenem resistance and other β-lactam resistance	• AmpC and other β-lactamases • Multidrug efflux pumps • Deletion of membrane porins
	Fluoroquinolones	DNA gyrase and topoisomerase mutations
	Aminoglycosides	Aminoglycoside-modifying enzymes
Acinetobacter spp.	Cephalosporin and Carbapenem resistance	• Cephalosporinases • Carbapenemases • Multidrug efflux pumps • Porin mutations • Penicillin-binding protein changes
	Aminoglycoside resistance	Aminoglycoside-modifying enzymes
	Fluoroquinolone resistance	DNA gyrase and topoisomerase mutations

CRE: What's in the Name

Resistance Category Definitions

- MDR: resistant to >1 agent in 3 or more antimicrobial categories
- XDR: nonsusceptible to >1 agent in all but 2 categories
- PDR: resistant to all categories
- Intrinsic resistance to specific antimicrobial agent would automatically eliminate that agent from being included in defining resistance

1. Fraimow H et al. *Crit Care Clin.* 2013;29:895-821.

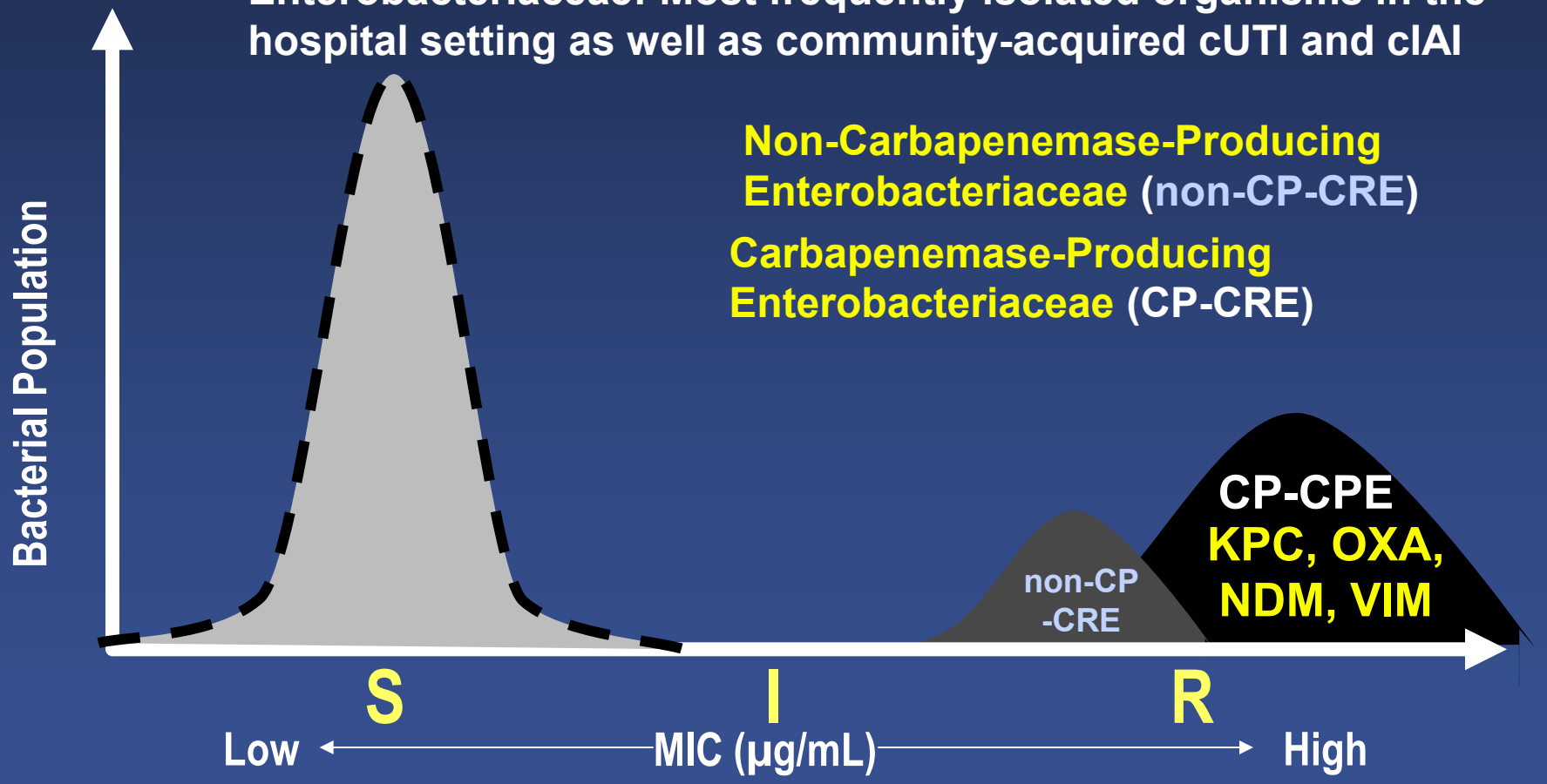
Enterobacteriaceae: Old Friends → New Challenges

- 68 yo morbidly obese male with a h/o right sided heart failure, COPD and chronic kidney disease
- Recurrent nephrolithiasis with bilateral stents
- Recurrent UTIs with multiple urologic procedures
- Multiple hospitalizations → Rehabilitation facilities
- Recent *Proteus mirabilis* UTI / BSI → ceftriaxone
- 3 wks after completion of therapy, presents acutely ill to ED
  - Intubated and transfer to the medical intensive care unit
  - Septic shock → vasopressor therapy & renal failure → CRRT
  - Initiated on meropenem 1g q12
  - Blood & urine cultures from admission → **MDR *K. pneumoniae***
    - » Reported as Pan-β-lactam resistant, including carbapenems
      - **Ertapenem-R / Meropenem-S**

Enterobacteriaceae: Old Friends → New Challenges

- How would this organism be reported @ your institution?
  - Carbapenem-resistant enteric [CRE]
  - Carbapenemase-producing enteric [CPE]
  - Non-carbapenemase carbapenem resistance enteric [non-CP-CRE]

Reduced Potency of β-Lactams in the Face of Carbapenemase-Resistant Enterobacteriaceae (CRE)



Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs* 2018 Apr;27(4):325-338

CRE: Multiple Resistance Mechanisms

Non-carbapenemase producing

Mutation causing outer membrane impermeability (porin loss / modification)

+

ESBL / AmpC β-lactamase production

- Low-level resistance
- Not transferable
- Selected under treatment
- Sporadic cases / outbreaks

Carbapenemase producing

(KPC, OXA-48, MBLs)

Jacoby *et al* – AAC 2004
Doumith *et al* – JAC 2009

Nordmann et al EID 2011
Canton *et al* – CMI 2012

Slide courtesy of Dr. Gian Maria Rossolini

Resistance Mechanisms and Susceptibility Among Carbapenem-Resistant Enterobacteriaceae in Connecticut, 2017

CRE Detection and Typing (N=147)

- **CP-CRE = 31%**
  - » **Majority → KPC = 85%**, NDM = 11%, OXA-48 = 3%, IMI = 1%
- **Non-CP-CRE = 69%**

	ETP	MEM	ATM	FEP	CAZ	CZA	C/T	CST	LEV	TGC	TOB
CP-CRE, n=46	2	9	2	17	7	91	4	97	26	93	35
Non-CP-CRE, n=101	3	76	12	69	9	98	14	88	67	79	84

ERT = ertapenem; MEM = meropenem; ATM = aztreonam; FEP = cefepime; CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; C/T = ceftolozane-tazobactam; CST = colistin; LEV = levofloxacin; TGC = tigecycline; TOB = tobramycin

Durante AJ, et al. Abstract 2411, IDWeek San Francisco, CA, Oct 6, 2018

Outcomes With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-R Enterobacteriaceae Bacteremia

- 83 unique episodes of monomicrobial CRE bacteremia
  - 37 (45%) CP-CRE and 46 (55%) non-CP-CRE
  - Majority of CP-CRE isolates were bla $_{KPC}$ (92%), followed by bla $_{NDM}$ (5%) and bla $_{OXA\text{-}48\text{-}type}$ (3%)
  - CP-CRE more likely to have MEM MIC ≥16 µg/mL, while non-CP-CRE MEM ≤1 µg/mL (P value < .001)
  - Carpabenems given to 84% of CP-CRE and 95% of non-CP-CRE MEM ≤1 µg/mL
    - » Meropenem 2g q8h
  - 18 (22%) patients died within 14 days, including 12 (32%) in the CP-CRE group and 6 (13%) in the non-CP-CRE group

Tamma PD, et al. Clin Infect Dis 2017;64(3):257-264.

CRE: Multiple Resistance Mechanisms

Non-carbapenemase producing

Carbapenemase producing
(KPC, OXA-48, MBLs)

- **Higher-level of resistance**
- **Transferable (plasmid)**
- **Association with high-risk clones (HiRiCs)**

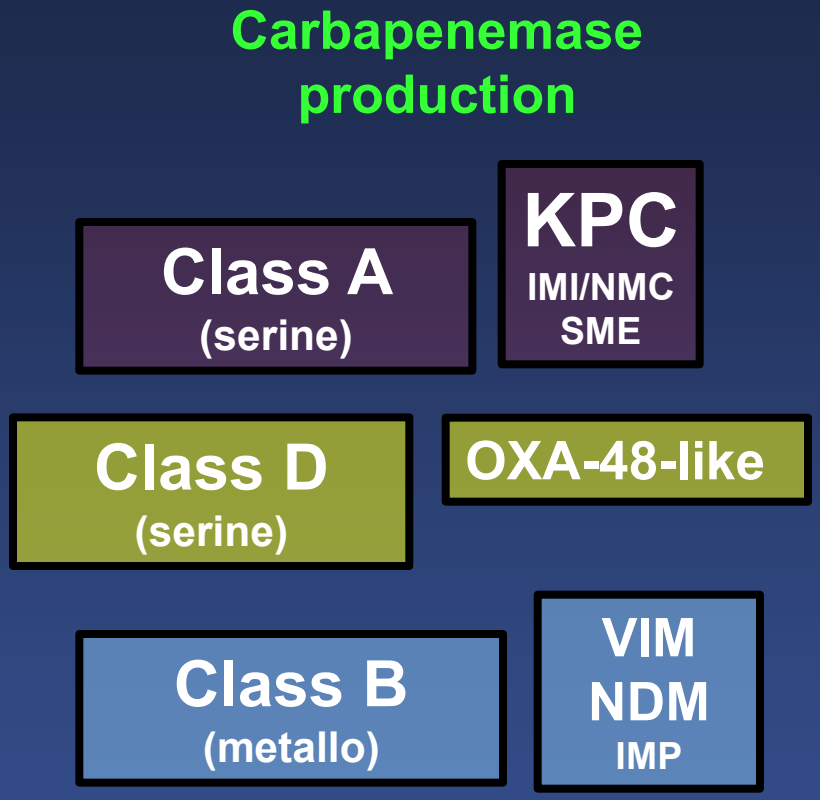
Potential for Rapid Dissemination

Jacoby *et al* – AAC 2004
Doumith *et al* – JAC 2009

Nordmann et al EID 2011
Canton *et al* – CMI 2012

Slide courtesy of Dr. Gian Maria Rossolini

CRE: Multiple Resistance Mechanisms



Nordmann et al EID 2011
Canton *et al* – CMI 2012

Slide courtesy of Dr. Gian Maria Rossolini

Management of CRE
(Historical Perspective)

- **Avoid Colistin Monotherapy[1,2]**
  - » **Poor Pulmonary Penetration → Aerosol**
- **Combination Therapy[3*]**
  - » **Colistin 9MU load, 4.5MU q12-8** [Algorithmic Dosing[4,5]]

PLUS

» **Meropenem 2g q8 Prolonged Inf (3hr)**

PLUS

» **Tigecycline 200mg load, 100mg q12**

*aminoglycosides, fosfomycin

[1]Daikos GL et al. Antimicrob Agents Chemother 2014;58: 2322; [2]Qureshi ZA et al. *Antimicrob Agents Chemother.* 2012;56:2108-13; [3]Management of KPC-producing Klebsiella pneumoniae infections. Bassetti M, et al. Clin Microbiol Infect. 2018 Feb;24(2):133-144; [4]Nation RL et al. Clin Infect Dis. 2016;62:552-558; [5]Nation RL et al. Clin Infect Dis. 2017;64(5):565-571

Double Carbapenem Therapy for Carbapenemase-Producing *K. pneumoniae*

Mechanism of Action

- **Ertapenem preferentially hydrolyzed by KPC carbapenemases & since only so many units of enzyme produced per unit time this effectively neutralized hydrolysis of 2nd compound → thus effective activity**
  - Bulik and Nicolau. Antimicrob Agents Chemother 2011;55(6):3002-3004

- **Characterization of Porin Expression in *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing *K. pneumoniae* Identifies Isolates Most Susceptible to the Combination of Colistin and Carbapenems**
  - Hong et al. Antimicrob. Agents Chemother. 2013, 57(5):2147-2153

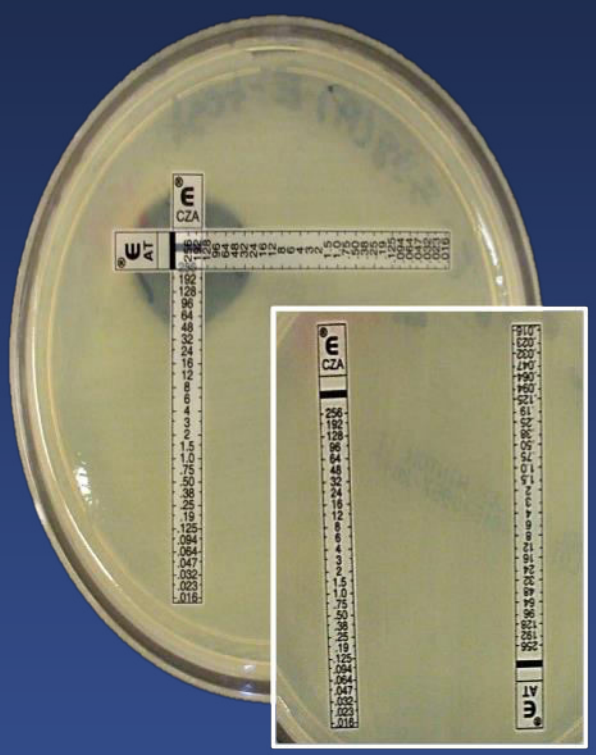
Novel β-lactam / β-lactamase Inhibitors for Carbapenemase-Producing Enterobacteriaceae

- **β-lactam plus Novel Inhibitor**
  - **Ceftazidime - Avibactam [KPC, OXA]**
  - **Meropenem - Vaborbactam [KPC]**
  - **Imipenem - Relebactam [KPC]**
  - **Aztreonam - Avibactam [MBL]**
  - **Cefepime - VNRX-5113 [KPC, OXA, MBL]**
  - **Cefepime - Zidebactam [KPC, OXA , MBL]**
  - **Meropenem - Nacubactam [KPC, MBL]**

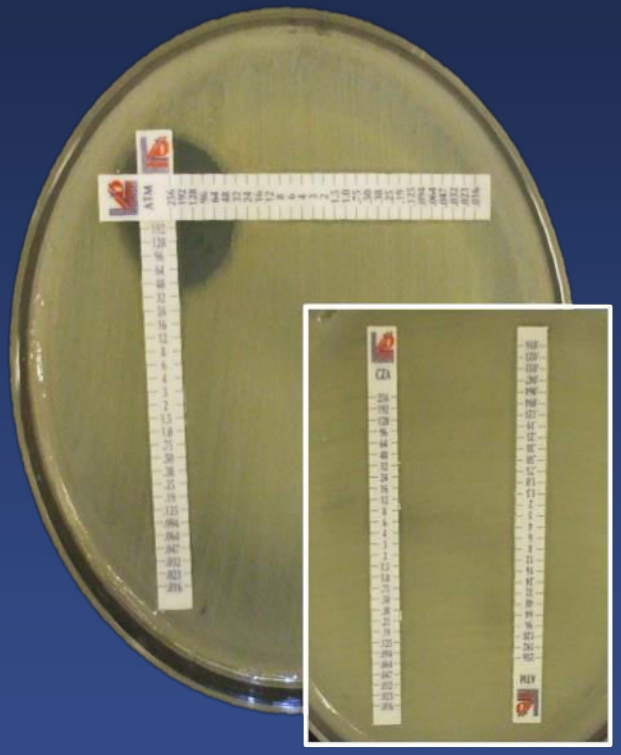
KPC: *K. pneumoniae* carbapenemase; OXA: oxacillinase; MBL: metallo-β-lactamase
Except Ceftazidime-Avibactam, referenced combinations are not licensed by EMA [status: Phase II or III, preregistration]

Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs* 2018 Apr;27(4):325-338

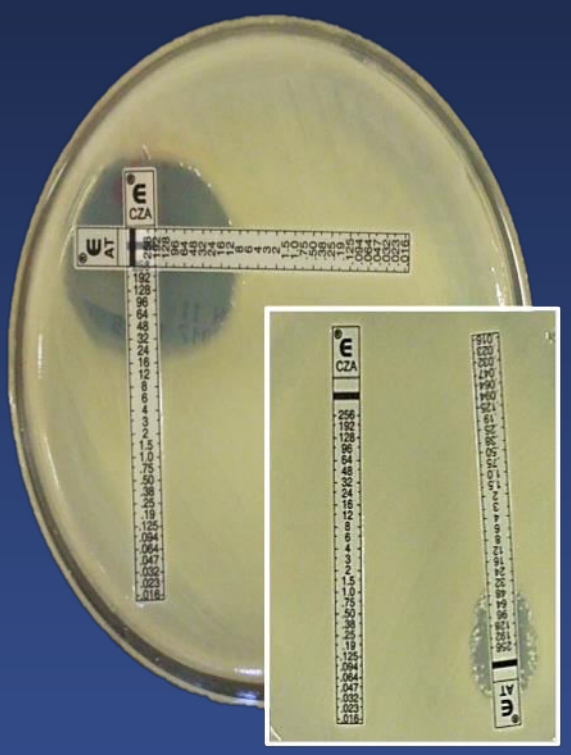
Enterobacteriaceae Co-Producing Metallo- and Serine-β-lactamases



E. coli
NDM-1, OXA-1, -2, -9
CMY-6, CTX-M-15, TEM-1B



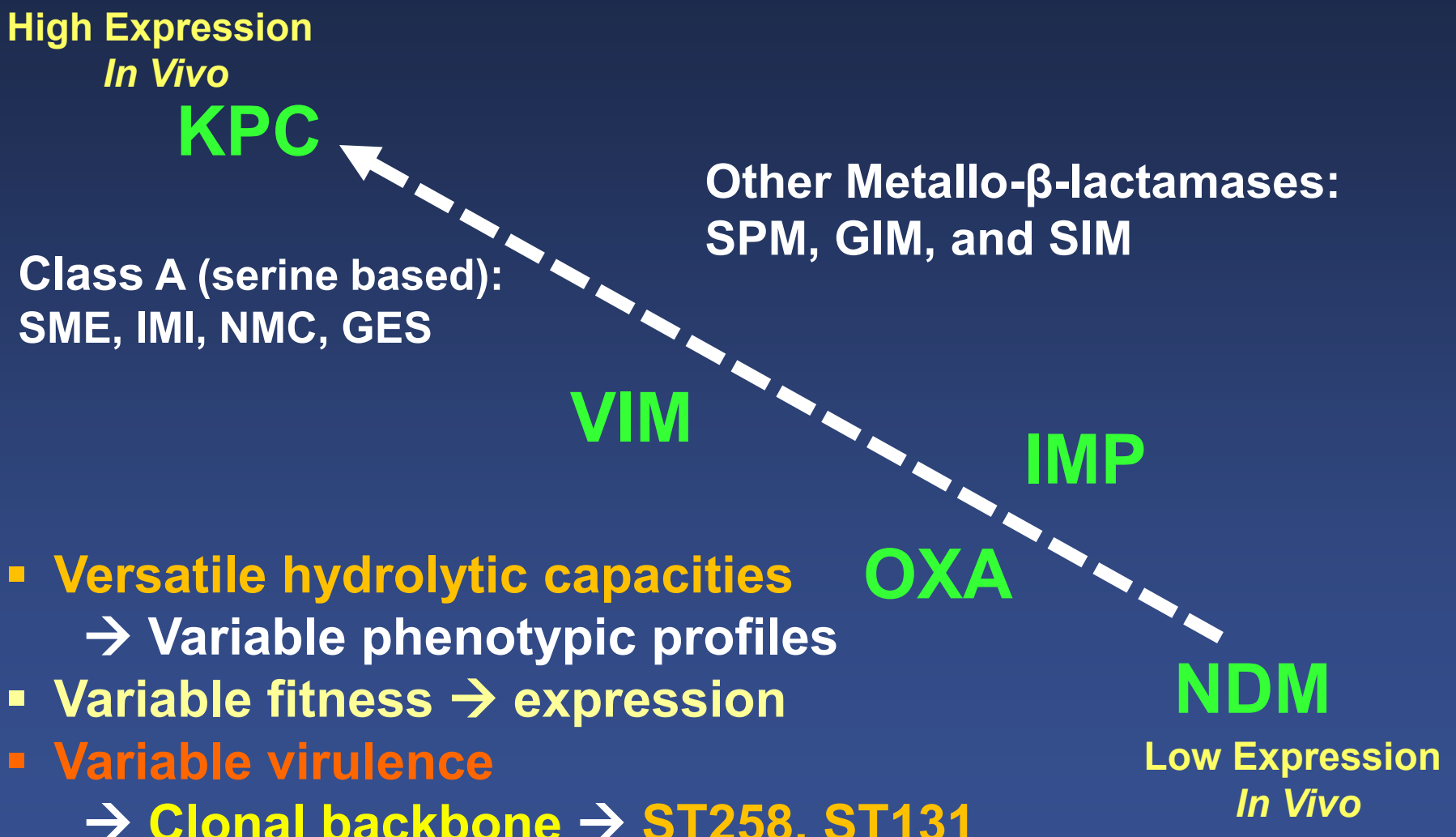
K. pneumoniae
VIM-1, OXA-9
SHV-12, TEM-1A



K. pneumoniae
IMP-4, OXA-1
SFO-1, TEM-1B, OKP-B-2

Avery LM, Nicolau DP. *International Journal of Antimicrobial Agents* (2018), doi: 10.1016/j.ijantimicag.2018.07.011 [In press].

Evolving *In Vivo* Understanding of Carbapenemases



- Versatile hydrolytic capacities
  → Variable phenotypic profiles
- Variable fitness → expression
- Variable virulence
  → Clonal backbone → ST258, ST131

Carbapenemase-Resistant Enterobacteriaceae (CRE): Can We Define a Universal Treatment Strategy?

NO !

Considerations for Treatment Regimen

- CRE variant:
  - » Non-Carbapenemase-Producing-CRE
  - » Carbapenemase-Producing-CRE
- Phenotypic profile → Often Multi-Drug Resistant
- Genotypic profile → Differing enzymology [i.e., type (serine, metallo); multiple enzymes]
- Severity / Site of Infection
- Host status
- Due to nature & complexity of host / resistance profiles → Differing combination regimens will likely be required