The State of Carbapenem Resistance in the United States

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Disclosures

- I have received federally funded support from the following organizations in the past 12 months:
  - National Institute of Health
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
  - Food and Drug Administration

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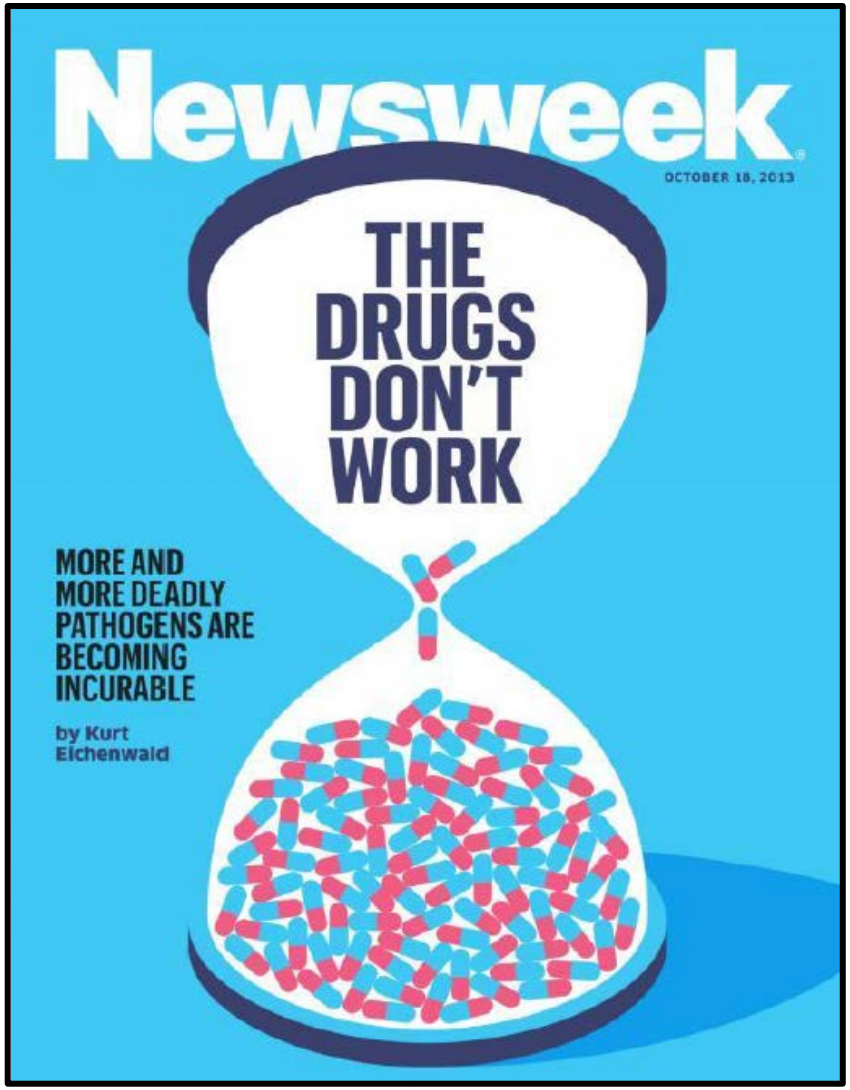
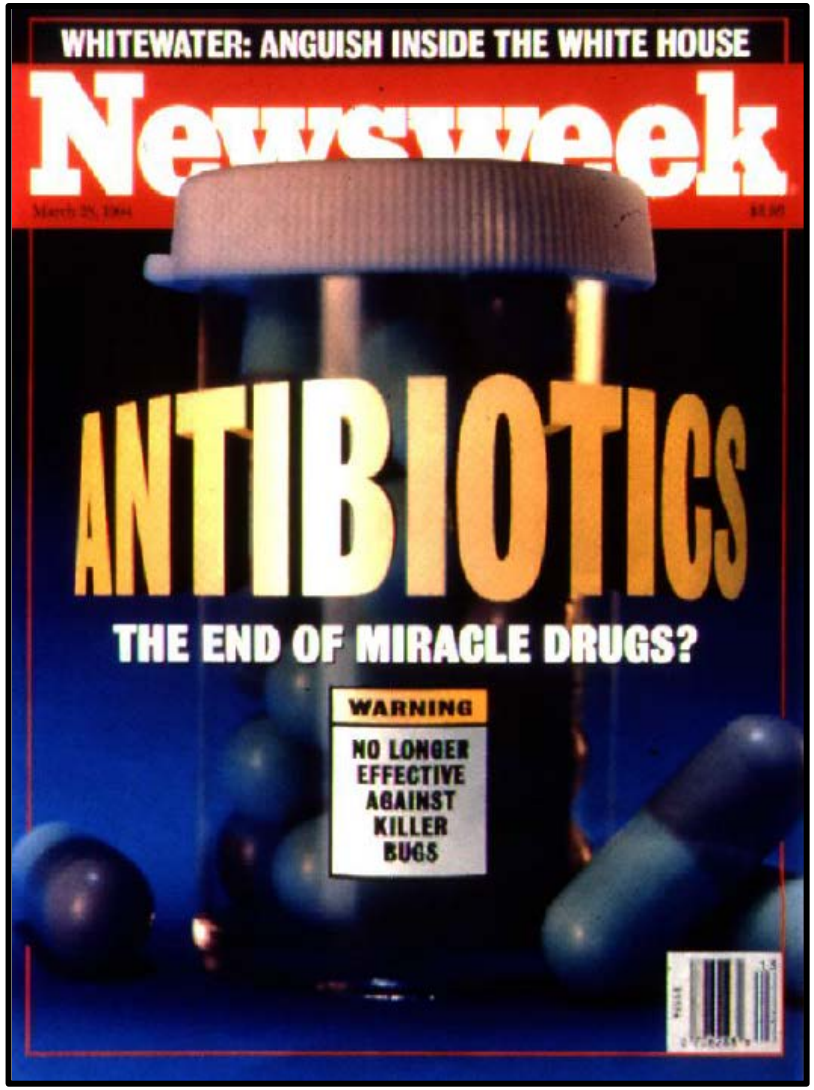
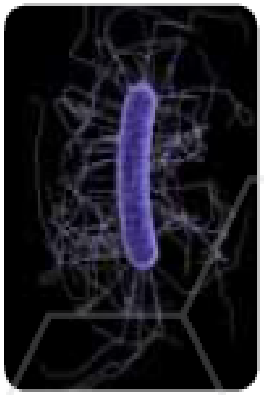
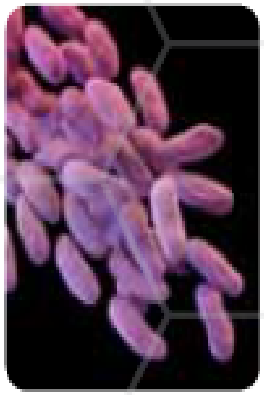
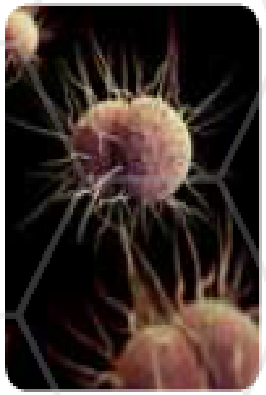
  - Pfizer
  - Merck

Objectives

- Discuss the evolution of gram-negative resistance in *Enterobacteriaceae* in the United States
- Discuss the epidemiology of carbapenemases in the United States
- Discuss the diagnosis of carbapenemases in the United States
- Discuss the treatment of carbapenemases in the United States


Newsweek
OCTOBER 18, 2013
THE DRUGS DON'T WORK
MORE AND MORE DEADLY PATHOGENS ARE BECOMING INCURABLE
by Kurt Eichenwald


WHITEWATER: ANGUISH INSIDE THE WHITE HOUSE
Newsweek
ANTIBIOTICS
THE END OF MIRACLE DRUGS?
WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS

THREAT LEVEL
URGENT

These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile

Carbapenem-resistant **Enterobacteriaceae**

Drug-resistant ***Neisseria gonorrhoeae***

How Did We Get Here?

- Bacterial resistance is not a new phenomenon
  - Multiple resistance determinants have been found in bacteria from environments separated from human activity for millions of years
- Current crisis of antibiotic resistance reflects the rapid expansion and diversification of resistance under antibiotic selection pressure
  - For decades the resistance profiles of common gram-negative organisms was relatively predictable and stable

Lechuguilla Cave, New Mexico

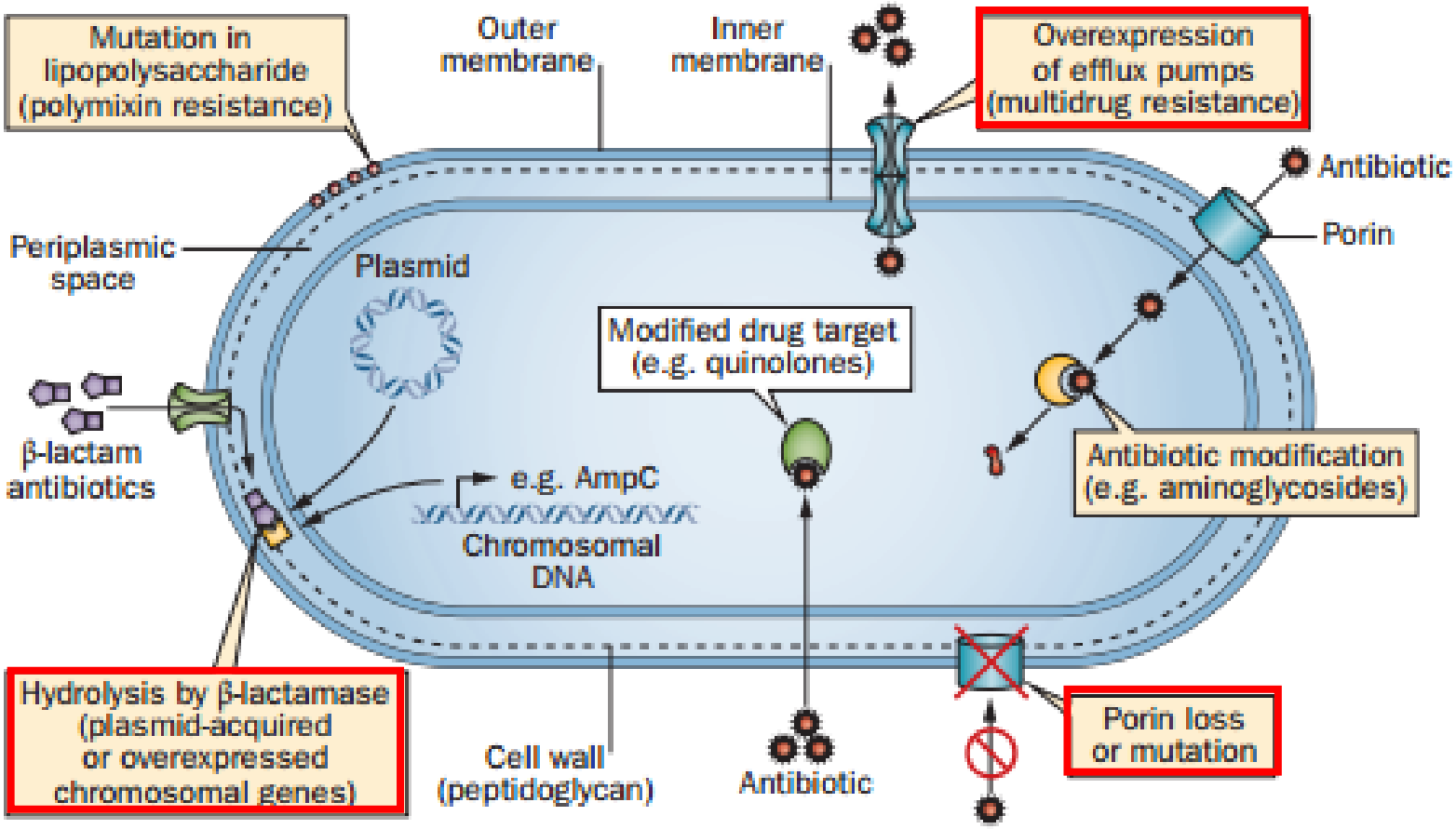
Bhullar, et al. Plos One. 2012;7:e34953.

CRE are Epidemiologically Important

- CRE bacteremia have been associated with mortality upwards of 60%
- In addition to carbapenem resistance, CRE often carry genes conferring high levels of resistance to many other antibiotics, leaving very limited therapeutic options
- CRE have spread throughout the United States and the world
  - Prevalence of carbapenem-resistance among *Klebsiella* spp. causing healthcare-acquired infections in children and adults in US hospitals was 13% between 2009-2010

Zarotou O, et al. Clin Microbiol Infect 2011;17:1798. Munoz-Price, et al. Lancet Infect Dis 2013; 18.

Mechanisms of Carbapenem Resistance



Zowawi, et al. Nat Rev Urol 2015;12:570.

Carbapenemases

Ambler Class	Some Representative Carbapenemases	Inhibitors	Notable Differences in Hydrolysis of β-lactams*
Class A (Serine at active site)	**KPC**, IMI, SME	Boronic acid, partially inhibited by clavulanic acid and tazobactam	Hydrolyze members of all β-lactam classes
Class B (Zinc at active site)	Metallo-β-lactamases (VIM, IMP, **NDM**)	Metal chelating agents	Unlikely to hydrolyze aztreonam
Class D (Serine at active site)	**OXA-48-like**, OXA-23-like, OXA-58-like	Slightly inhibited by clavulanic acid and EDTA	Weak hydrolyzers of third-generation cephalosporins

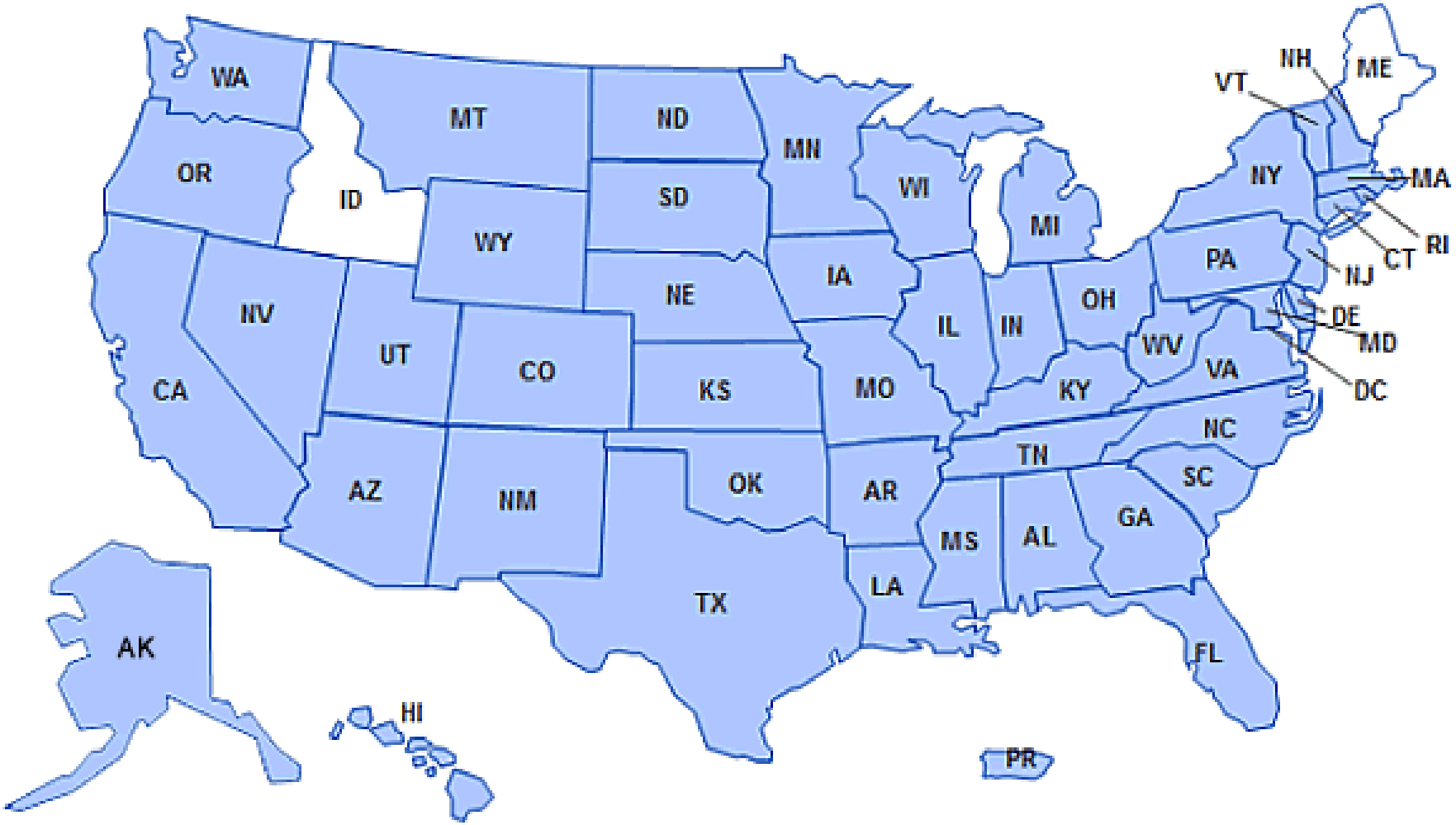
*Because mobile genetic elements carrying carbapenemase genes may also carry ESBL genes (**Class A**) and/or AmpC encoding-genes (**Class C**), anticipated antibiotic susceptibility profiles for β-lactams may appear inconsistent

KPCs: Epidemiology

- KPCs initially reported in a *K. pneumoniae* strain isolated in North Carolina in 1996
- By 1997, KPC-producing organisms appeared in hospitals in NYC
  - In a city-wide surveillance study in 2006, 38% of *K. pneumoniae* clinical isolates produced KPCs
- KPCs have since spread across the United States
  - Eastern states >> Mid-western > Southern or Western states
- *K. pneumoniae* sequence types found in Israel, Italy, China, and Brazil are all closely related to ST258 which predominates in the US suggesting a common origin, mostly likely from the mid-Atlantic US

Yigit, et al. Antimicrob Agents Chemother 2001; 45:1151. Bradford, et al. Clin Infect Dis 2004; 39:55. Bratu, et al. Arch Intern Med 2005; 165:1430. Kitchel, et al. Antimicrob Agents Chemother 2009; 53:3365. Gupta et al. Clin Infec Dis 2011; 53:60. Schwaber, et al. Clin Infect Dis 2011; 52:848. Schwaber, et al. Clin Infec Dis 2014; 52:697

KPC-producing CRE reported to the CDC as of April 2016

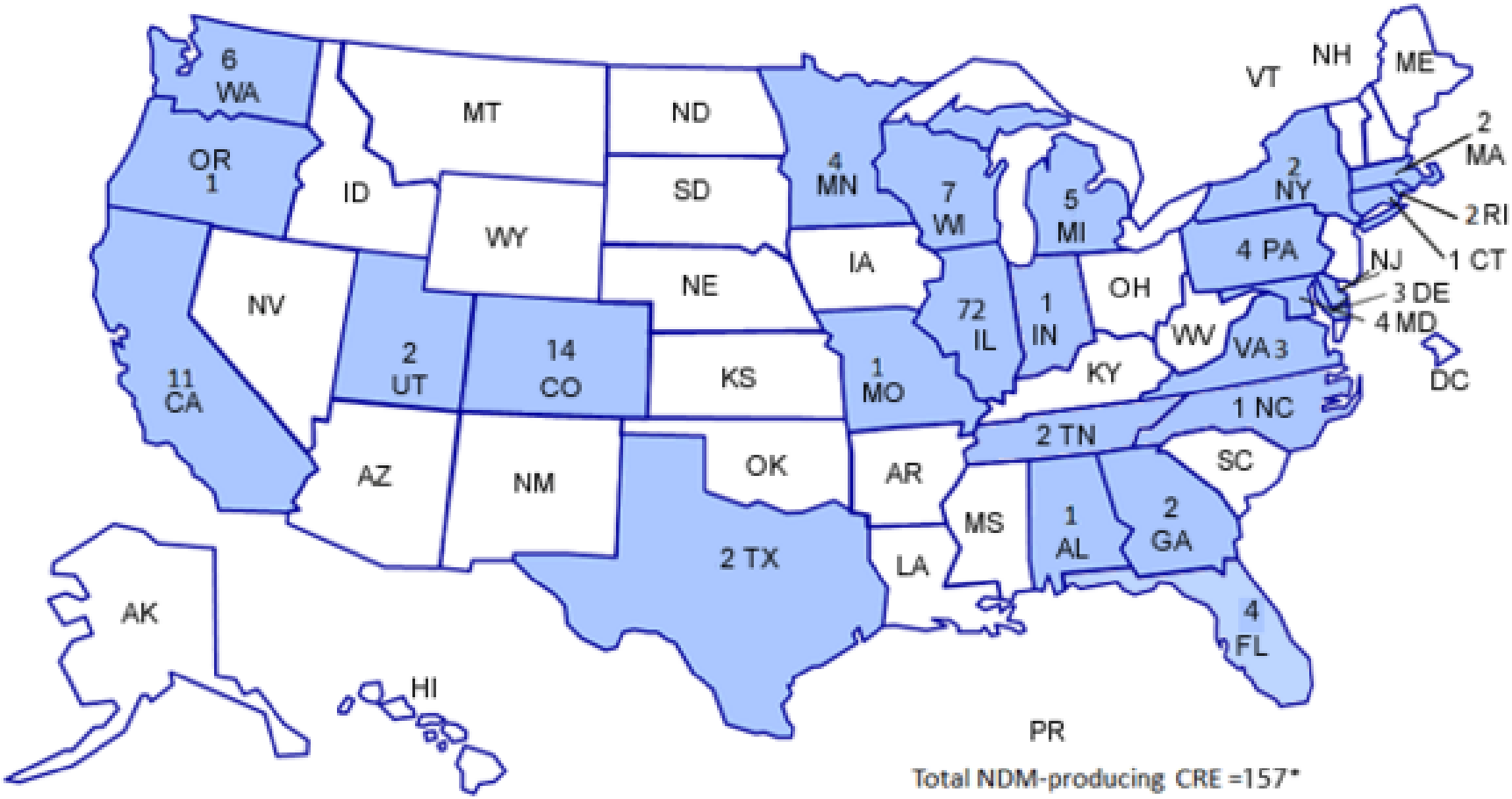


NDM-Producing *Enterobacteriaceae*

- First identified in 2006 in a Swedish national who had recently received medical care in India
- In 2010, the prevalence of NDM production in clinical isolates from Indian patients was 5%
- In 2010, the prevalence of NDM production in stool isolates from Pakistani patients was 19%
- NDM-producing bacteria have since been reported all over the world
  - Even more rapid spread than KPCs
- bla_{NDM} genes detected in organisms in tap water in New Delhi and have made their way into community-associated pathogens (i.e., *Escherichia coli*, *Salmonella enterica*, *Vibrio cholerae*)

Yong, et al. Antimicrob Agents Chemother 2009; 53:5046. Castanheira, et al. Antimicrob Agents Chemother 2011; 55: 1274. Castanheira, et al. Diagn Microbiol Infect Dis 2013; 75:210. Day, et al. Diagn Microbio Infect 2013; 75:187. Walsh, et al. Lancet Infect Dis 2011; 11:355. Darley, et al. Lancet 2012; 380:1358.

NDM-producing CRE Isolates Reported to CDC as of April 2016



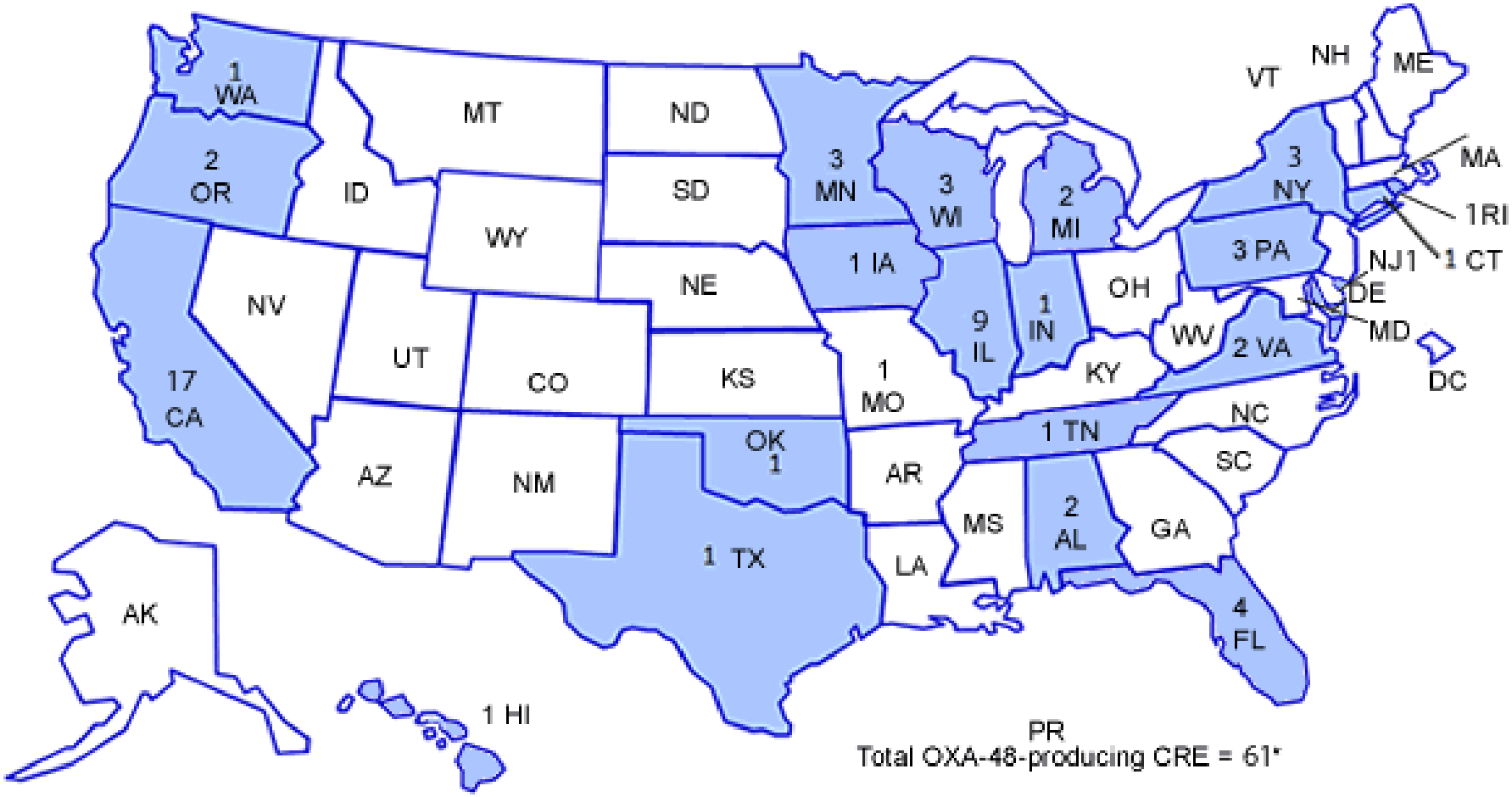
OXA-48-like Producing *Enterobacteriaceae*

- *bla*$_{\text{OXA-48}}$ gene was first found in a *K. pneumoniae* strain isolated in Turkey in 2001

- Mostly reported in Mediterranean, Northern Africa, and South Asia
  - Spreading throughout Europe and Asia
  - Still relatively rare in US

Poirel, et al. Antimicrob Agents Chemother 2004; 48:15. Poirel, et al. J Antimicrob Chemother 2012; 67:1597.

OXA-48-like Producing CRE Isolates Reported to the CDC as of April 2016



Does Knowing the Mechanism of Carbapenem-Resistance Matter for Treatment Decisions?

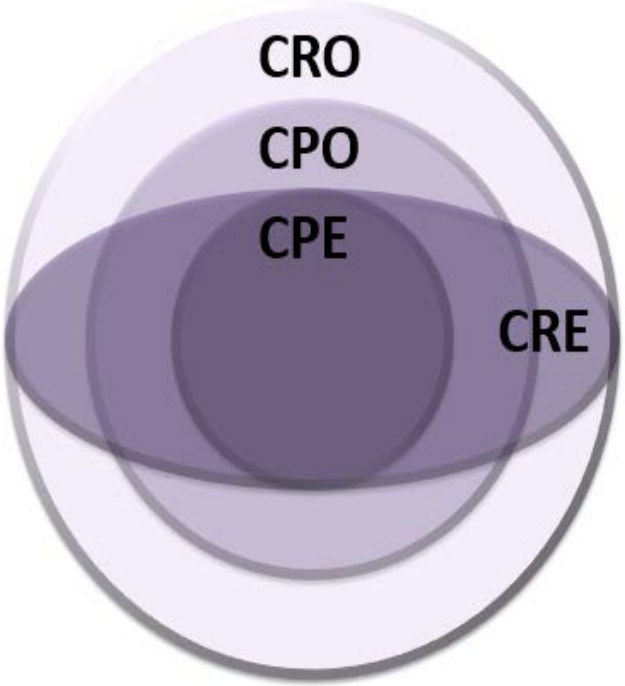
Most microbiology laboratories don't differentiate CP CRE from non-CP CRE

- If they do, they generally use phenotypic testing

Antibiotic therapy is generally the same regardless of the mechanism of carbapenem resistance

But, there are some antibiotics hydrolyzed by certain carbapenemases and not others

- This is particularly relevant with ceftazidime-avibactam and some agents in Phase 2 & 3 studies



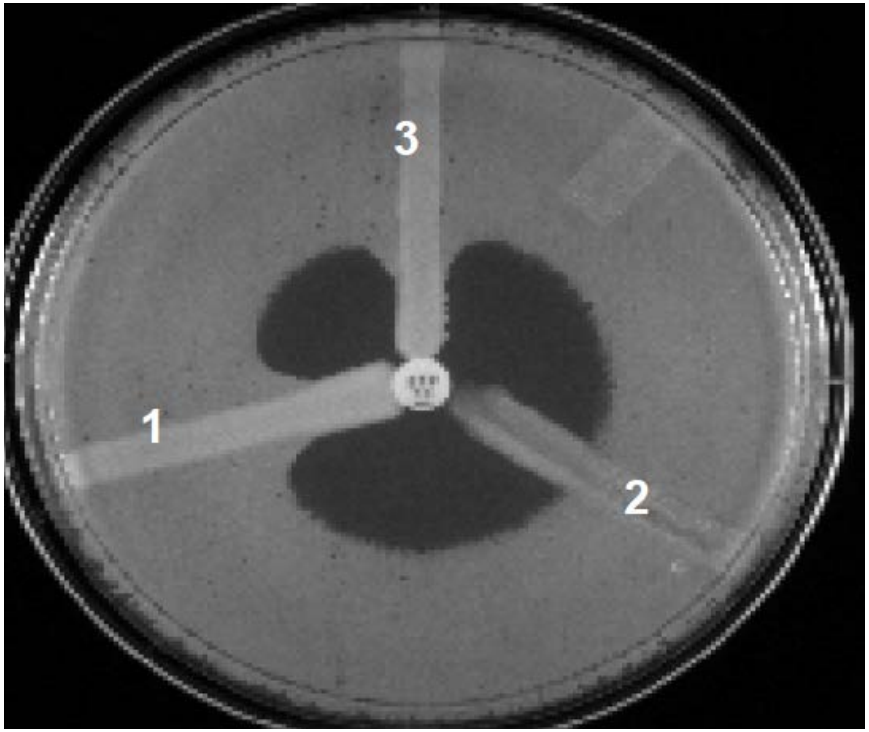
Diagnostic Methods

Anticipated *in vitro* Susceptibility Pattern for *Klebsiella pneumoniae*

Drug	Wild type	AmpC	ESBL	KPC	NDM	OXA-48-like
Ampicillin	R[1]	R	R	R	R	R
Piperacillin-tazobactam	S	S/R	S/R	R	R	R
Cefoxitin	S	R	S	R	R	R
Ceftriaxone	S	R	R	R	R	S/R
Cefepime	S	S	S/R	R	R	S/R
Aztreonam	S	R	R	R	S	R
Ertapenem	S	S	S	S/R	S/R	S/R
Meropenem	S	S	S	S/R	S/R	S/R

[1]The majority of *K. pneumoniae* isolates are resistant to ampicillin due to production of narrow-spectrum TEM of SHV β-lactamases

Modified Hodge Test



Culture-based test to detect release of carbapenemases into agar media

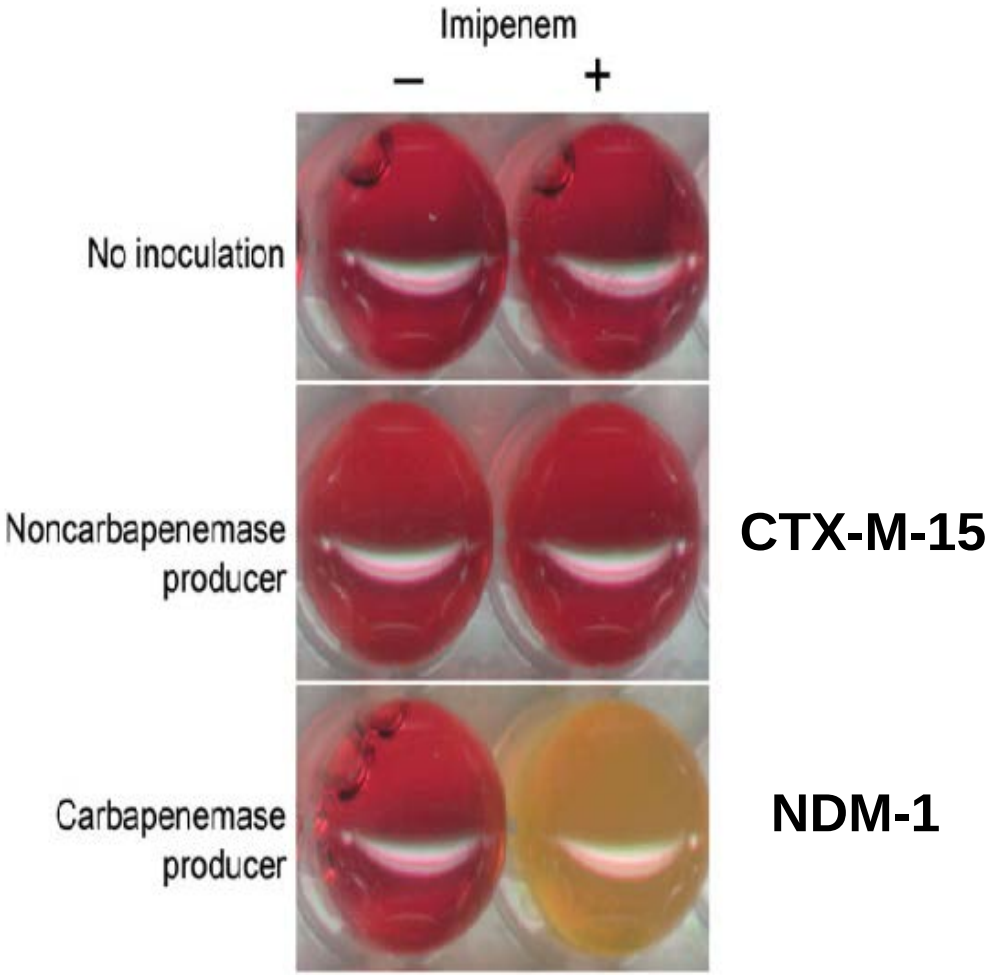
Modified Hodge Test

Pros	Cons
Can be performed without any special equipment or reagent	Results may be subjective
Not costly	Results available about 3 days (at earliest) after culture collected
	False positive results seen with ESBLs or AmpCs
	MβLs may remain undetected leading to false-negative results
	Poor for non-fermenters

Cavalhaes, et al. J Antimicrob Chemother 2010; 65:249. Girlich, et al. J Clin Microbiol 2012; 50:477.

Carba NP Test & Other Chromogenic Assays

- Hydrolysis of imipenem by carbapenemases extracted from isolates
- Color changes observed in microtiter wells



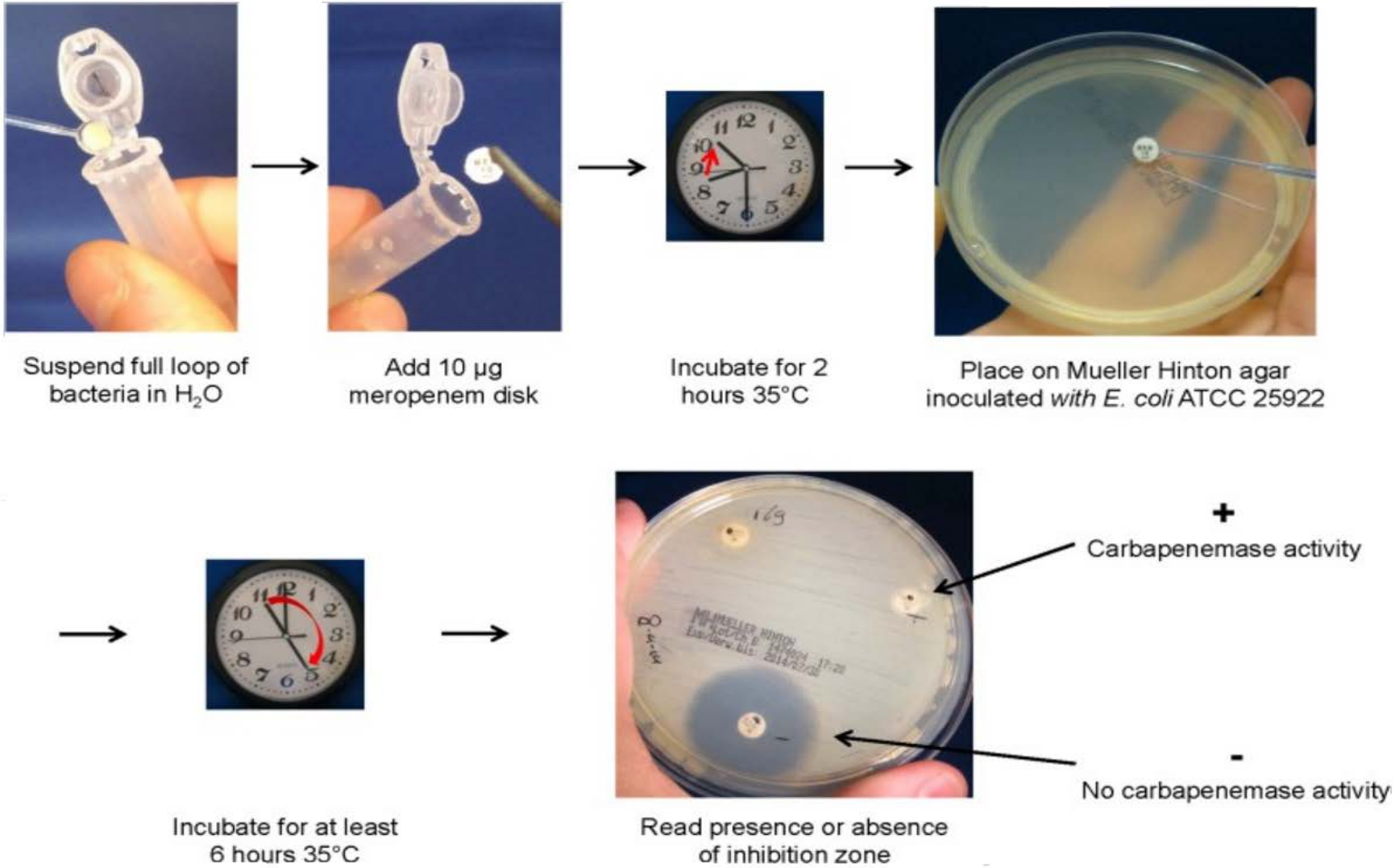
Nordmann, et all. Emerg Infect Dis 2012; 18:1503. Dortet, et al. Antimicrob Agents Chemother 2014; 58:2441.

Carba NP Test

Pros	Cons
Results within 2 hours (generally 30 minutes)	Not always as reliable for OXA-types
Sensitivity and specificity approach 100%	Results may be subjective
No specific training needed	Fresh reagents need to be prepared daily
Works for non-fermenters	
Cost is under $1 per test	

Nordmann, et al. Emerg Infect Dis 2012;18: 1503. Dortet, et al. Antimicrob Agents Chemother 2014; 58:2441.

Carbapenem Inactivation Method (CIM)



Van der Zwaluw, et al. Plos One; 2015:1.

Verigene Gram-Negative Blood Culture Assay (Nanophere™)

- Nonamplified assay that relies on nucleic acid extraction from positive blood cultures, followed by microarray-based detection using probes
- Identifies 8 genus or species targets
  - *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. aeruginosa*, *S. marcescens*, *Acinetob*acter spp., *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp.
- Identifies 6 genetic resistance determinants
  - $bla_{\text{CTX-M}}$, $\boldsymbol{bla_{\text{KPC}}}$, $\boldsymbol{bla_{\text{NDM}}}$, $\boldsymbol{bla_{\text{OXA}}}$, $\boldsymbol{bla_{\text{VIM}}}$, $\boldsymbol{bla_{\text{IMP}}}$

Ledeboer, et al. J Clin Micro 2015;53:2460.

FilmArray Blood Culture Identification Assay (BioFire™)

- Rapid, multiplex PCR panel
- Gram-negative organisms
  - *E. coli, K. oxytoca, K. pneumoniae, E. cloacae, Serratia* spp., *Proteus* spp., *A. baumannii, H. influenzae, N. meningitidis, P. aeruginosa*
- Gram-positive organisms
  - *Staphylococcus* spp., *S. aureus, Streptococcus* spp., *S. agalactiae, S. pyogenes, S. pneumoniae, Enterococcus* spp., *Listeria monocytogenes*
- Yeasts
  - C. albicans, C. glabrata, C. parapsilosis, C. krusei, C. tropicalis
- Resistance mechanisms
  - *mecA, vanA/vanB*, ***bla*$_{\mathbf{KPC}}$**

Banerjee, et al. Clin Infect Dis 2015:61.

Molecular Tests

Pros	Cons
Highly sensitive and specific	Costly (Verigene ~$80 per panel and BioFire ~$120 per panel)
Identify actual β-lactamase producing gene	Don’t detect genes not included in the panel
Results available within 3 hours	Cannot detect novel β-lactamase genes
	Useful to “rule in” drug resistance and escalate therapy if targets detected, but cannot “rule out” resistance so unlikely to impact decisions to de-escalate antibiotics

Treatment

General Treatment Principles for Managing CRE

- Mainstay of therapy for CRE is a combination of at least two agents with *in vitro* activity (if available)
- Carbapenem resistance does not always translate into clinical failure with carbapenem agents
  - Carbapenems may still have activity against organisms with MICs of up to 8-16 mcg/ml
  - Current CLSI breakpoints are 1 mcg/ml for doripenem, meropenem, and imipenem

Observational Studies Evaluating Combination Therapy for CRE Bacteremia

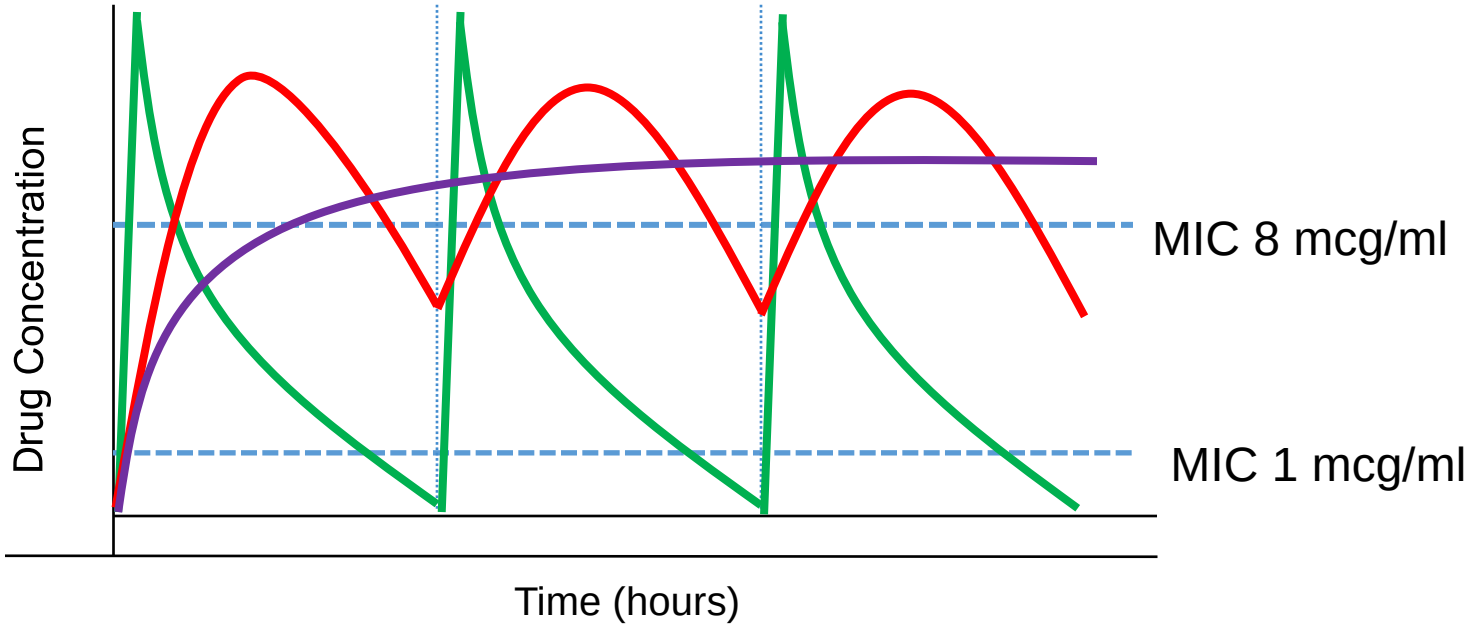
	Treatment	Combination versus Monotherapy Mortality
Zakotou et al Greece	Combination therapy (n=20) Monotherapy (n=15)	In hospital: 0% versus 47%
Qureshi et al USA	Combination therapy (n=15) Monotherapy (n=9)	28 day: 13% versus 58%
Tumbarello et al Italy	Combination therapy (n=79) Monotherapy (n=46)	30 day: 34% versus 54%
Daikos et al Greece	Combination therapy (n=103) Monotherapy (n=72)	28 day: 27% versus 44%
Tzouvelekis et al*	Combination therapy (n=441) Monotherapy (n=346)	All cause: 19% versus 40%

***Systematic review that found that mortality rates for combination therapy were 30% for carbapenem-sparing regimens and 20% for carbapenem-containing regimens**

Limitations with Existing Studies Evaluating Role of Combination Therapy for CRE Infections

- Observational
- Small sample sizes
- Various mechanisms of carbapenem resistance
- Different definitions of MIC levels indicating susceptibility
- Varying sources of infection
- Different combinations tested
  - Sometimes 2 drugs, sometimes 3 drugs
  - Both may have *in vitro* activity, one may have *in vitro* activity, or none may have *in vitro* activity
- Adequacy of empiric therapy not evaluated
- Attributable mortality not evaluated
  - Many competing reasons for death

Extended-Infusion Carbapenems



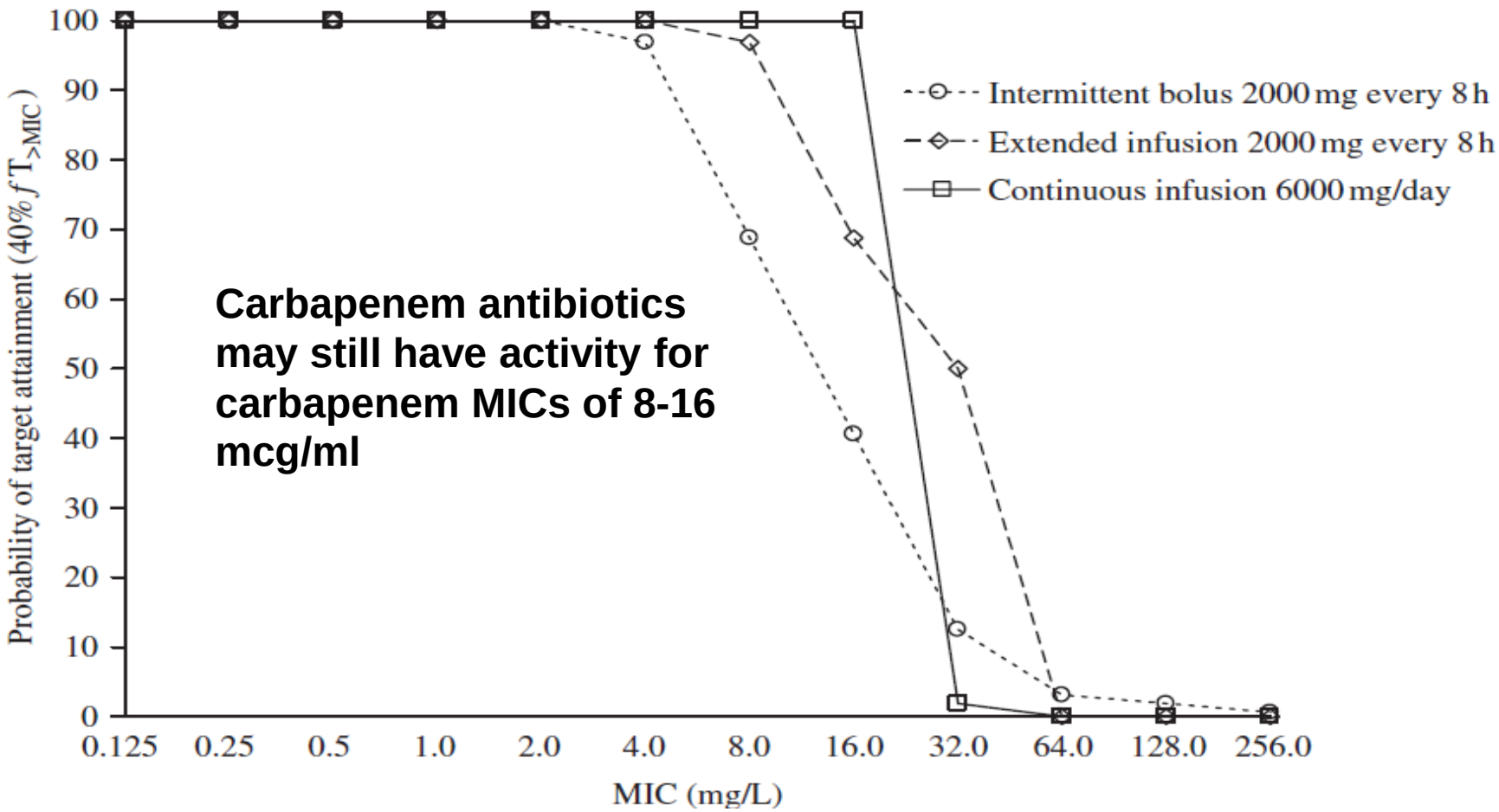
Intermittent infusion (30 minutes)

Extended infusion (3 hours)

Continuous infusion (24 hours)

At least 40% fT>MIC needed to achieve optimal target attainment for carbapenems

Extended-Infusion Meropenem



Roberts JA, et al. J Antimicrob Chemother 2009;64:142

What about other Carbapenems?

β-lactam & Concentration	Dose & Infusion Strategy	Stability at room temperature
Meropenem (50 mg/mL in NS)	40 mg/kg/dose (max 2000 mg/dose) IV q8h, each dose infused over 3 hours	8 hours
Imipenem-cilastatin (5 mg/mL in NS)	25 mg/kg/dose (max 1000 mg/dose) IV q6h, each dose infused over 3 hours	4 hours
Doripenem (5 mg/mL in NS)	20 mg/kg/dose (max 500 mg/dose) IV q8h, each dose infused over 4 hours*	12 hours
*Studied as a 4-hour prolonged infusion in the treatment of VAP in adults		

Remember to account for time it takes for a drug to get from the pharmacy refrigerator to the patient's bedside!

Patel, et al. Am J Health-Syst Pharm: 1997. 54: 412. Sakka, et al. Antimicrob Ag Chemother. 2007;51:3304. Psathas, et al. Clin Ther. 2008;30:2075. Cannavino CR, et al. Pedatr Infect Dis J 2015;11:1264.

First-line agents	Second-line agents
Prolonged-infusion meropenem 40 mg/kg/dose IV every 8h h, infused over 3h; max 2 grams IV every 8h, infused over 3h **OR** **Ceftazidime-Avibactam** **PLUS** **Aminoglycoside*** **OR** **Colistin** 5 mg/kg IV loading dose of colistin base activity, followed by 2.5 mg/kg/dose IV every 12h of colistin base activity **Polymixin B** < 1 year: 2 mg/kg every 12h >1 year: 2.5 mg/kg IV loading dose followed by 1.25-1.5 mg/kg every 12h	**Fosfomycin (Oral for Urinary source)*** <18 years: 2 grams PO (1 dose) ≥18 years: 3 grams PO (1 dose) **Fosfomycin (IV)** 100 mg/kg/dose every 6h, max 4 grams IV every 6h **Tigecycline** 100-150 mg IV every 12h (Children: 3 mg/kg loading dose, followed by 2mg/kg/dose IV every 8h)

*Can use as monotherapy for cystitis

Hsu AJ & Tamma PD. Clin Infect Dis 2014;58:1439.

Polymixins

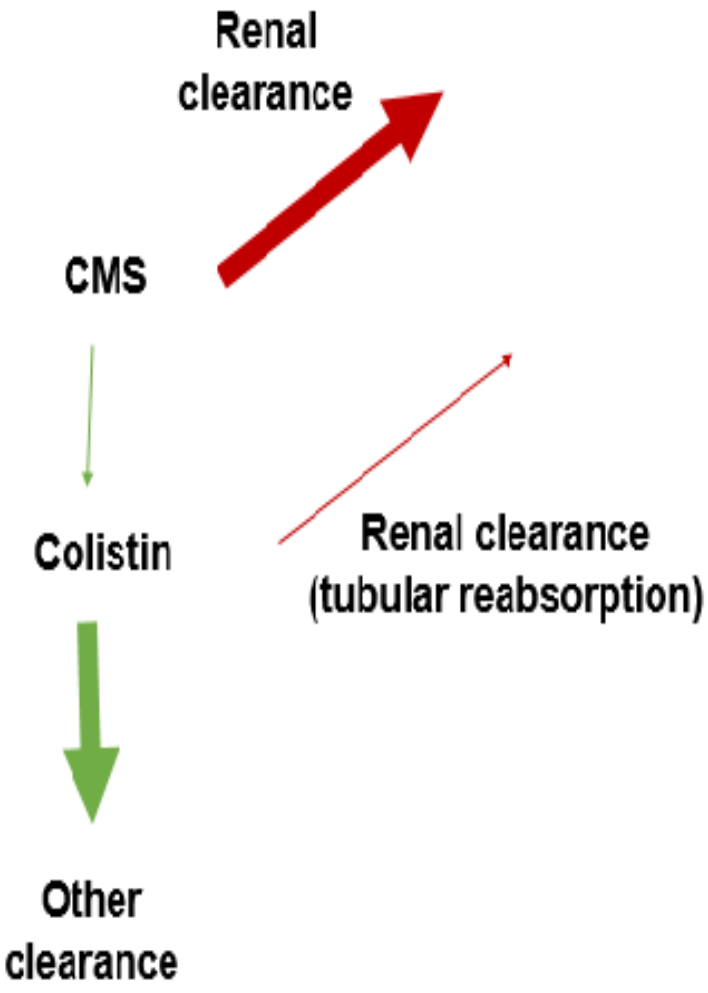
- Two systemic polymixins commercially available, polymixin B and polymixin E (colistin)
  - Similar antibacterial spectra of activity
  - Poor activity against *Proteus, Serratia, Providentia, Burkholderia, Stenotrophomonas*
  - Prone to resistance
  - No registered ongoing or planned head to head trials in Clinicaltrials.gov comparing polymixin B and colistin efficacy

- Bind to anionic LPS and displaces Ca^{2+} and Mg^{2+} from gram-negative outer membrane, leading to permeability changes in cell membrane

- Became clinically available before contemporary drug-development procedures so there are substantial gaps in knowledge of their PK-PD
  - Loading dose recommended for both agents

Colistin

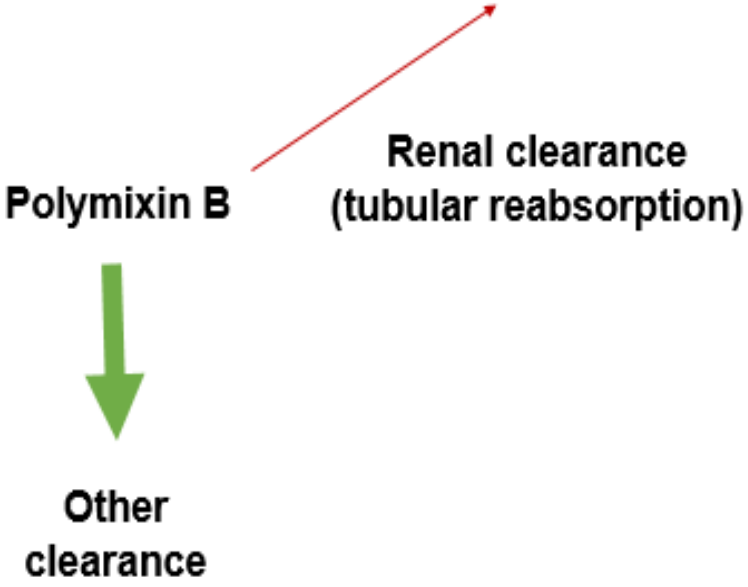
- Administered parenterally as inactive prodrug colistin methanesulfonate (CMS), which is slowly and incompletely converted to colistin (~7%)
- Rapid and extensive renal clearance of CMS may reduce systemic availability of colistin
  - Dosage requirement for renal insufficiency
  - Difficult to achieve adequate colistin plasma concentrations when treating infections caused by organisms with MICs of >0.5 mcg/ml in patients with normal renal function



Li, et al. J Antimicrob Chemother 2004; 53:837. Kwa, et al. Diag Microbiol Infect Dis 2008; 60:163. Garoznik SM, et al. Antimicrob Agents Chemother 2011;55:3284.

Polymixin B

- No renal adjustment needed
- Doses ≥200 mg/day associated with lower hospital mortality than standard dosing for adults
- Doses ≥200 mg/day exceed package insert's maximum daily dose (2.5 mg/kg/day) recommendation
- Lack of clinical safety data for polymyxin B doses >3 mg/kg/day
- No registered ongoing or planned head to head trials comparing different polymixin B dosing regimens



Sandri, et al. Clin Infect Dis 2013;57:524. Elias, et al. J Antimicrob Chemother 2010;65:2231. Pastewski, et al. Ann Pharmacother 2008;42:1177. Sobieszczyk M, et al. J Antimicrob Chemother 2004;54:566. Furtado, et al. Int J Antimicrob Chemother Ag 2007;30:315. Salvatore, et al. Pediat Infect Dis J 2011;30:538.

Adverse Events Associated with Polymixins

- Major adverse events are nephrotoxicity & neurotoxicity
- Nephrotoxicity
  - Occurs in ~40-60% of patients
  - Usually reversible upon discontinuation of colistin
  - ~20-30% less nephrotoxicity associated with polymixin B
- Neurotoxicity
  - Occurs in <5% of patients
  - May manifest as paresthesias, seizures, neuromuscular blockade
  - Usually reversible upon polymixin discontinuation

Pogue, et al. Clin Infec Dis 2011; 53:879. Sandri, et al. Clin Infect Dis 2013; 57:524. Tamma, et al. Pediatr Infec Dis J 2012;32:17. Falagas, et al. Clin Infec Dis 2005; 40:1333. Kwon, et al. Int J Antimicrob Agents 2010; 35:473. Akajabagor, et al. Clin Infect Dis 2013; 57:1300. Phe K, et al. Antimicro Ag Chemo 2014;58:2740.

Tigecycline

- FDA-approved for community-acquired pneumonia, complicated intra-abdominal infections, and skin and skin structure infections
- Designed to be poor substrate for tetracycline-specific efflux pumps
  - Activity against many gram-negatives (not *Pseudomonas* spp.)
- Tigecycline monotherapy associated with increased mortality in meta-analysis of RCTs
  - Large volume of distribution results in low concentrations in blood, epithelial lining fluid of the lungs, and urinary tract
  - FDA discourages use of tigecycline when alternate agents are available
- Better outcomes with 100-150 mg every 12 hours
  - Pediatric dose is extrapolated from higher adult dose as agent exhibits linear pharmacokinetics
- 30% will have nausea and emesis that has led to drug discontinuation in clinical trials (consider antiemetic)

Stein GE, et al. Clin Infect Dis 2006;43:518. Yahav D, et al. J Antimicro Chemother 2011;66:1963. Falagas ME, et al. *Curr Drug Metab.* 2009;10:13 http://www.fda.gov/D-150rugs/DrugSafety/ucm369580.htm.

Oral Fosfomycin

- Both oral and intravenous formulations available
  - Only oral formulation available in US
- Inhibits one of the first steps in peptidoglycan assembly, disrupting bacterial cell wall synthesis
- Cystitis: A single oral dose in 3-4 ounces of cool water
- Pyelonephritis: A single oral dose every 2 days
  - High urinary levels (100 mcg/mL) persist for >48 hours
  - Duration unclear (ranges from 2-16 weeks in literature)
  - Newer data suggest fosfomycin can be administered daily and appears to be well-tolerated
  - Creatinine clearance <50 mL/min, reduce dose by 50%
- Does not concentrate well in tissues outside of the genitourinary tract

Patel, et al. Drugs. 1997;53:637. Pullukcu, et al. Int J Antimicrob Agents. 2007;29:62. Neuner, et al. Antimicrob Agents Chemother. 2012;56:5744. Grayson, et al. 2015;1:1141. Grayson, et al. Clin Infect Dis 2015;;61:1141.

Select Anticipated CRE Drugs on the Horizon

Agent	Class A	Class B	Class D
Ceftazidime-Avibactam (FDA approved)			
Cefotolozane-Tazobactam (FDA approved)*			
Aztreonam - Avibactam			
Ceftaroline - Avibactam			
Imipenem - Relibactam			
Meropenem - Vaborbactam			
Plazomicin (Aminoglycoside)			
Eravacycline (Tetracycline)			
Brilacidin (Cell membrane disrupter)			
BAL30072 (β-lactam)			

*FDA approved in 2014 for the treatment of complicated intra-abdominal infections and complicated urinary tract infections; active against ESBL-producing organisms (particularly $bla_{CTX\text{-}M}$) and MDR Pseudomonas

Ceftazidime-Avibactam
FDA Approved February 2015

- Generally active against Enterobacteriaceae and *P. aeruginosa* producing Class A β-lactamases (ESBLs, KPCs) and Class C β-lactamases (AmpCs) and some Enterobacteriaceae producing Class D β-lactamases (OXAs)
  - No activity against Class B carbapenemases
  - Less active against anaerobes compared to other βL-βLIs
- Phase 2 & 3 clinical data indicate it is effective and well-tolerated for complicated urinary tract infections and intra-abdominal infections
  - **Did not specifically include CRE isolates**
- Ongoing studies for healthcare-associated pneumonia
- Etests available to test susceptibilities
  - FDA breakpoint ≤8/4 mcg/ml for Enterobacteriaceae and *P. aeruginosa*

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntinfectiveDrugsAdvisoryCommittee/UCM425459.pdf.

Ceftazidime-Avibactam Dosing

Age	Dose for patients with creatinine clearance of ≥50 ml/min
≥3 months to <12 years (<40kg)*	50 mg/kg ceftazidime and 12.5 mg/kg avibactam over 2 hours every 8 hours
≥12 years*	2000 mg ceftazidime and 500 mg avibactam over 2 hours every 8 hours
Adults	2000 mg ceftazidime and 500 mg avibactam over 2 hours every 8 hours

*****Dosing based on NCT01893346: Phase 1 study of pharmacokinetics, safety, tolerability of a single dose of ceftazidime-avibactam in children 3 months to <18 years of age (presented at ICAAC 2015)

Conclusions

- CRE are a growing problem and optimal diagnostics still being evaluated
- Effectively treating CRE infections remain a daunting clinical challenge
  - Combination therapy recommended for invasive infections
  - Consider using prolonged-infusion carbapenem therapy for carbapenem MICs up to 8-16 mcg/ml
- Judicious use of antibiotics and proper infection control practices can decrease their emergence and transmission

Thank you!

Questions?