



# *XDR Acinetobacter (and Enterobacteriaceae):* What are the options?

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**The introduction of antibacterial drug therapy in the 1940s led to a dramatic reduction in illness.**

**The emergence of drug-resistant bacteria is reversing the trend**

**The current antibiotic crisis  
differs from those in the past:**

**-several different organisms are  
involved**

**-there are no immediate  
solutions on the horizon**

# Outline

- MRSA and VRE
- XDR gram-negative organisms
  - Acinetobacter
  - KPCs/NDM-1
  - Treatment options

# MRSA & VRE

Pathogen	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank
CoNS	5,178 (15.3)	1	3,900 (34.1)	1
<i>Staphylococcus aureus</i>	4,913 (14.5)	2	1,127 (9.9)	4
<i>Enterococcus</i> species		3		2
<i>E. faecalis</i>	1,177 (3.5)		627 (5.5)	
<i>E. faecium</i>	1,888 (5.6)		942 (8.2)	
NOS	1,028 (3.0)		265 (2.3)	
<i>Candida</i> species		4		3
<i>C. albicans</i>	2,295 (6.8)		673 (5.9)	
Other <i>Candida</i> spp. or NOS	1,333 (3.9)		669 (5.9)	
<i>Escherichia coli</i>	3,264 (9.6)	5	310 (2.7)	8
<i>Pseudomonas aeruginosa</i>	2,664 (7.9)	6	357 (3.1)	7
<i>Klebsiella pneumoniae</i>	1,956 (5.8)	7	563 (4.9)	5
<i>Enterobacter</i> species	1,624 (4.8)	8	443 (3.9)	6
<i>Acinetobacter baumannii</i>	902 (2.7)	9	252 (2.2)	9
<i>Klebsiella oxytoca</i>	359 (1.1)	10	99 (0.9)	10
Other	5,267 (15.6)		1,201 (10.5)	
Total	33,848 (100)		11,428 (100)	

NOTE. Of the 28,502 cases of HAI reported, 4,671 (16.4%) were polymicrobial. associated bloodstream infection; CoNS, coagulase-negative staphylococci; NOS, no pneumonia.

# MRSA & VRE

Gram-positive organisms

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Vancomycin-resistant *Enterococcus* (VRE)

Vancomycin

Linezolid

Daptomycin

Tigecycline

Synercid

Bactrim

Clindamycin

Ceftobiprole

# MDR Gram-Negatives



# GNRs cause 1/3 hospital infections

Pathogen	Overall <sup>a</sup>		CLABSI	
	No. (%) of pathogenic isolates	Rank	No. (%) of pathogenic isolates	Rank
CoNS	5,178 (15.3)	1	3,900 (34.1)	1
<i>Staphylococcus aureus</i>	4,913 (14.5)	2	1,127 (9.9)	4
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<i>C. albicans</i>	2,295 (6.8)		673 (5.9)	
Other <i>Candida</i> spp. or NOS	1,333 (3.9)		669 (5.9)	
<i>Escherichia coli</i>	3,264 (9.6)	5	219 (2.7)	8
<i>Pseudomonas aeruginosa</i>	2,664 (7.9)	6		7
<i>Klebsiella pneumoniae</i>	1,956 (5.8)	7		5
<i>Enterobacter</i> species	1,624 (4.8)	8	443 (3.9)	6
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# *XDR Acinetobacter / Enterobacteriaceae*

Sensitive to  $\leq 2$  antibiotic classes not including  
tigecycline or polymyxin  
(Resistant to Carbapenem antibiotics)

*Enterobacteriaceae*=

*Klebsiella*

*E. coli*

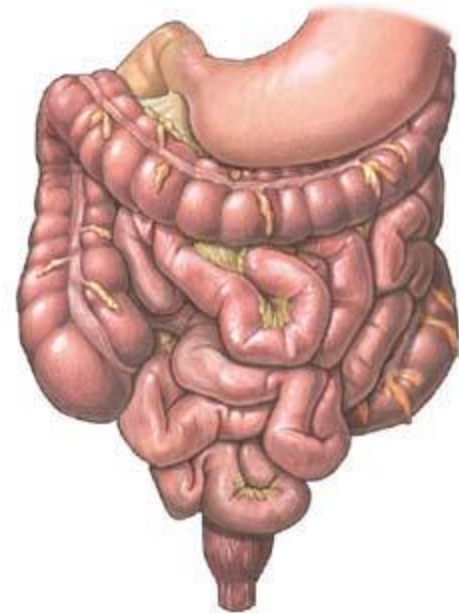
*Enterobacter, Citrobacter, Serratia.....*

Siegel 2007 CDC

International Consortium Draft Proposal

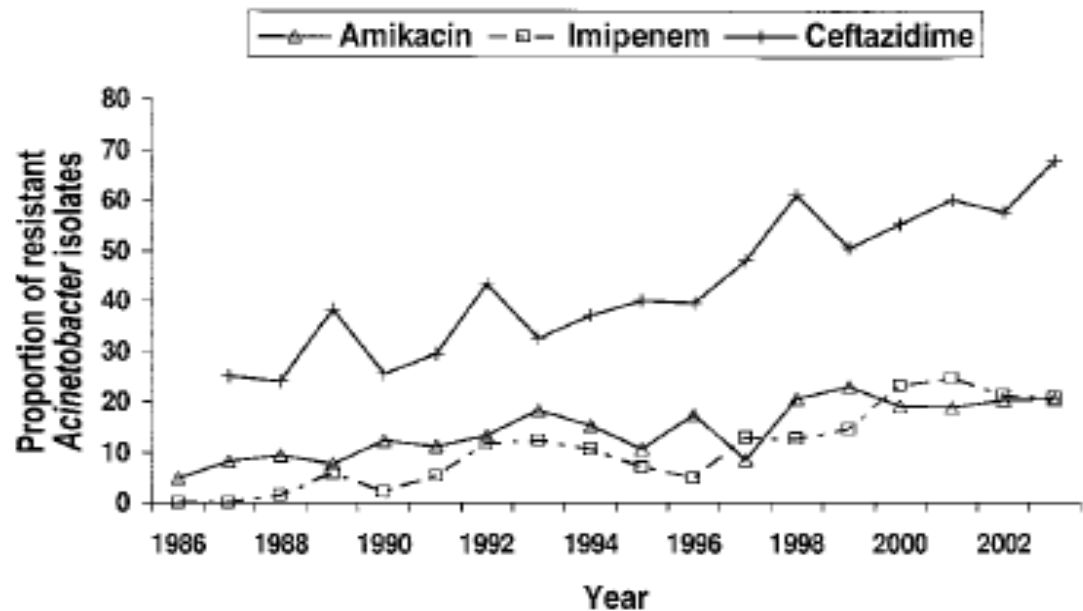
# Carbapenem resistance

- Most mechanisms cleave carbapenems
- Mobile resistance elements transmitted between species (esp. *Enterobacteriaceae*)
- Mixing of bacteria in GI track
- Increased resistance due to:
  - Antibiotic pressure
  - Patient-to-patient transmission



# *Acinetobacter baumannii*

- Ubiquitous in the environment
- In the 1990s increasing carbapenem resistance
- By 2007, 1/3 isolates R to carbapenems
- 10-30% Attributable mortality



# Acinetobacter Worldwide



FIG. 2. Countries that have reported an outbreak of carbapenem-resistant *Acinetobacter baumannii*. Red signifies outbreaks reported before 2006, and yellow signifies outbreaks reported since 2006.

	All	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
<i>Acinetobacter</i> species	435 (8.8)	149 (5.6)	61 (17.1) <sup>b</sup>	99 (13.8) <sup>b</sup>	17 (3.7)	9 (4.4)	8 (14.8) <sup>b</sup>	92 (19.2) <sup>b</sup>

Peleg et al. Clin Rev Micro 2008  
 Vincent et al. JAMA 2009

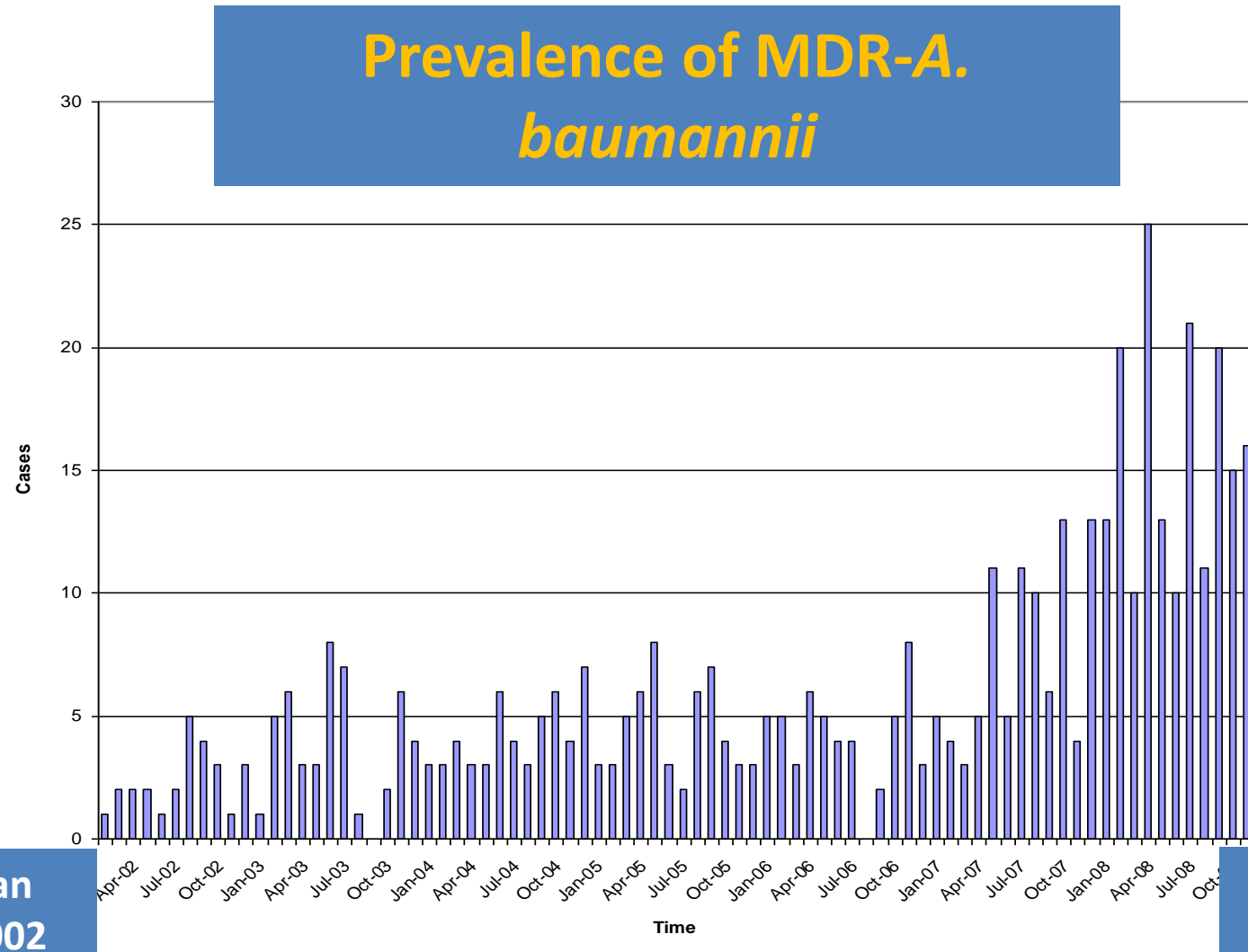
# *Acinetobacter* in NYC

- 1990s in NYC, 12 hospitals reported outbreaks in ICUs
- High mortality
- 1997 Brooklyn, NYC, 5% of GN isolates XDR *Acinetobacter*
- 2007 all NYC hospitals with endemic *Acinetobacter* (little standardization in management)
- 2013 XDR *Acinetobacter* decreasing and CRE stable

Manikal et al. CID 2000

Morgan et al. ICHE 2009

# One Maryland Institution's Experience



# Carbapenem Resistant *Enterobacteriaceae* (CRE)

- *KPC most common* (*Klebsiella* producing carbapenemase)
- NDM-1 increasing
- Most commonly in *Klebsiella*, but also
  - *E. coli* & other *Enterobacteriaceae*
- Resistance to all except polymyxin, tigecycline, some aminoglycosides



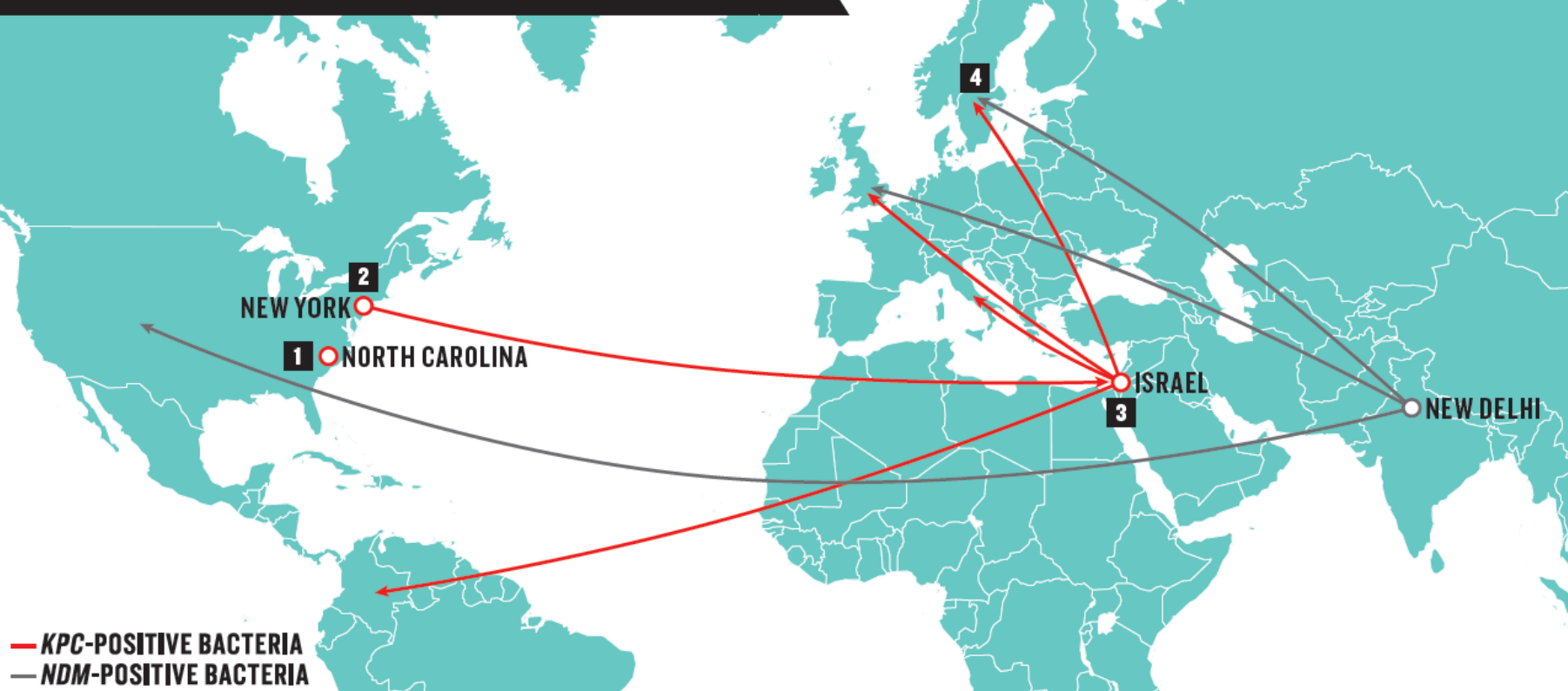
# Epidemiology of CRE

- 2007 CDC data, 8% of all *Klebsiella* isolates carbapenem resistant (under 1% in 2000)
- Spread by transfer of colonized patients
- Long Term Acute Care Hospitals (LTACHs) important



# THE RESISTANCE MOVEMENT

Carbapenem-resistant Enterobacteriaceae have been on the move since at least 1996.



## Carbapenem

1999–2001



2002–2005



2006–2010



Proportion of resistant isolates:

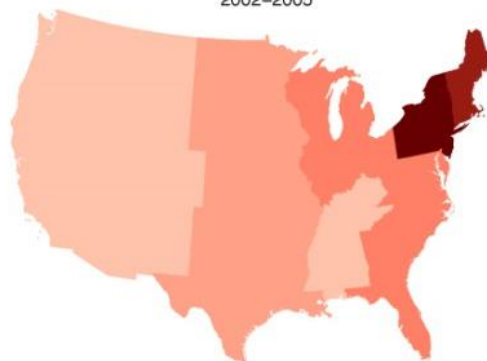
0 – .001 .001 – .01 .01 – .02 .02 – .03 .03 – .04 .04 – .05 .05 – 1

## 3rd Gen. Cephalosporins

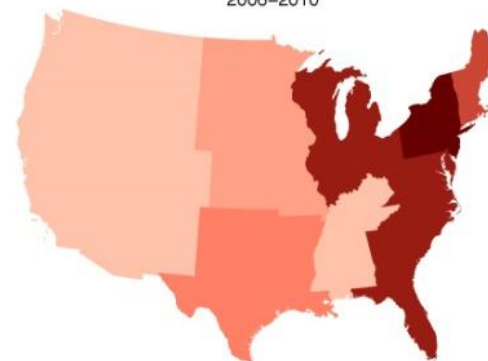
1999–2001



2002–2005



2006–2010



Proportion of resistant isolates:

0 – .025 .025 – .05 .05 – .075 .075 – .1 .1 – .125 .125 – .15 .15 – 1

Note: Data for 2010 available through July.

Data source: Braykov NB, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in Resistance to Carbapenems and Third- Generation Cephalosporins among Clinical Isolates of *Klebsiella pneumoniae* in the United States, 1999–2010. *Infect Control and Hospital Epidemiology*. 2013; 34(3)

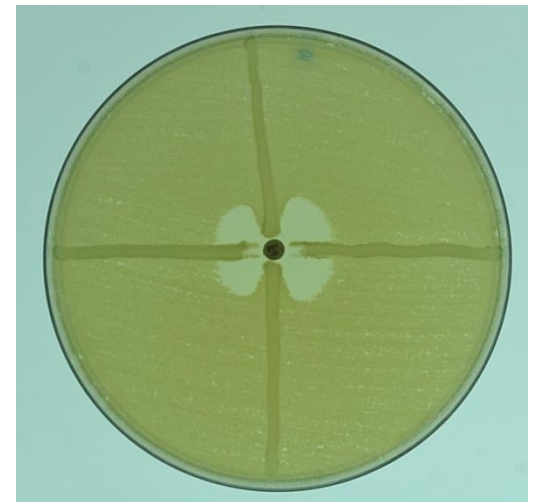


# Identification of CRE

- New CLSI cutoff for carbapenems ( $\text{MIC} \leq 1$ ) appears to reliably detect KPCs – issued in 2010, not used by all labs

(otherwise, Modified Hodge Test or Ertapenem to detect)

- Check with your lab!



# NDM-1 *Enterobacteriaceae*

- New Delhi Metallo-beta-lactamase-1
- *Klebsiella* > *E. coli* > other *Enterobacteriaceae*
- First identified in Sweden in patient hospitalized in India

Yong, AAC 2009

Kumarasamy, LID 2010



# NDM-1 outsourced

USA

Canada

Africa

Taiwan

China

Australia

Other European countries

(secondary spread in countries)



Kumarasamy, LID 2010

Various authors, ICAAC 2010

# Summary CRE

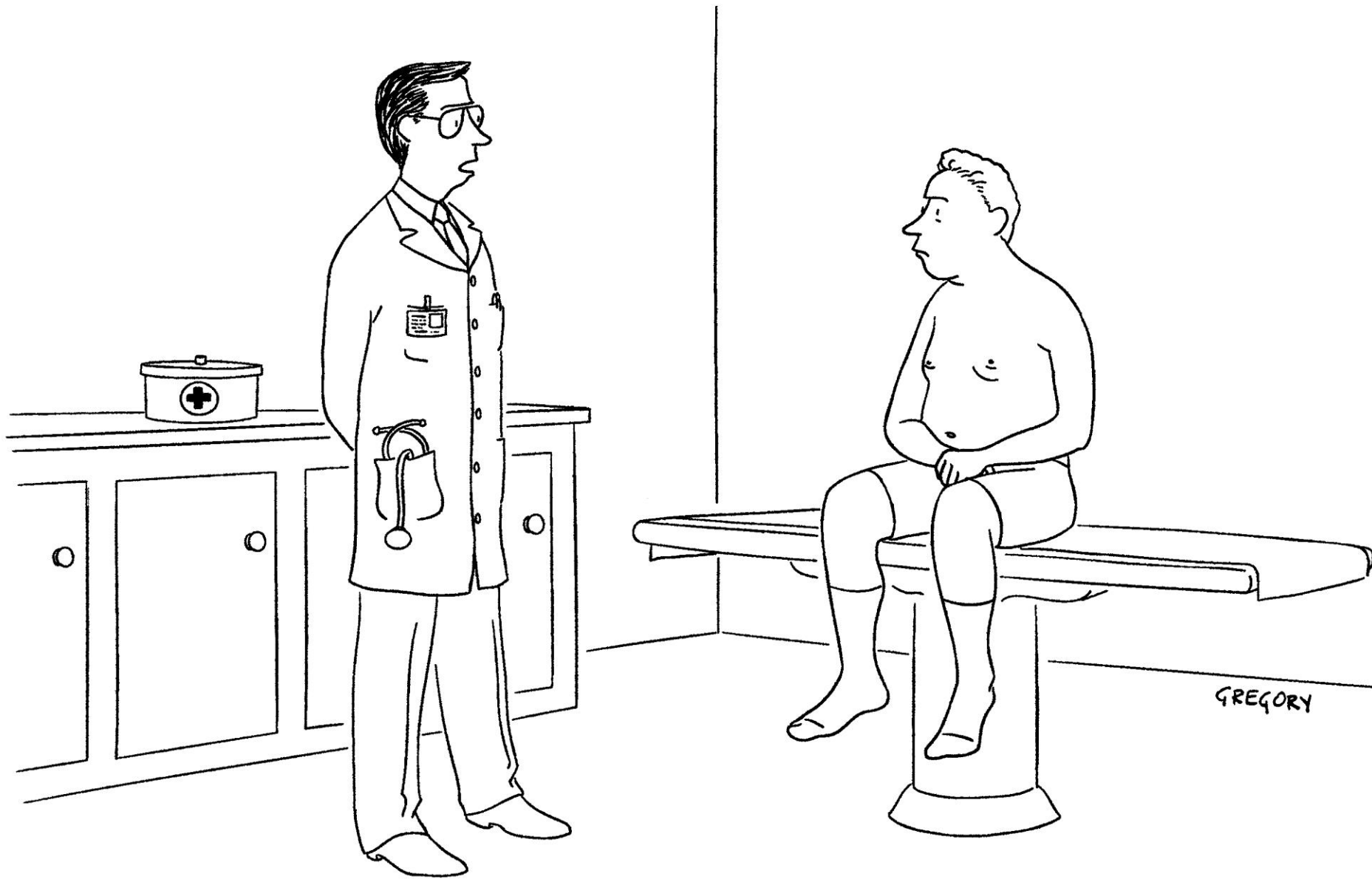
## KPCs

- *Klebsiella* > *E. coli*, *Enterobacter* etc.
- Carbapenem resistance not always detected

## NDM-1

- Very similar to KPC

Treatment

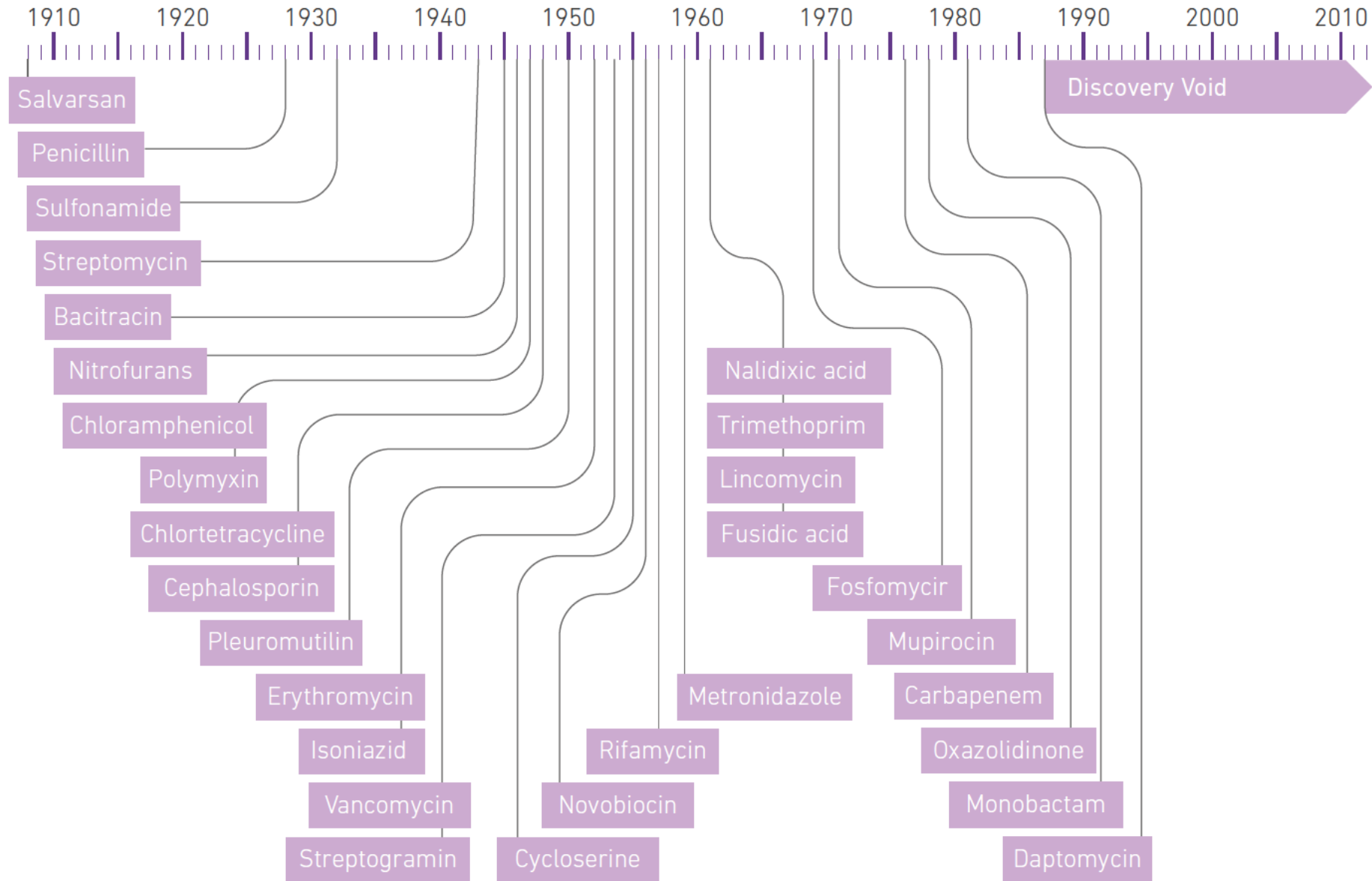


*"Your infection may be antibiotic-resistant, but let's see how it responds to intensive litigation."*



## Figure 1 Dates of discovery of distinct classes of antibacterial drugs

Illustration of the “discovery void.” Dates indicated are those of reported initial discovery or patent.



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

# Drugs used against carbapenem R Acinetobacter and Enterobacteriaceae

	Efficacy	Toxicity	Notes
Tigecycline	+	+	Development of resistance. Poor efficacy
Polymyxin	++	++	High toxicity
Aminoglycosides	+	++	High renal toxicity Primarily urine
Fosfomycin	?	-	Oral and only approved for UTI
Carbapenems	—	+	Continuous dose
Sulbactam	+	+	Acinetobacter only

# Polymyxins

- Developed 1950-1960
- Active against
  - Pseudomonas/Acinetobacter
  - Enterobacteriaceae and other GNR
- Nephrotoxic/ototoxic/neurotoxic
  - Use curtailed in 1970's
- Polymyxin-B /Polymixin-E (Colistin)

# Polymyxin E (colistin)

- No large studies on efficacy or toxicity
- Current use:
  - 2.5 – 5.0 mg/kg/day in 2-4 divided doses
  - not to exceed 300 mg/d
- Safety, efficacy, optimal dose uncertain

# Polymyxin toxicity

- Nephrotoxicity
  - Incidence 5%
- Neurotoxicity
  - Incidence 30%
  - Perioral paresthesia
  - Ataxia
  - Reversible

# Tigecycline activity

- Gram Positive Cocci
  - S. aureus (MSSA and MRSA), Streptococci, Enterococci (VRE)
- Gram Negative Bacilli
  - E. Coli. Klebsiella. Stenotrophomonas
- Anaerobes
  - Bacteroides
- **NOTE: Not active against 3 Ps!!**
  - Proteus, Providencia, Pseudomonas**

Development of resistance during treatment/ worse outcomes than comparators

# Tigecycline toxicities

- Nausea, Vomiting
- Hepatitis
- Pancreatitis
- Catabolic state (BUN rise)
- Pseudotumor cerebri

# Carbapenem antibiotics

- Imipenem, meropenem, doripenem
- Not ertapenem
- May inhibit growth despite organism resistance
- Extended-duration infusion for CRE
- In combination with other antibiotics



# Aminoglycosides

- Concentration dependent killing
- Renal and ototoxic side effects
- Daily Dosing:
  - Gentamicin 5-8 mg/kg q24h
  - Amikacin 15 mg/kg q24h
- Daily Dosing:
  - Less nephrotoxic
  - May be more effective
  - Use for short courses

# Fosfomycin

- Approved for urinary tract infection
- Only available as oral drug in USA (3 gm)
  - complicated UTI 3 gm q2-3 days x3 doses
- 60% of CRE susceptible
- Side effects—headache, rash, diarrhea
- IV fosfomycin has been used for CRE in Greece (12 patients)
  - 18% mortality
  - 2-4 gm q6 hours

# Sulbactam

- Typically available only as ampicillin-sulbactam
- Intravenous
- active against some *A. baumannii*

# Aztreonam/Ciprofloxacin etc.

- May work for some CRE, based on susceptibility testing
- Limited experience with serious infections

# Rifampin

- 300 mg oral/iv 3x day
- Side effects: Rash, diarrhea, LFT elevation
- Drug interactions (CYP3A4 induction)
- Resistance develops easily
- Only use in combination

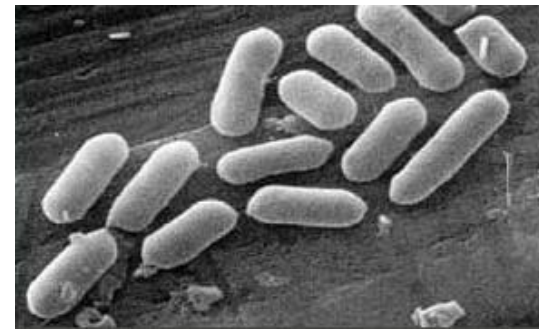
# Combination therapy

- Used because of
  - High mortality
  - Emergence of resistance during treatment
  - Few effective drugs
- Colistin +
  - tigecycline
  - extended-infusion carbapenem
  - Gentamicin or other aminoglycoside
  - rifampin

# Fecal transplant?

- 13 year old girl colonized with CRE (KPC) during chemotherapy
- R tigecycline, I gentamicin
- Bacteremia 33 days, septic arthritis
- Colistin, doripenem extended infusion, rifampin and plazomicin (experimental drug)
- Fecal transplant
- Colonization cleared 2 weeks later (with no evidence of KPC x8 months)

# Summary



- XDR gram-negatives much more difficult to manage than MRSA/VRE
- Increasing XDR Acinetobacter/Enterobacteriaceae
- Treatment focus on
  - Combination therapy
  - Balancing side effects with benefits



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