When treatments go awry: C diff, pneumonia, resistance, oh my!

GMCCP Fall Educational Event/Business Meeting
Wednesday November 16th, 2016

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Disclosures

- Sara Revolisnki: Recipient of an Antimicrobial Stewardship Grant from Cubist Pharmaceuticals (Merck)
- Peer review has confirmed that the disclosure is unrelated to the content of this presentation and the presentation is free from bias

C. d$ff Happens. An Update on Risk Factors and Treatment

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Objectives

- Describe the risk factors for *Clostridium difficile* infection (CDI)

- Discuss treatment options for the management of CDI

Background

- CDI is defined as an acute onset of diarrhea (3 or more loose stools in 24 hours) with microbiologic evidence of toxigenic *C. difficile*
- *C. difficile* is associated with significant morbidity and mortality
  - Affects over 500,000 patients each year
  - 14,000 deaths annually

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Shields K. *Anaerobe.* 2015;34:59.
Surawicz CM. *Am J Gastroenterol.* 2013;108:478.

Pathogenesis

- Disruption of intestinal microbiota is key
  - Impairs resistance to colonization allowing *C. difficile* to propagate

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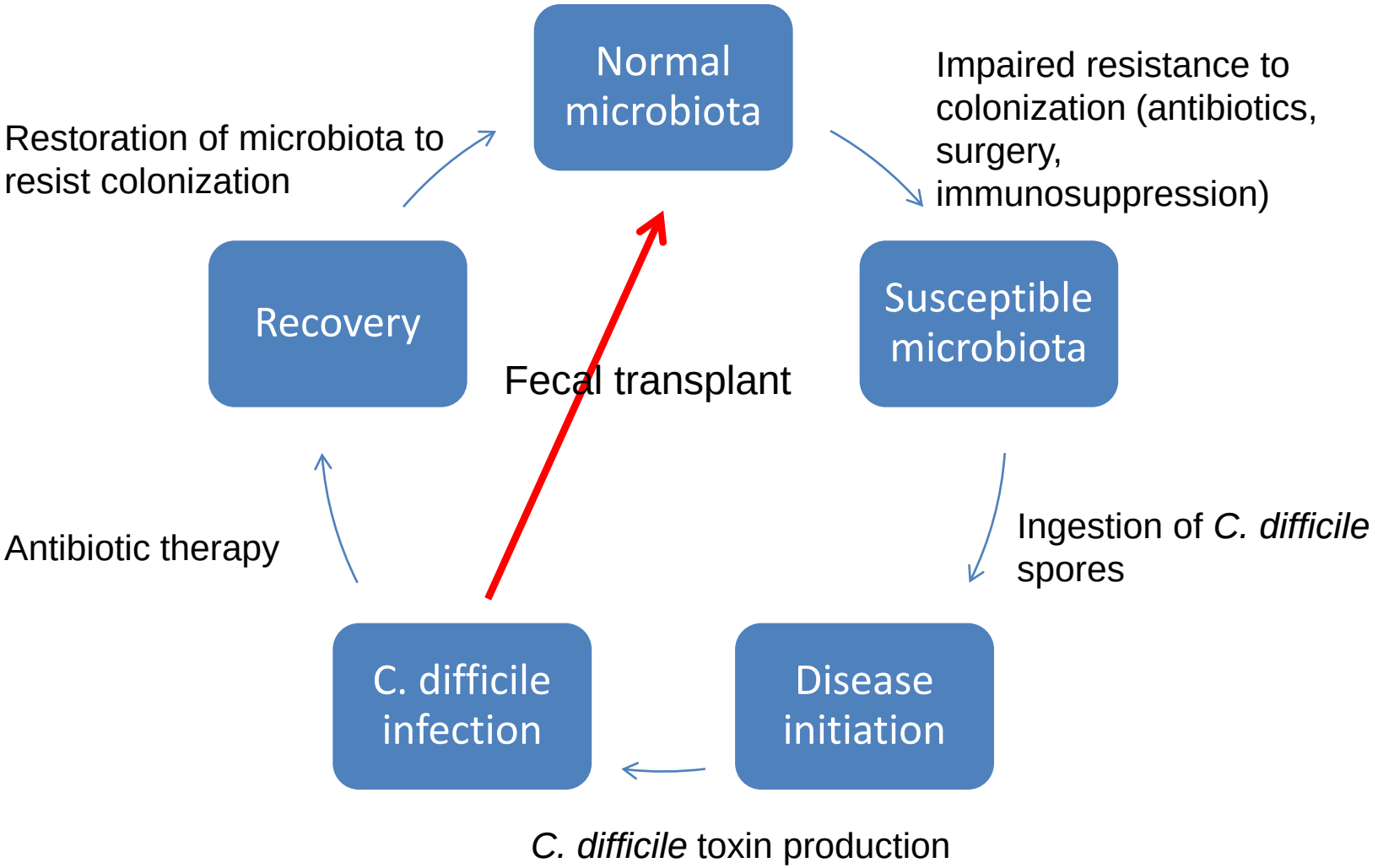
Vincent C. *Antibiotics.* 2015;4:230.

Pathogenesis



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Rao K. *J Hosp Med.* 2016;11:56.

RISK FACTORS

TP is a 79 yo male patient admitted to the hospital with fevers found to be secondary to *C. difficile* colitis.

PMH

- P
  (
- h
- C

PSH

- Pancreatico-duodenectomy (9/15/16)

Current Medications

daily

12.5

ng po

1

11/10/16

What risk factors does this patient currently have for C. difficile colitis?

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Prior Antibiotic Use

- One of the most identified risk factors for CDI
- Patients must have exposure to organism
  - Colonization
  - Acquisition
- Risk of CDI is increased during antibiotic therapy and for several weeks to months after therapy cessation

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Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Owens, Jr. RC. *Clin Infect Dis*. 2008;46:S19.

What Influences Antibiotic Risk?

- Broad spectrum of antibiotic coverage
- Intrinsic activity against *C. difficile*
- Anaerobic activity
- Antibiotic resistance
- Administration of multiple antibiotics
- Prolonged duration of therapy
- Stimulation of toxin production

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Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Owens, Jr. RC. *Clin Infect Dis*. 2008;46:S19.

Antibiotics with Highest Risk of CDI

Antibiotic	Odds Ratio
Fluoroquinolones	2.0 – 12.7
Cephalosporins	1.6 – 5.4
Clindamycin	1.8 – 4.8
Beta-lactam/beta-lactamase inhibitor	1.9

Owens, Jr. RC. *Clin Infect Dis*. 2008;46:S19.

Acid Suppressive Therapy

- Decreased acid preserves ingested organisms
- Proton pump inhibitors (PPIs) may alter intestinal microbiota
- PPIs may directly impair leukocyte activity

Kwok CS. *Am J Gastroenterol.* 2012; 107:1011.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Acid Suppressive Therapy

Association with CDI	Odds Ratio (95% Confidence Interval)
Primary CDI with PPI use	1.74 (1.47-2.85)
Recurrent CDI with PPI use	2.51 (1.16-5.44)
Primary CDI with H2RA use	1.50 (1.23-1.83)
CDI with H2RA use compared to PPI use	0.71 (0.53-0.97)
PPI plus antibiotics compared to PPI alone	1.96 (1.03-3.70)

PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist

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Kwok CS. *Am J Gastroenterol.* 2012; 107:1011.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Other Medications

- Chemotherapy
  - Antibiotic effects
  - Disruption of microbiota (mucositis, etc.)
  - Immunosuppression

- Antidepressants?

Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Rogers MAM. *BMC Medicine.* 2013;11:121
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Co-morbidities

- Immunosuppression
- Inflammatory bowel disease
- Depression
- Renal impairment

Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Debast SB. *Clin Microbiol Infect.* 2014;20 (Suppl. 2): 1.
Dubberke ER. *Clin Infect Dis*. 2007;45:1543.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Other

- Age
- Hypoalbuminemia
- Hospital admission in past 60 days
- Length of hospital admission
- Previous history of CDI
- Invasive procedures
  - Tube feeding
  - Mechanical ventilation
  - Gastrointestinal surgery

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Dubberke ER. *Clin Infect Dis*. 2007;45:1543.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

TP is a 79 yo male patient admitted to the hospital with fevers found to be secondary to *C. difficile* colitis.

PMH

- Pancreatic cancer (diagnosed 08/16)
- Hypertension
- CDI (1/15/16)

PSH

- Pancreatico-duodenectomy (9/15/16)

Current Medications

- Pantoprazole 40 mg
- po daily
- Lisinopril/HCTZ 20/12.5 mg po daily
- Ciprofloxacin 250 mg po BID for E. coli UTI started 2 days ago
- FOLFIRINOX: cycle 1 11/10/16

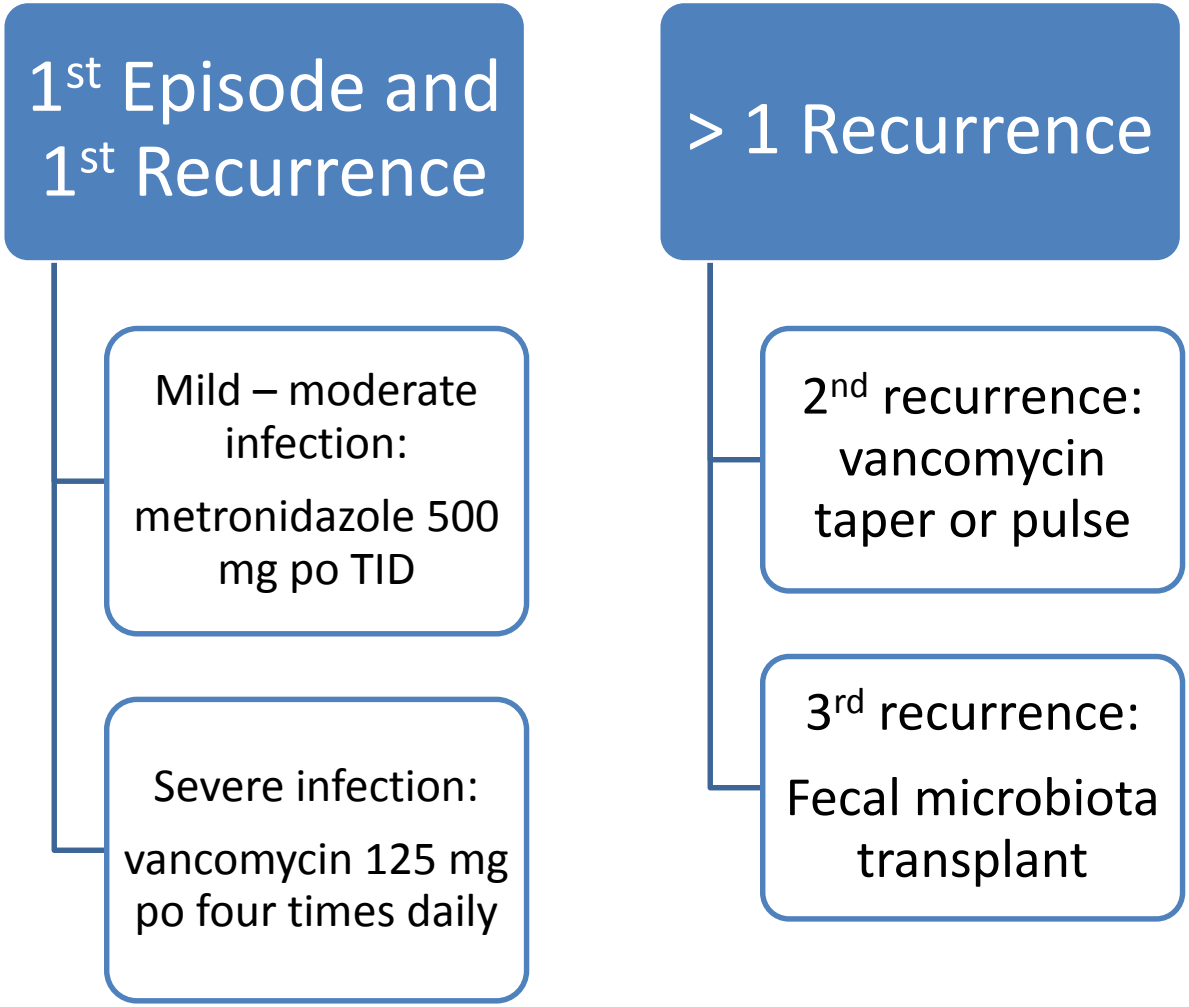
TREATMENT OPTIONS

CD is a 46 yo otherwise healthy female presenting to her primary care physician with complaints of watery diarrhea

- Reports 4 watery stools per day
- Also complains of mild abdominal pain
- Labs
- Vita
  temperature of 100.8 F.
- *C. difficile* nucleic acid amplification test result is positive (first episode)

How should CD be treated?

Guideline Recommendations



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Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Vancomycin for Severe CDI

- A comparison of vancomycin and metronidazole for treatment of CDI stratified by disease severity

- Prospective, randomized controlled trial
  - Metronidazole 250 mg po four times daily plus liquid placebo four times daily
  - Vancomycin 125 mg po four times daily plus tablet placebo four times daily

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Zar FA. *Clin Infect Dis*. 2007;45:302.

Vancomycin for Severe CDI

Outcome (%)	Metronidazole	Vancomycin	P-value
Clinical cure, overall	84	97	0.006
Clinical cure, mild disease	90	98	0.36
Clinical cure, severe disease	76	97	0.02
Relapse	14	7	0.27

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Zar FA. *Clin Infect Dis*. 2007;45:302.

Vancomycin vs Metronidazole

- Multicenter, double-blind, active-controlled study randomly assigned patients to tolevamer, metronidazole, or vancomycin
  - Metronidazole 375 mg po every 6 hours
  - Vancomycin 125 mg po every 6 hours

- Tolevamer found to be inferior to both metronidazole and vancomycin

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Johnson S. *Clin Infect Dis*. 2014;59:345.

Vancomycin vs Metronidazole

Outcome (%)	Metronidazole	Vancomycin	p-value
Clinical success, overall	72.7	81.1	0.020
Clinical success, mild disease	78.7	82.7	0.54
Clinical success, moderate disease	73.9	82.2	0.14
Clinical success, severe disease	66.3	78.5	0.059
Recurrence	23.0	20.6	NS

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Johnson S. *Clin Infect Dis*. 2014;59:345.

Vancomycin vs Metronidazole

- Post-hoc multivariate regression analysis found the following factors to be significantly associated with clinical success
  - Vancomycin treatment
  - Treatment naïve status
  - Mild or moderate disease severity

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Johnson S. *Clin Infect Dis*. 2014;59:345.

Negative Impact of Antibiotics for CDI

- Disruption of intestinal microbiota
- Selection for other pathogens (i.e. vancomycin-resistant *Enterococcus spp.*[VRE])

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Rao K. *J Hosp Med.* 2016;11:56.

Fidaxomicin

- No recommendations for use outlined in national guidelines in the United States
- European guidelines list fidaxomicin as an alternative to metronidazole and vancomycin
- Theoretical benefits
  - Less disruption of intestinal microbiota
  - Active against many strains of VRE

Cohen SH. *Infect Control Hosp Epidemiol.* 2010;31:431.
Debast SB. *Clin Microbiol Infect.* 2014;20 (Suppl. 2): 1.
Surawicz CM. *Am J Gastroenterol*. 2013;108:478.

Fidaxomicin vs Vancomycin

- Prospective, multicenter, randomized controlled trial conducted in the US and Canada
  - Fidaxomicin 200 mg po BID for 10 days
  - Vancomycin 125 mg po four times daily for 10 days

Outcome (%)	Fidaxomicin	Vancomycin	P-value
Clinical cure	88.2	85.8	NS
Recurrence*	15.4	25.3	0.005
Global cure	74.6	64.1	0.006

*recurrence was not significantly different for patients with the NAP1/BI/027 strain

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Louie TJ. *N Engl J Med.* 2011;364:422.

Fidaxomicin vs Vancomycin

- Post-hoc analysis of two phase 3 randomized controlled trials to evaluate fidaxomicin versus vancomycin in Canadian patients
- Clinical response similar between groups
- Fidaxomicin associated with lower rates of recurrence

Recurrence Rates (%)	Fidaxomicin	Vancomycin	P-value
Age ≥ 65	16.0	30.9	0.026
Concomitant antibiotics	16.2	38.7	0.036
Non-BI strain	11.8	28.3	0.004

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Lee C. *Can J Infect Dis Med Microbiol*. 2016;doi:10.1155/2016/8048757.

Fecal Microbiota Transplant (FMT)

- Purpose: restore normal intestinal microbiota
  - Prevents *C. difficile* spores from proliferating
  - Eradicates C. difficile spores?

- Primarily studied for treatment of recurrent CDI

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Rao K. *J Hosp Med.* 2016;11:56.
Vincent C. *Antibiotics.* 2015;4:230.

Transplant Procedure

- Not standardized
- Stool screening must be completed
- Antibiotics must be held for 24-48 hours prior to procedure
- Instillation of stool
- Antimotility agents

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Rao K. *J Hosp Med.* 2016;11:56.

FMT Success

- Overall resolution of about 92%

- Reduces recurrence of CDI
  - Recurrence after FMT is about 4%
  - Recurrence of CDI after antibiotic treatment occurs in up to 35% of patients

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Gough E. *Clin Infect Dis.* 2011;56:994.

FMT Success

- Efficacy may be dependent on
  - Transplant technique (colonoscopy vs via nasogastric tube vs via stool capsules)
  - Donor relationship
  - Volume of transplanted stool
  - Treatment prior to FMT

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Gough E. *Clin Infect Dis.* 2011;56:994.

CD is a 46 yo otherwise healthy female presenting to her primary care physician with complaints of watery diarrhea

- Reports 4 watery stools per day
- Also complains of mild abdominal pain
- Labs are normal except for a white blood cell count of 13.5
- Vital signs are normal except for a temperature of 100.8 F.
- *C. difficile* nucleic acid amplification test result is positive (first episode)

How Should CD Be Treated?

A. Metronidazole 500 mg po TID

B. Vancomycin 125 mg po four times daily

C. Fecal microbiota transplant

D. Fidaxomicin 200 mg po BID

Hospital-acquired Pneumonia (HAP) and Ventilator-associated Pneumonia (VAP): Update on the Guidelines

GMCCP Fall Education Event

11/16/2016

Claire Dysart, PharmD, BCPS

Infectious Diseases Pharmacist, Milwaukee VAMC

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Objectives

- Explain major updates in the recently published guidelines for managing patients with hospital-acquired or ventilator-associated pneumonia.
- Design an appropriate antibiotic regimen for a patient with hospital-acquired pneumonia based on risk factors for drug-resistant pathogens.

Definitions

- Hospital-acquired pneumonia (HAP)
  - Pneumonia diagnosed > 48 hours after hospital admission
- Ventilator-associated pneumonia (VAP)
  - Pneumonia diagnosed > 48 hours after endotracheal intubation
- Diagnosis: new lung infiltrate on radiographic imaging, plus clinical evidence including new onset fever, purulent sputum, leukocytosis, and decline in oxygenation

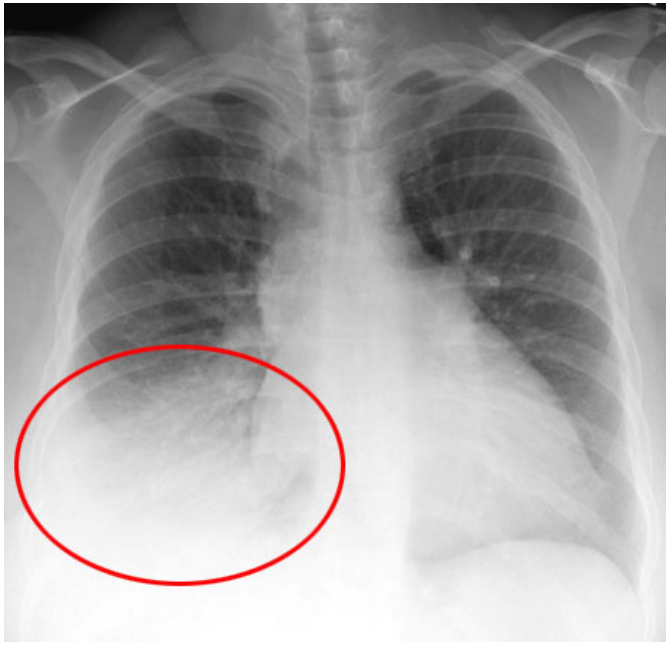
Epidemiology

- HAP and VAP together account for the most common hospital-acquired infections (HAIs)
  - 22% of all HAIs in multistate point-prevalence survey[1]
  - Recent meta-analysis estimates a 13% mortality rate associated with VAP[2]
  - Excess costs of ~ $40,000 associated with VAP per patient[3]

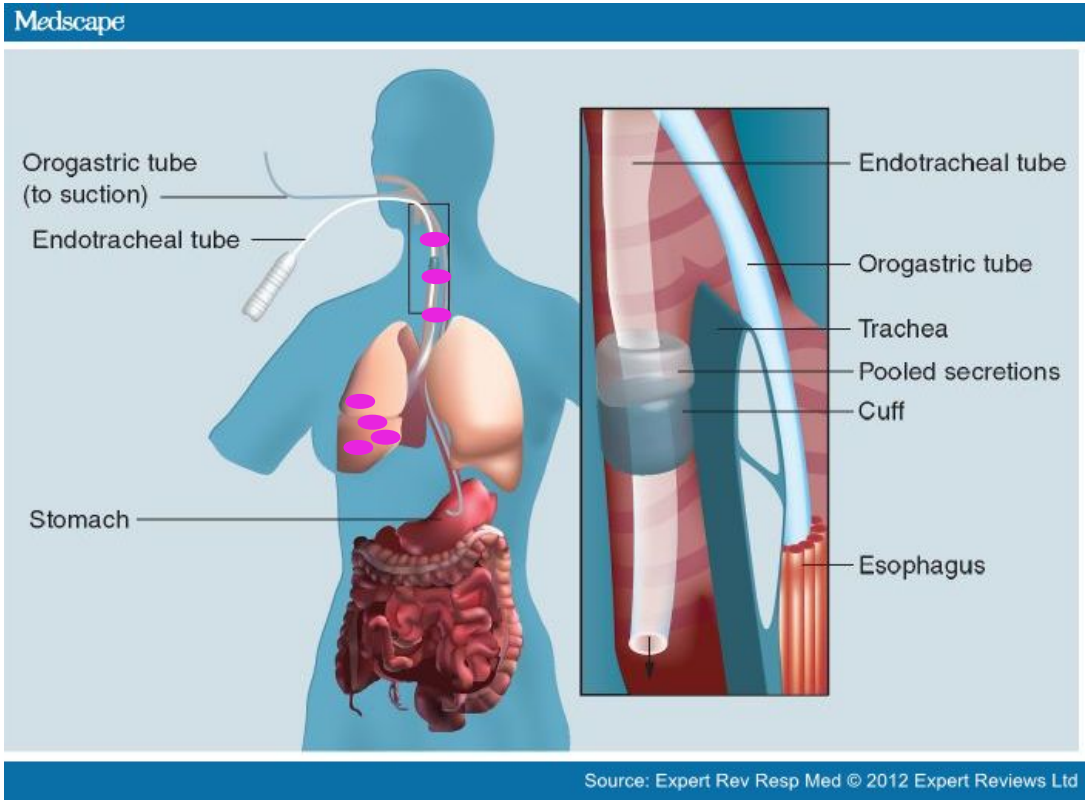
Pathogenesis[4]

- Microbes enter the respiratory tract via:
  - Microaspiration of organisms colonizing the oropharyngeal tract
  - Direct contact with contaminated environmental reservoirs such as respiratory devices and water reservoirs (VAP)
  - Hematogenous spread from other site in body (less frequent)
- Normal host defenses are impaired or patient is exposed to high inoculum or virulent pathogen
- Thickened alveolar walls become inflamed and fill with mucus → impaired gas exchange
- Complications: empyema, pleural effusions, respiratory failure, septic shock, prolonged mechanical ventilation, and renal failure
  - Complications associated with HAP occur in ~ 50% of patients[5]

Pathogenesis



http://intensivecarehotline.com/clinical-pictures/pneumonia/



Diagnostics

- Panel suggests noninvasive sampling with semiquantitative cultures (ie. endotracheal aspiration)
  - No benefit demonstrated with invasive sampling (bronchoscopic techniques) versus non-invasive techniques
  - Noninvasive sampling is associated with less complications
- Bottom line – OBTAIN CULTURE DATA!

Bacterial Etiologies

- Staphylococcus aureus (MRSA > MSSA)
- Streptococcus spp.
- Gram-negative bacilli
  - E. coli, Enterobacter spp., Stenotrophomonas maltophilia, Pseudomonas, Acinetobacter, etc.
- Legionella (nosocomial epidemic)
- Anaerobes (aspiration)

Important Changes from 2005 Guidelines

- Use of Grading of Recommendation Assessment, Development and Evaluation (GRADE) methodology for evaluation of evidence
- Removal of healthcare-associated pneumonia ("HCAP") concept
  - Patients with risk factors for MDR pathogens will be addressed in the new CAP guidelines
- Each hospital should generate antibiograms to guide optimal choice of empiric antibiotics
  - Minimize unnecessary use of dual Gram-negative and empiric MRSA coverage
  - Minimize patient harm and emerging antibiotic resistance

Antibiogram- Example

ANTIMICROBIAL SUSCEPTIBILITY DATA FOR 2014

GRAM NEGATIVE RODS PERCENT SUSCEPTIBLE	NUMBER OF ISOLATES	AMPICILLIN	AMP/SULBACTAM	CEFAZOLIN	CEFEPIME	CEFTAZIDIME	CEFTRIAXONE	CIPROFLOXACIN	GENTAMICIN	MEROPENEM	PIPERACILLIN	PIP/TAZOBACTAM	TRIMETH/SULFA	TOBRAMYCIN	ESBL (%Pos)
ESCHERICHIA COLI	749	56	62	87	99	-	96	77	92	100	-	96	77	-	3
ENTEROBACTER SP.	82	-	-	-	-	-	-	94	100	100	-	91	100	-	-
KLEBSIELLA SP.	276	-	80	86	100	-	97	99	99	100	-	95	95	-	0
PROTEUS SP.	146	75	84	53	100	-	98	70	93	-	-	100	73	-	-
SERRATIA SP.	21	-	-	-	100	-	95	95	100	100	-	100	100	-	-
CITROBACTER SP.	41	-	-	29	100	-	90	100	100	100	-	100	85	-	-
PS. AERUGINOSA	228	-	-	-	89	-	-	76	87	83	-	87	-	93	-
ACINETOBACTER SP.	20	-	95	-	-	-	-	85	90	-	-	-	85	-	-

GRAM POSITIVE COCCI PERCENT SUSCEPTIBLE	NUMBER OF ISOLATES	AMPICILLIN	CEFOTAXIME	CEFTRIAXONE	CIPROFLOXACIN	CLINDAMYCIN	ERYTHROMYCIN	GENTAMICIN	LEVOFLOXACIN	PENICILLIN	OXACILLIN	TRIMETH/SULFA	TETRACYCLINE	VANCOMYCIN
STAPH. AUREUS	388	-	-	-	-	78	48	99	-	0	60	100	96	100
COAG. NEG STAPH.	50	-	-	-	-	-	-	-	-	0	51	-	80	100
ENTEROCOCCUS	241	85	-	-	63	-	-	-	-	85	-	-	-	91
STREP. PNEUMONIAE	26	-	-	*	-	-	-	-	96	67	-	-	-	-

* 100% susceptible for meningitis interpretations; 96% susceptible for non-meningitis i

Note: Data includes inpatient, outpatient, and ER isolates and evaluated per the CLSI M39 document.
Blank areas are either not tested, not active or not appropriate.

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Important Changes from 2005 Guidelines Continued

- Short course of therapy for **most** patients with HAP or VAP independent of bacterial pathogen (7 days)
  - Exceptions: necrotizing lung infections, abscesses, empyema
- Pharmacokinetic/pharmacodynamic optimization of antibiotic therapy
  - Recommend antibiotic dosing be determined based on PK/PD data versus manufacturer's prescribing information (ie. Prolonged infusions of anti-Pseudomonal beta-lactams)

Empiric Treatment for HAP

- Cover *S. aureus* (MSSA), *P. aeruginosa*, and other Gram-negative bacilli in **all** empiric regimens
- Use of MRSA agent or dual anti-Pseudomonal agents depends on specific risk factors
  - Dual coverage should include two antibiotics from two separate classes
- Patients may be eligible for single agent depending on these risk factors!

Empiric MRSA Coverage - HAP

- Patient should receive one anti-MRSA agent if one or more of the following risk factors present:
  - Prior intravenous antibiotics within 90 days
  - Patient hospitalized in a unit where > 20% of S. aureus are MRSA (or unknown)
  - High risk for mortality*

*High risk of mortality defined as > 25% chance of death. Risk factors include septic shock or need for mechanical ventilation

Empiric Anti-Pseudomonal Coverage - HAP

- Dual anti-Pseuduomonal coverage indicated for patients with one or more of the following risk factors:
  - Prior intravenous antibiotics within 90 days
  - High risk for mortality
  - Significant structural lung disease such as cystic fibrosis or bronchiectasis

Empiric Treatment for VAP

- Cover *S. aureus* (MSSA), *P. aeruginosa*, and other Gram-negative bacilli in **all** empiric regimens
- Use of MRSA agent or dual anti-Pseudomonal agents depends on specific risk factors
  - Dual coverage should include two antibiotics from two separate classes
- Patients may be eligible for single agent depending on these risk factors – but these are *slightly* different than those for MRSA/MDR HAP

Empiric MRSA Coverage - VAP

- Patient should receive anti-MRSA agent if one or more of the following risk factors present:
  - Prior intravenous antibiotics within 90 days
  - Patient hospitalized in a unit where > 10-20% of *S. aureus* are MRSA (or unknown)

Empiric Anti-Pseudomonal Coverage - VAP

- Dual anti-Pseuduomonal coverage indicated for patients with one or more of the following risk factors:
  - Prior intravenous antibiotics within 90 days
  - Septic shock at the time of VAP diagnosis
  - Acute respiratory distress syndrome (ARDS) preceding VAP
  - Five or more days of hospitalization prior to VAP
  - Acute renal replacement therapy prior to VAP
  - Patient hospitalized in unit with > 10% Gram-negative pathogens are resistant to preferred monotherapy agent (or if unknown resistance rates in the ICU)

Dual Anti-Pseudomonal Coverage- Why is it necessary?

- From an empiric standpoint, dual coverage increases the probability of least one anti-agent initiated that will be active against the pathogen
- Guidelines also state the following: “if local or regional data suggest a low prevalence of MRSA and **low antibiotic resistance rates among gram-negatives**, then a single agent active against both *P. aeruginosa* and MSSA or one agent active against MSSA combined with one agent active against Pseudomonas and other gram-negatives is likely adequate.”
- AND, “Empiric therapies should be informed by patient-specific risk factors for antimicrobial-resistant pathogens and the distribution of pathogens and antibiotic resistance in the local practice environment .”

Dual Anti-Pseudomonal Coverage – The Evidence

- Panel identified 7 eligible trials comparing outcomes in patients receiving monotherapy vs. combination therapy
- Found no differences in mortality, clinical response, ADRs, or acquired drug resistance
- Some of these trials excluded patients with comorbid illnesses and patients known to be colonized with drug-resistant organisms

HAP/VAP Antibiotic Agents

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

[e] Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].

[f] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

Pathogen-directed Therapy

- All patients with HAP or VAP should be treated with pathogen-directed therapy once microbiolgical data is available and septic shock resolves
- Streamline or narrow coverage to target pathogen, may eventually be able to switch to oral antibiotic therapy once patient is stable
- Prevents avoidable toxicities and emerging drug resistance
- Duration: 7 days (for most patients)

Role of Inhaled Antibiotics

- For patients with HAP/VAP due to Gram-negative pathogens susceptible only to aminoglycosides or polymixins, suggest inhaled aminoglycoside or polymixin *in addition* to systemic therapy
- Also reasonable to consider adjunctive inhaled antibiotics for patients not clinically responding to systemic therapy alone (regardless if pathogen is MDR or not)

Other Key Recommendations

- Avoid aminoglycosides if other Gram-negative agents with adequate activity are available
  - Suboptimal lung penetration, toxic, associated with poorer clinical outcomes compared to other classes
- Avoid polymixins/colistin if other Gram-negative agents with adequate activity are available
  - Toxicity concerns, preserve for more resistant pathogens as “last resort”
- Use of procalcitonin biomarker
  - NOT recommended for use of decision to initiate antibiotics
  - May be used to guide therapy along with clinical criteria for potential discontinuation of antibiotics, however has been shown to shorten antibiotic exposures when recommended treatment durations were longer

Patient Case Assessment Question 1

A patient who has been hospitalized for 10 days develops HAP and is transferred to the ICU for mechanical ventilation and vasopressor support. This institution's antibiogram shows Pseudomonas resistance rates greater than 10% for cefepime and piperacillin/tazobactam. Which of the following is the most appropriate empiric antibiotic regimen?

A. Vancomycin and ceftriaxone
B. Vancomcyin and cefepime
C. Linezolid, piperacillin/tazobactam, and levofloxacin
D. Colistin

Patient Case Assessment Question 2

A patient started on empiric vancomycin, piperacillin /tazobactam, and intravenous tobramycin for VAP is stabilized in the ICU and transferred to the medicine floor with improved clinical status. The patient's sputum culture has revealed *Pseudomonas aeruginosa* which is sensitive to both piperacillin/tazobactam and tobramycin. Which of the following is the most appropriate pathogen-specific therapy?

A. Continue all three antibiotics for remainder of treatment.
B. Continue vancomycin and tobramycin; discontinue piperacillin/tazobactam.
C. Continue piperacillin/tazobactam; discontinue vancomycin and tobramycin.
D. Discontinue all intravenous antibiotics and start inhaled tobramycin alone.

References

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3. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. Infect Control Hosp Epidemiol 2012; 33:250–6.
4. Rello J, Quintana E, Castella J, et al. Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 1991; 100(2):439.
5. Sopena N, Sabria M; Neunos Study Group. Multicenter study of hospital-acquired pneumonia in non-ICU patients. Chest 2005; 127:213–9.
6. Kalil AC, Metersky ML, Muscedere J, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious disease society of America and the American thoracic society. Clin Infec Dis; 2016: 1-51.

Thank you!

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Essentials of Bacterial Resistance and Evolving Options for Management

Margaret Cook, PharmD, BCPS

Aurora St. Luke's Medical Center

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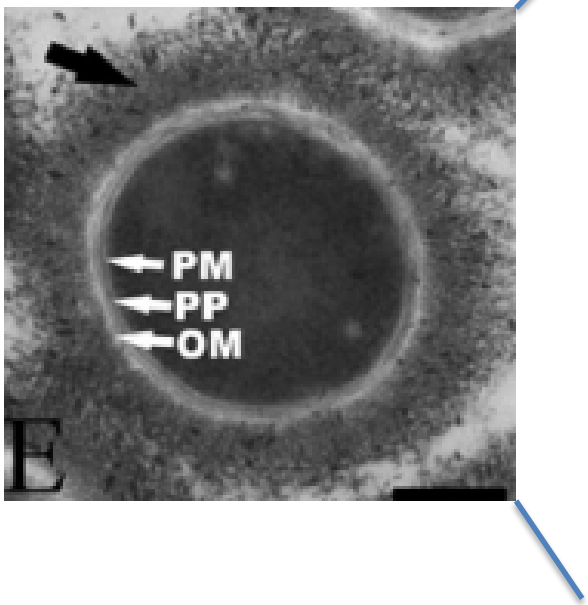
Objectives

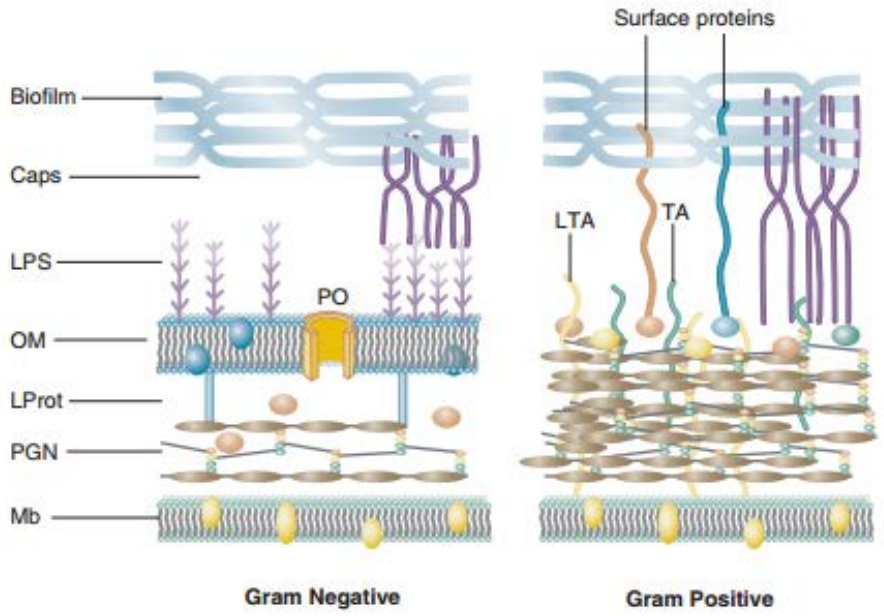
- Describe two mechanisms of resistance that impact therapeutic management of invasive bacterial infections.

- List three recently available agents, or combinations, that may offer options for the treatment of multidrug resistant pathogens.

Structure & Function

Gram-Positive and Gram-Negative Organisms





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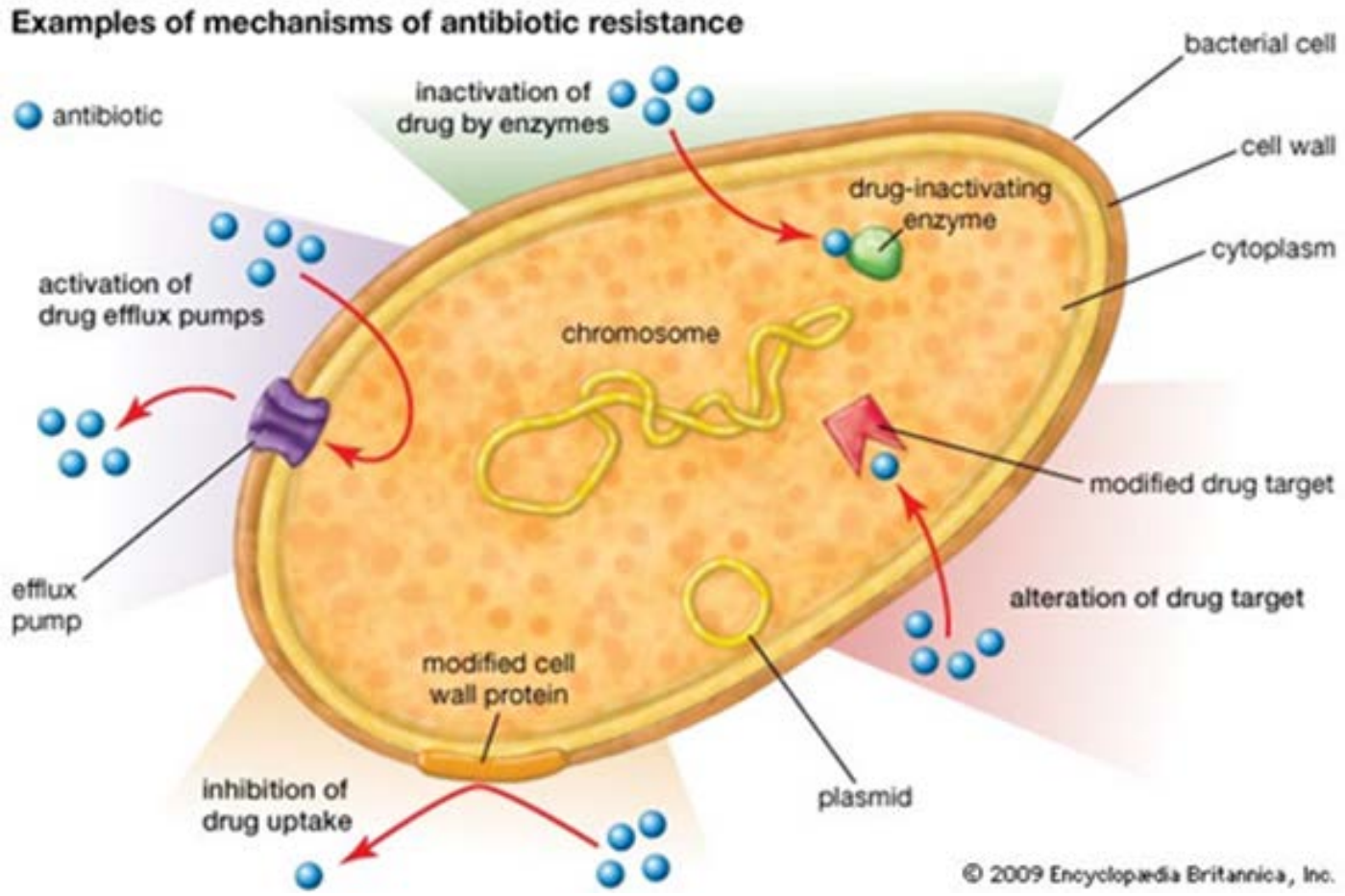
Source: Que YA, Moreillon P. Staphylococcus aureus. Mandells 2015. Stukalov O, et al. App Environ Micro 2008;74:5457.

Bacterial Resistance



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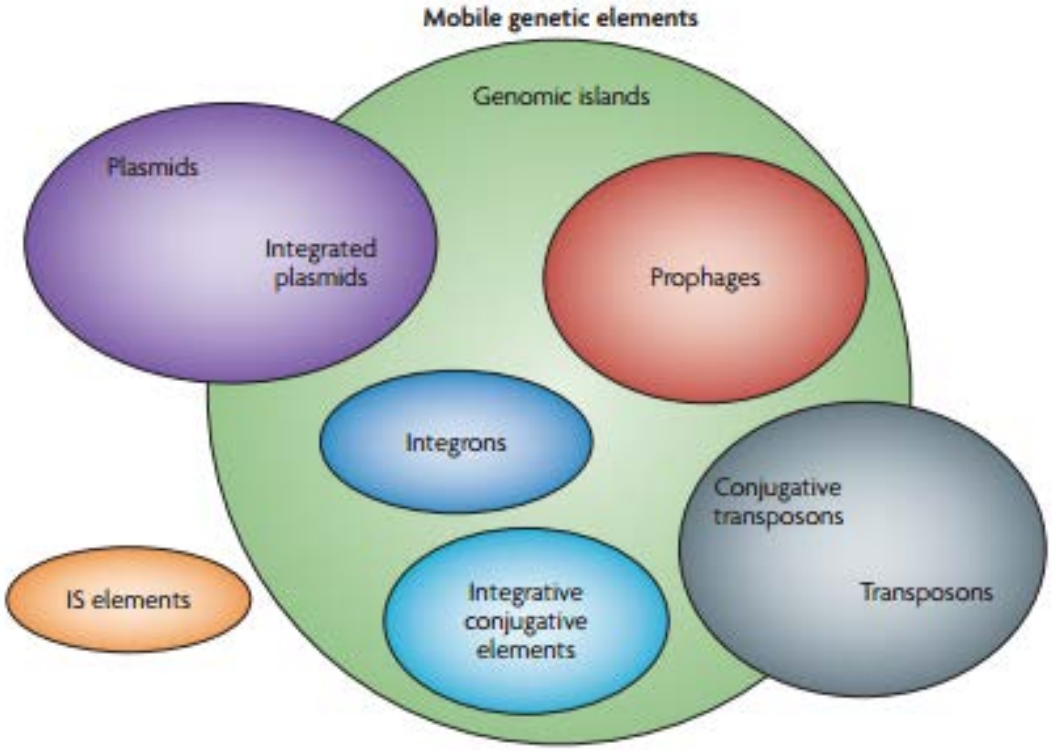
Source: M. Costello. Gram Negative Resistance 2013.

Mobile Genetic Elements

- **Plasmids and Integrative Conjugative Elements:** Allow for transfer of genetic material between organisms, from one bacteria to another bacteria.

- **Transposons / Integrons:** Allow for rearrangement of the genetic material (movement of resistance genes) within the genome of the bacteria.



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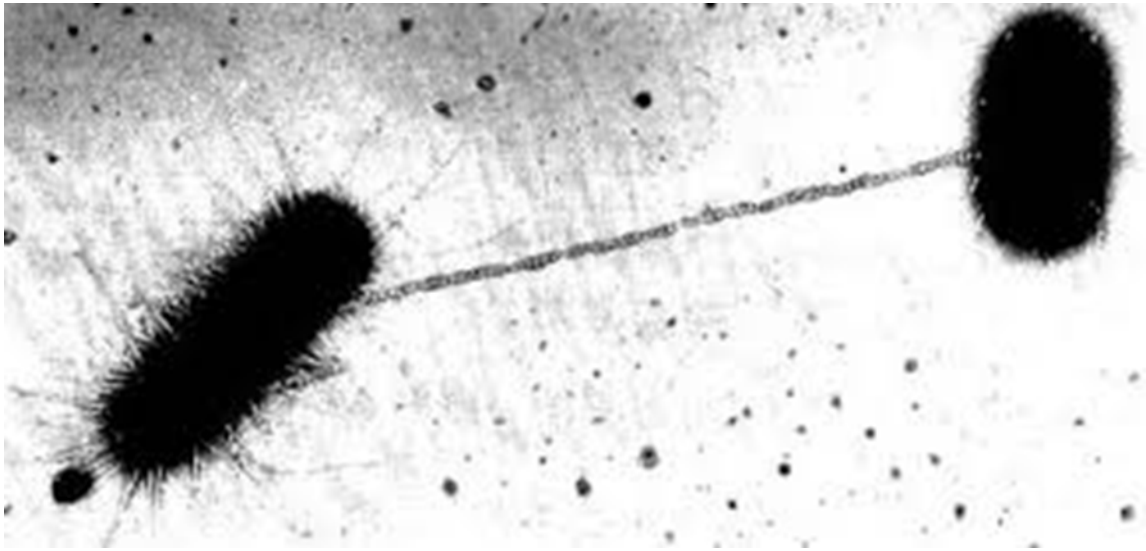
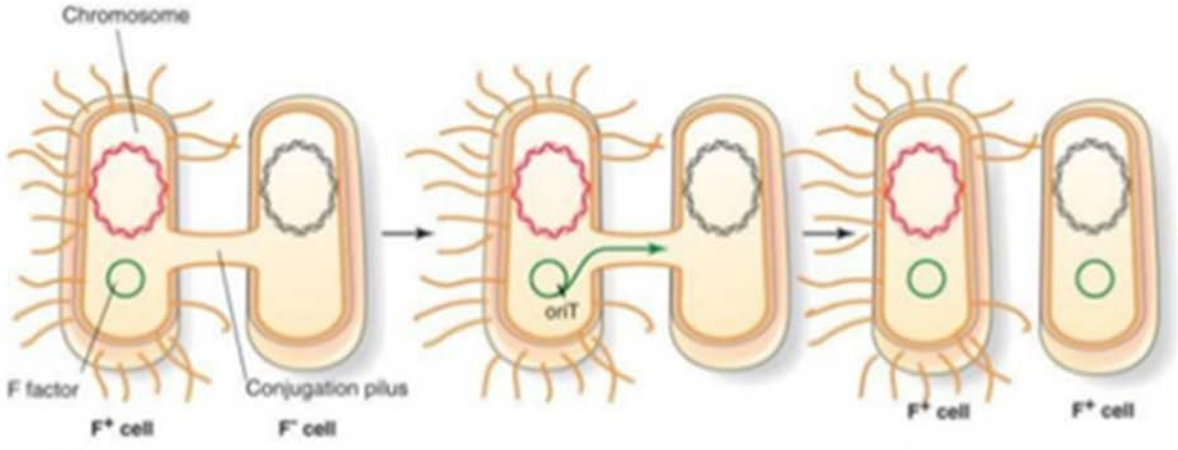
Source: Nature Reviews Microbiology 2010;8:373.

Sharing Genetic Pools

Acquisition of Resistance: Plasmids





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Source: Gilbert. D. IDBR 2012.

Molecular spread of antibiotic resistance genes

Bottom Line:

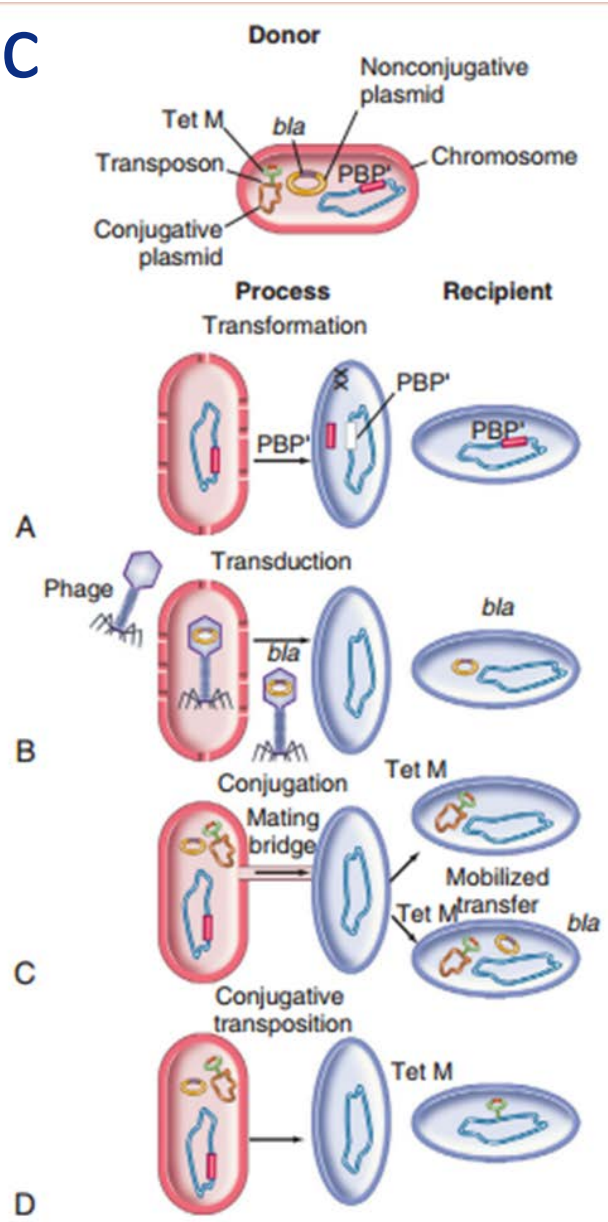
Organisms harbor multiple mechanisms of resistance and multiple methods to transfer genetic material.

Resistance can be intrinsic or acquired.

Maintenance comes at a metabolic cost.

Genes may be discarded by the organism if the pressure is no longer present

(i.e. the antibiotic is gone).



Source: Opal S, et al. Mandells. 2015.

Gram-Positive Resistance

Most Frequent Mechanisms

- *Staphylococcus aureus*
  - **MSSA:** Enzymatic inhibition - Penicillinase production
  - **MRSA: Progressive accumulation of multiple polymorphisms.**
    - Alteration of cell wall targets (hVISA - abnormally **thick cell wall**)
    - Modification of **cell wall charge / upregulation of PBP1** - Daptomycin
    - Alteration of target site - PBP2a (mecA) - Ceftaroline
    - Alteration of cell wall targets via plasmid mediated transfer of VanA from enterococcus. (VRSA)
- *Enterococcus* – unique mechanisms
  - **Diversion from the active site**
  - **Repulsion from the cell membrane**
  - Alteration of target enzymes (PBP5)
  - Altered ribosomal targets (aminoglycoside resistance)
  - Alteration of cell wall precursor targets (VRE)
  - Alteration of ribosomal targets (LZD resistance)

MSSA: Beta-Lactams vs Vancomycin

β-lactams are the standard of care for MSSA bacteremia.

- Vancomycin use is associated with increased mortality, bacteriologic and treatment failure.

- Switch from vancomycin to β-lactam therapy compared to β-lactams upfront still associated with higher infection-related mortality

McConeghy KW, et al. *Clin Infect Dis*. 2013;57(12):1760-1765.
Chang FY, et al. *Medicine.* 2003;82(5):333-339.
Stryjewski ME, et al. *Clin Infect Dis*. 2007;44(2):190-196.
Kim SH, et al. *Antimicrob Agents Chemother.* 2008;52(1):192-197.
Lodise TP, et al. *Antimicrob Agents Chemother*. 2007;51:3731-3733.

MRSA: Sustained Bacteremia

Clinical consequences

- Increased risk of **metastatic infection**: 45% after 10days
- Increased **mortality** rates with persistence ≥ 7 days: 58% vs 34%
- Three-fold increase in 30-day crude **mortality** rate with persistent MRSA bacteremia ≥ 7 days: 58.1% vs 16.7%.
- **Lower 30-day survival** for patients with persistent (41.9%) compared to nonpersistent MRSA bacteremia (83.3%).
- **Metastatic** risk increased in some reports as early as persistence of 3 or more days.

Source control - essential

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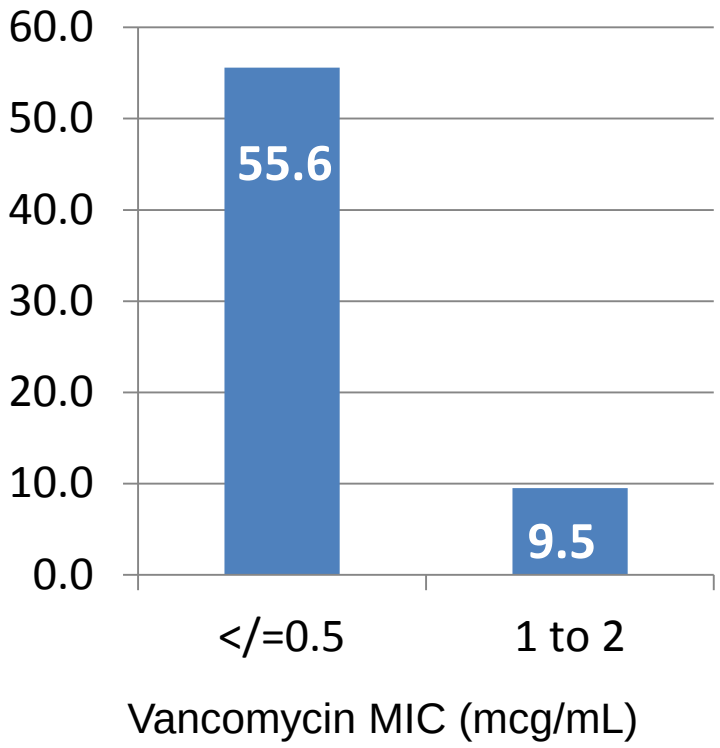
Source: Kullar et al, CID 2014;59:1455.

MRSA: MIC & Vancomycin Efficacy

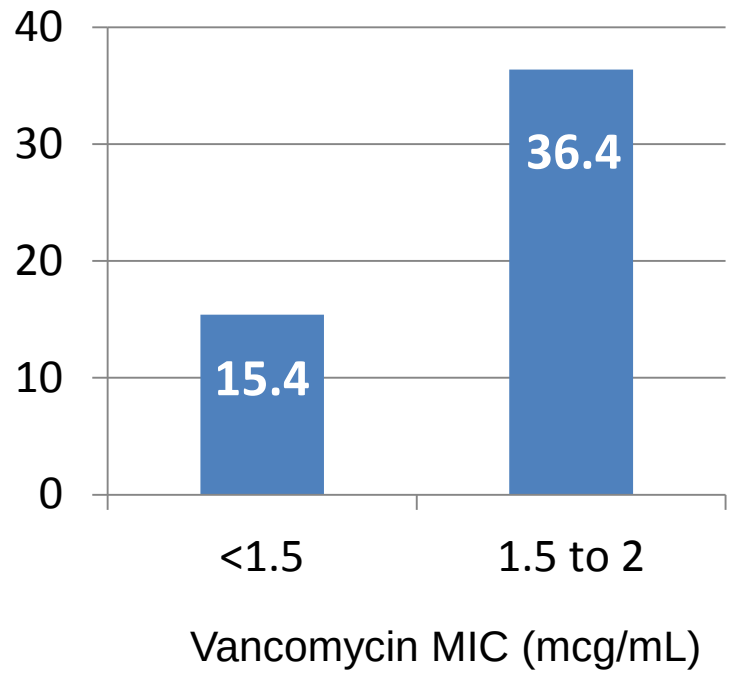
Treatment Success

Percent Response to Vancomycin - Based on MIC (n=30)



Treatment Failure

Percent Overall Failure Based on Vancomycin MIC (n=92)



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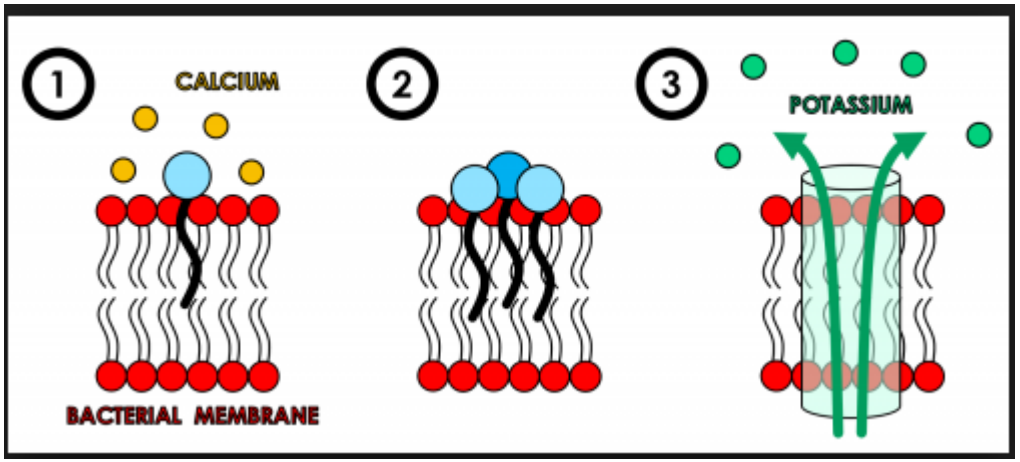
Source: Sakoulas G, et al. *J Clin Microbiol* 2004;42:2398.
Lodise TD, et al. *Antimicrob Agents Chemother* 2008;52:3315.

MRSA: A Case for Combination Therapy

Combinations to Avoid

- Vancomycin PLUS
  - Rifampin
  - Gentamicin
  - Exception: PVE – 3 drugs

Daptomycin MOA



What about B-lactams…..

- Vancomycin PLUS
  - Nafcillin
  - Ceftaroline
  - Cefazolin
- Daptomycin PLUS
  - Nafcillin
  - Ceftaroline
  - Cefazolin

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Source: https://uwaterloo.ca/leonenko-research-group

PBP1 Upregulation in *Staph aureus*

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Penicillin Binding Protein 1 Is Important in the Compensatory Response of *Staphylococcus aureus* to Daptomycin-Induced Membrane Damage and Is a Potential Target for β-Lactam–Daptomycin Synergy

Andrew D. Berti,[a] Erin Theisen,[b,c] John-Demian Sauer,[c] Poochit Nonejuie,[d] Joshua Olson,[d] Joseph Pogliano,[d] George Sakoulas,[e] Victor Nizet,[e] Richard A. Proctor,[c,f] Warren E. Rose[a]

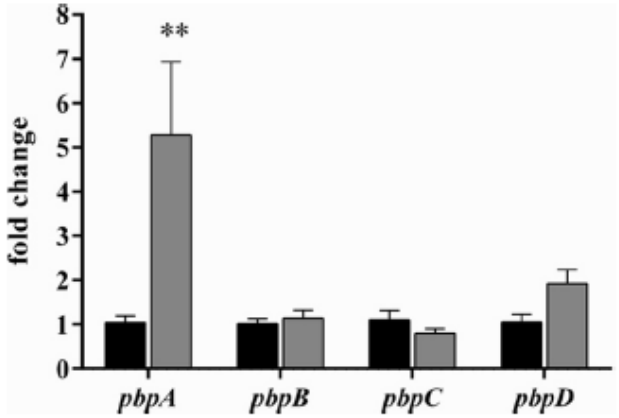

FIG 1 PBP expression profile following exposure to subinhibitory daptomycin. Black bars, no-antibiotic control; gray bars, 1/4× daptomycin MIC. Values marked with an asterisk denote statistically significant differences between daptomycin exposure and the no-antibiotic control (**, $P < 0.01$).

TABLE 2 Increase in daptomycin MICs in *S. aureus* COL upon *pbp1* induction

IPTG concn added (μM)	DAP MIC (mg/liter) in strain:	
	S. aureus COL	*S. aureus* $COL_{PspacPBP1}$
1	0.5	0.5
10	0.5	1
100	0.5	4
1,000	0.5	4

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Berti AD et al. AAC Jan 2016.

PBP1 Activity – Beta Lactams

Deciding on Combinations in *Staph aureus*

Relative activity at PBP1

- PBP1 appears to upregulate in Staph aureus following exposure to daptomycin in an effort to stabilize the cell membrane and allow for continued division.
- Coadministration of agents that target PBP1 augment the activity of daptomycin vs daptomycin non-susceptible *staph aureus*.

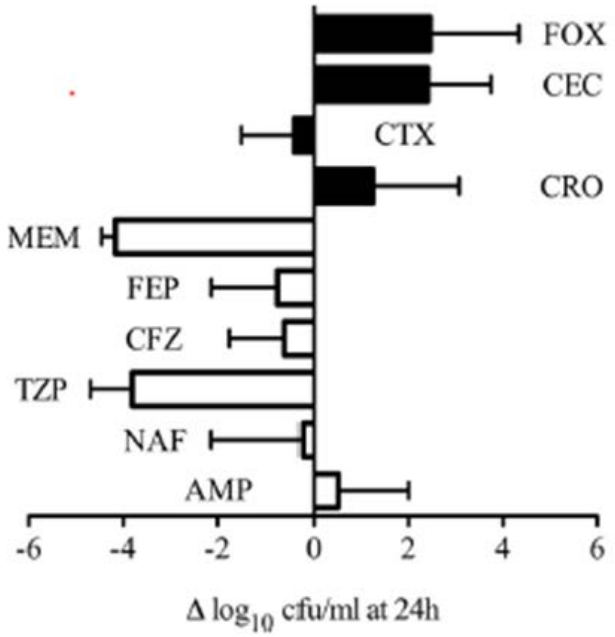
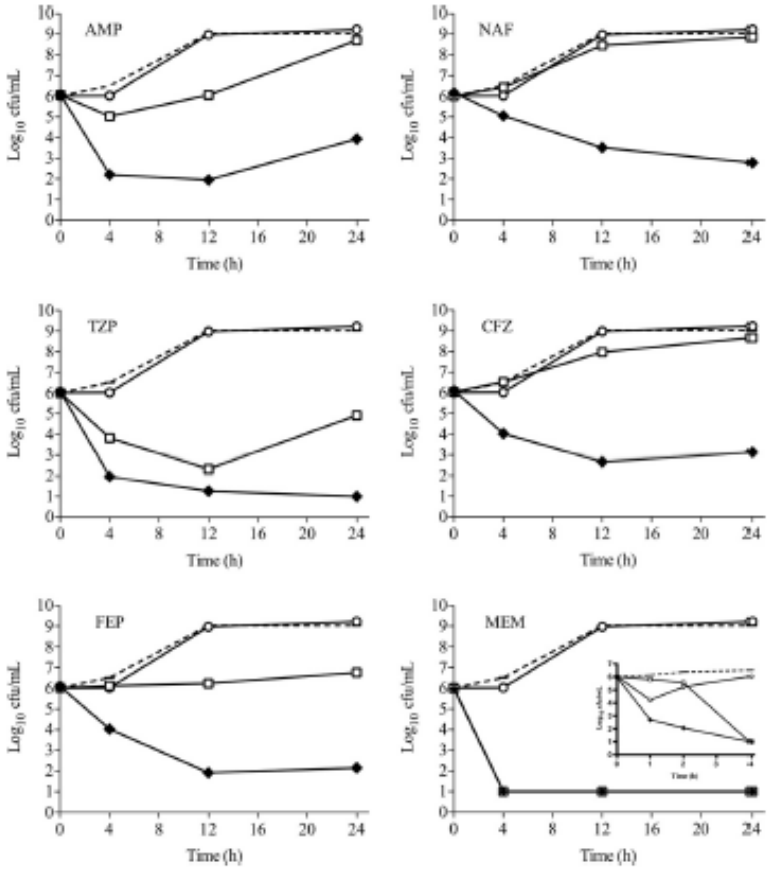


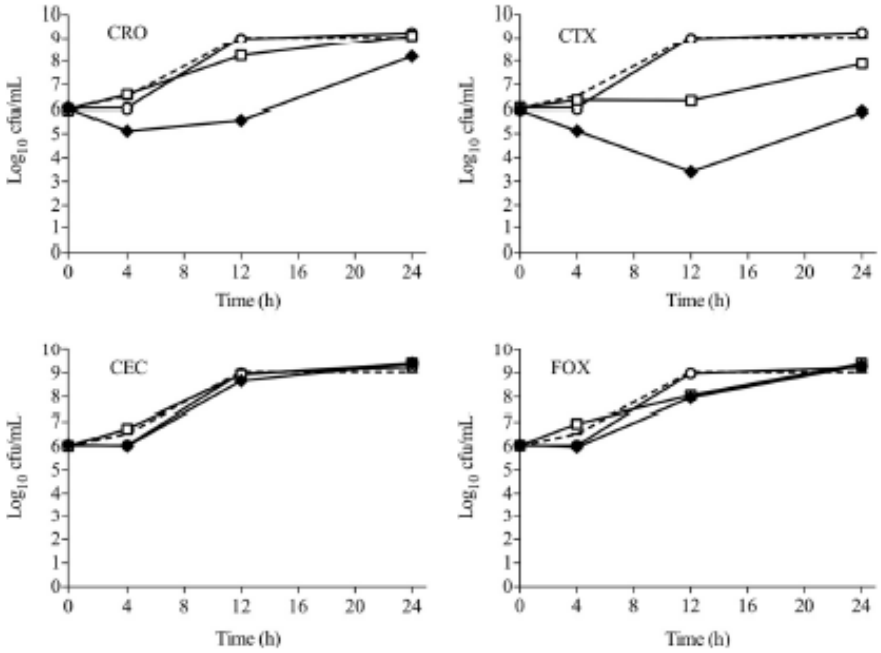
FIG 1 Activity of DAP in combination with β-lactam antibiotics against all five DNS MRSA strains tested. The change in the number of CFU/ml from time zero is presented as the mean with the standard error of the mean of the five strains. White bars, β-lactam antibiotics that preferentially bind to PBP1; black bars, β-lactam antibiotics that do not have PBP1 binding preference. Collectively, the mean activity in the PBP1 group was significantly greater than that in the non-PBP1 group (−1.50 versus 1.73 log CFU/ml, respectively; $P = 0.001$).

Berti AD, et al AAC 2013;57:5005.

Augmentation of Daptomycin in DNS MRSA and the Effect of PBP Selectivity

Enhanced activity in DNS MRSA with PBP1 active β-lactams





Lack of synergy observed with combination therapy vs DNS. (daptomycin plus β-lactams that act at other PBPs).

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Berti AD, et al AAC 2013;57:5005.

Augmentation of Host Defense Peptides

Nafcillin

Even though Nafcillin lacks direct activity vs MRSA…..

- Exposures to nafcillin significantly **increased killing of *S. aureus* by selected endogenous host defense peptides.**
- Pretreatment with nafcillin reduced MRSA virulence in a murine model.
- Similar augmentation of the innate immune system has been observed in vitro with ceftaroline

Cationic Host Defense Peptides Augmented by Nafcillin

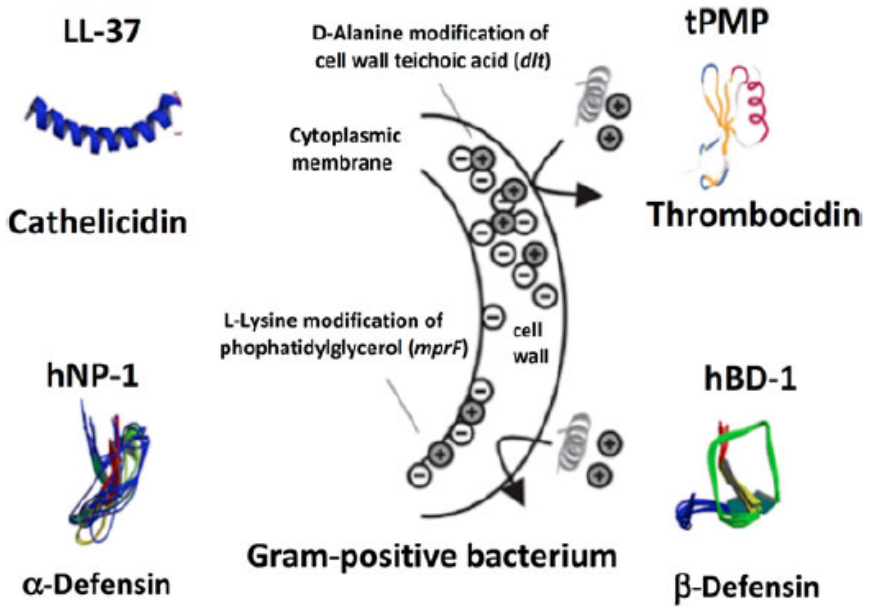

Figure 1. Examples of cationic antimicrobial host defense peptides. Abbreviations: hBD-1, human beta-defensin-1; hNP-1, human neutrophil peptide-1; mprF, multiple peptide resistance factor; tPMP, thrombin-induced platelet microbicidal protein.

Source: Dhand A, et al. Clin Infect Dis. 2011;53:158–63.
Sakoulas G, et al. Clin Ther. 2014.
Sakoulas G. et al. J Mol Med. 2014;92;139.
Kullar et al. CID 2014;59:1455.

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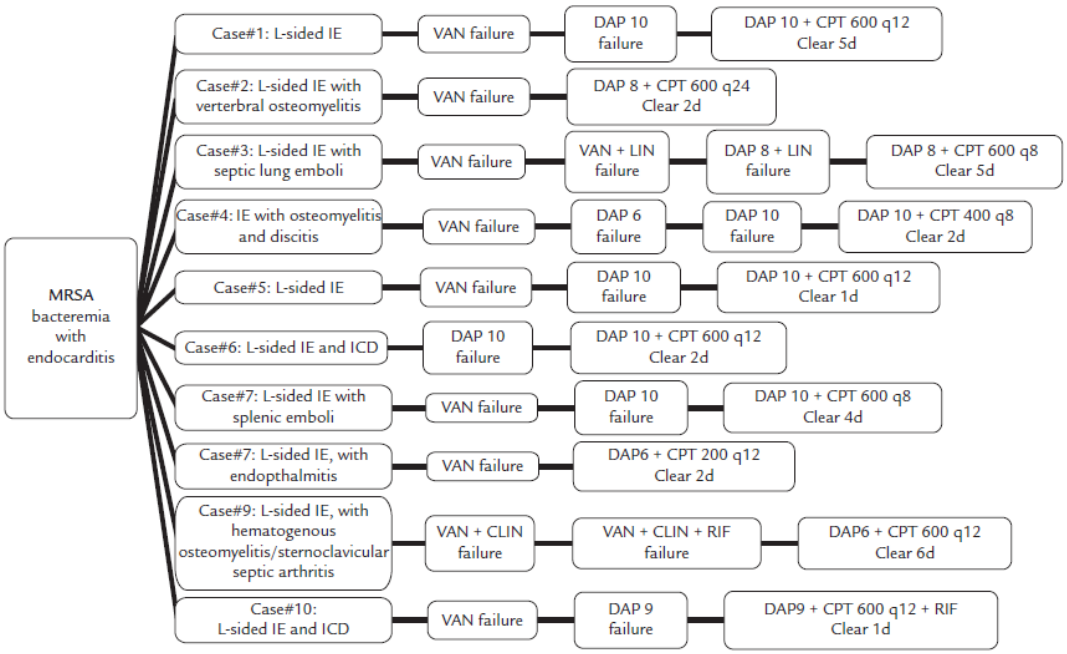
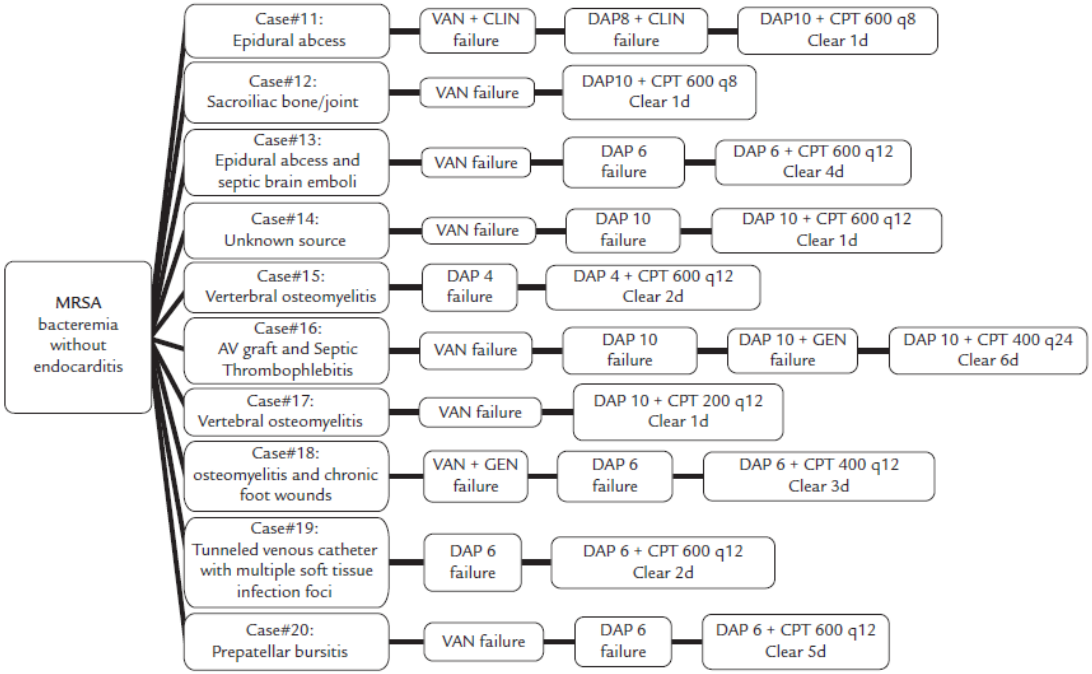


Salvage Therapy for Persistent Staphylococcal Bacteremia: Ceftaroline plus Daptomycin

Deep-seated , persistent Staph infections (n=26)

- Mean duration of bacteremia: 10 days (3-23).
- Mean time to clearance after Daptomycin + Ceftaroline: 2 days (1-6).
- **Survival: 25/26pts**

Source: Sakoulous et al Clin Therapeut 2014;36:1317.



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Question 1

Most all available β-lactams lack activity against MRSA. Choose the agent below presently available in the US that has retains activity against MRSA via affinity for penicillin-binding protein 2A (PBP2A):

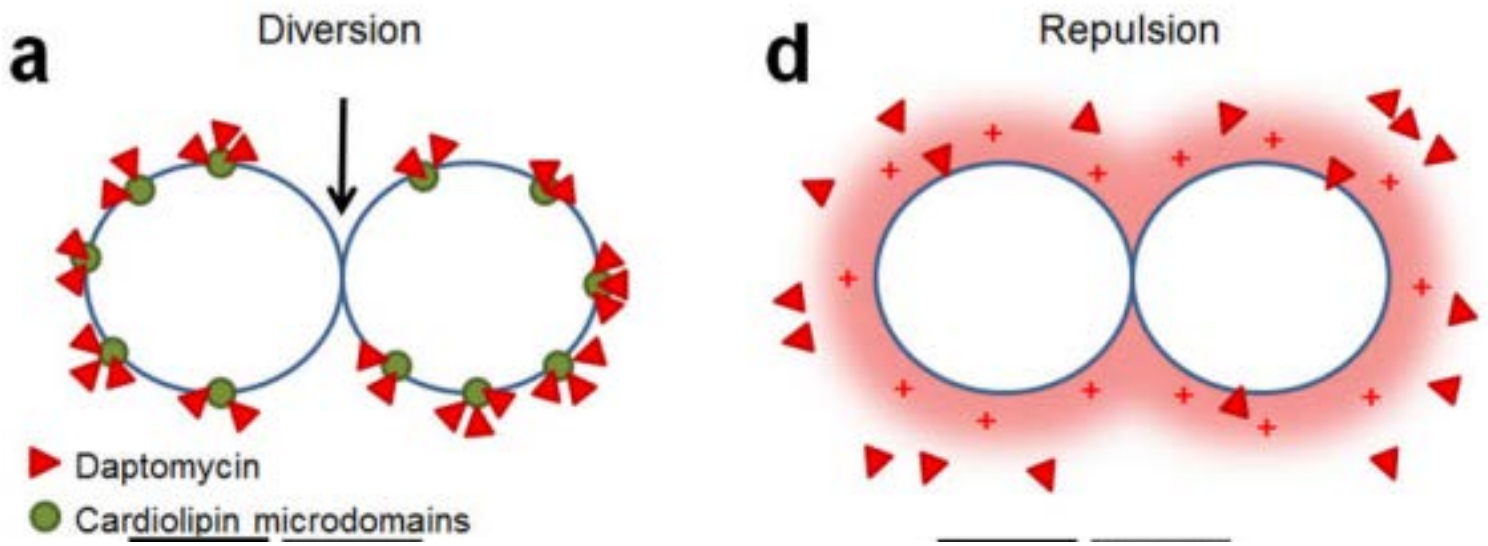
a) Ceftolozane / Tazobactam
b) Ceftazidime/Avibactam
c) Ceftaroline
d) Doripenem

Combination Therapy: VRE

Mechanism Resistance of *Enterococci* DIFFERENT from *Staph aureus*

Enterococci: Most Common - LiaFSR

Cluster of Genes well preserved in Enterococci - expressed under stress that lead to cell membrane adaptation and resistance to Daptomycin



Source: Tran et al. Ann NY Academ Sci 2015. .

Question 2

MA 53yo female with decompensated liver disease is admitted to the ICU with septic shock. Blood cultures are positive for vancomycin resistant enterococcus (VRE) with the following with the following susceptibilities: Ampicillin MIC >8 Resistant; Daptomycin MIC 4 Sensitive; Linezolid MIC 6 Resistant; Vancomycin MIC >16 Resistant. Daptomycin 6mg/kg is started. One week later blood cultures remain positive for VRE. Allergies: NKDA. SrCr 1.6mg/dL. Which of the following treatment options may be considered:

a) Continue Daptomycin and add gentamicin 1mg/kg q8h. Repeat blood cultures every 48hours until clearance.

b) Vancomycin for target trough 15-20mcg/mL plus gentamicin 1mg/kg q8h

c) Linezolid 600mg IV q8h

d) Daptomycin 10mg/kg plus Ceftaroline 600mg IV q12h

TABLE 2 Summary of changes induced on daptomycin-susceptible and -nonsusceptible VRE by ampicillin or ceftaroline

	Result[a]	
Characteristic	DAP-susceptible VRE	DAP-nonsusceptible VRE
Synergy with DAP		
AMP	+	–
CPT	+	+
Effect on cell wall thickness		
AMP	↓ ↓	↑
CPT	↓	↑
Effect on membrane fluidity		
AMP	–	–
CPT	–	↑
Poly-L-lysine binding		
AMP	–	↑
CPT	↑	↑
Bodipy-DAP binding		
AMP	–	↑
CPT	↑	↑
LL37 binding and activity		
AMP	↑	↑
CPT	↑ ↑	↑ ↑

[a] +, yes; –, no; ↓ ↓, more-marked decrease; ↓, decrease; ↑ ↑, more-marked increase; ↑, increase.

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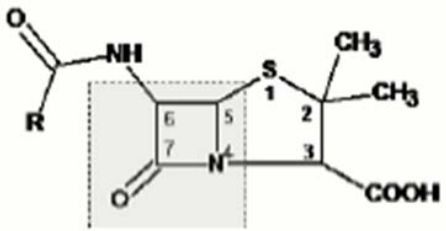
Source: Sakoulas G, et al. AAC 2014.

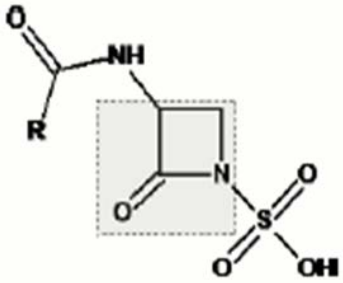
Gram-Negative Resistance

Focus on β-lactamases: Same Target / Smarter Enzymes

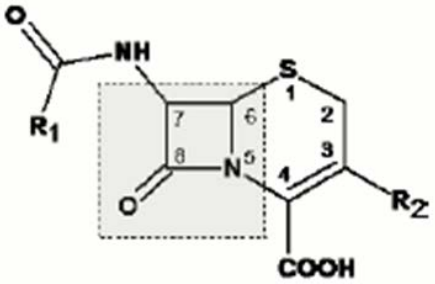
Penicillins



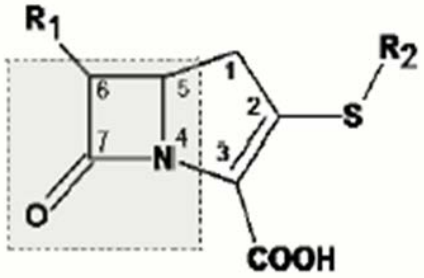
Monobactams



Cephalosporins



Carbapenems



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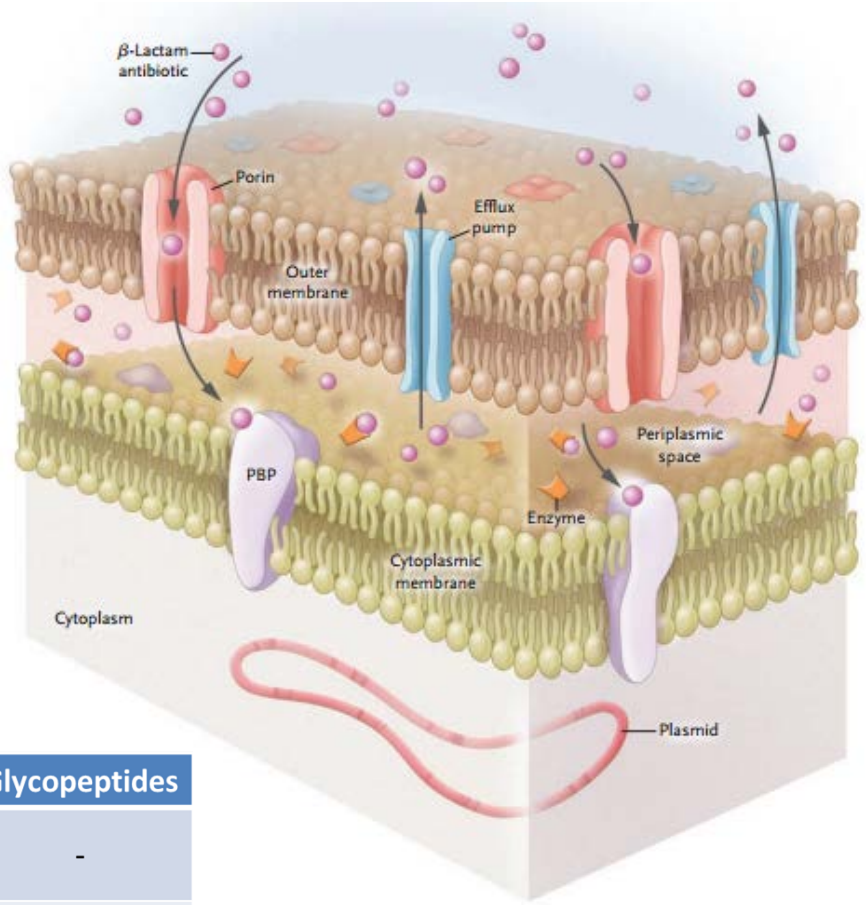
Gram-Negative Resistance

- Production of **β-lactamases**
  - Enzymatic destruction of antibiotic
  - ESBLs and carbapenemases
- **Permeability alteration/Porin Mutations**
  - Antibiotic entry is limited
  - Porins: barrel shaped proteins that cross cell membranes & act as a port through which nutrients, toxins & antibiotics diffuse
- Antibiotic extrusion by **efflux pumps**
  - Antibiotic is rapidly pumped out
  - Rapidly pump out antibiotics before they can act on target site
- **PBP alterations** (rare)
  - PBP 7-8 in A. baumanii

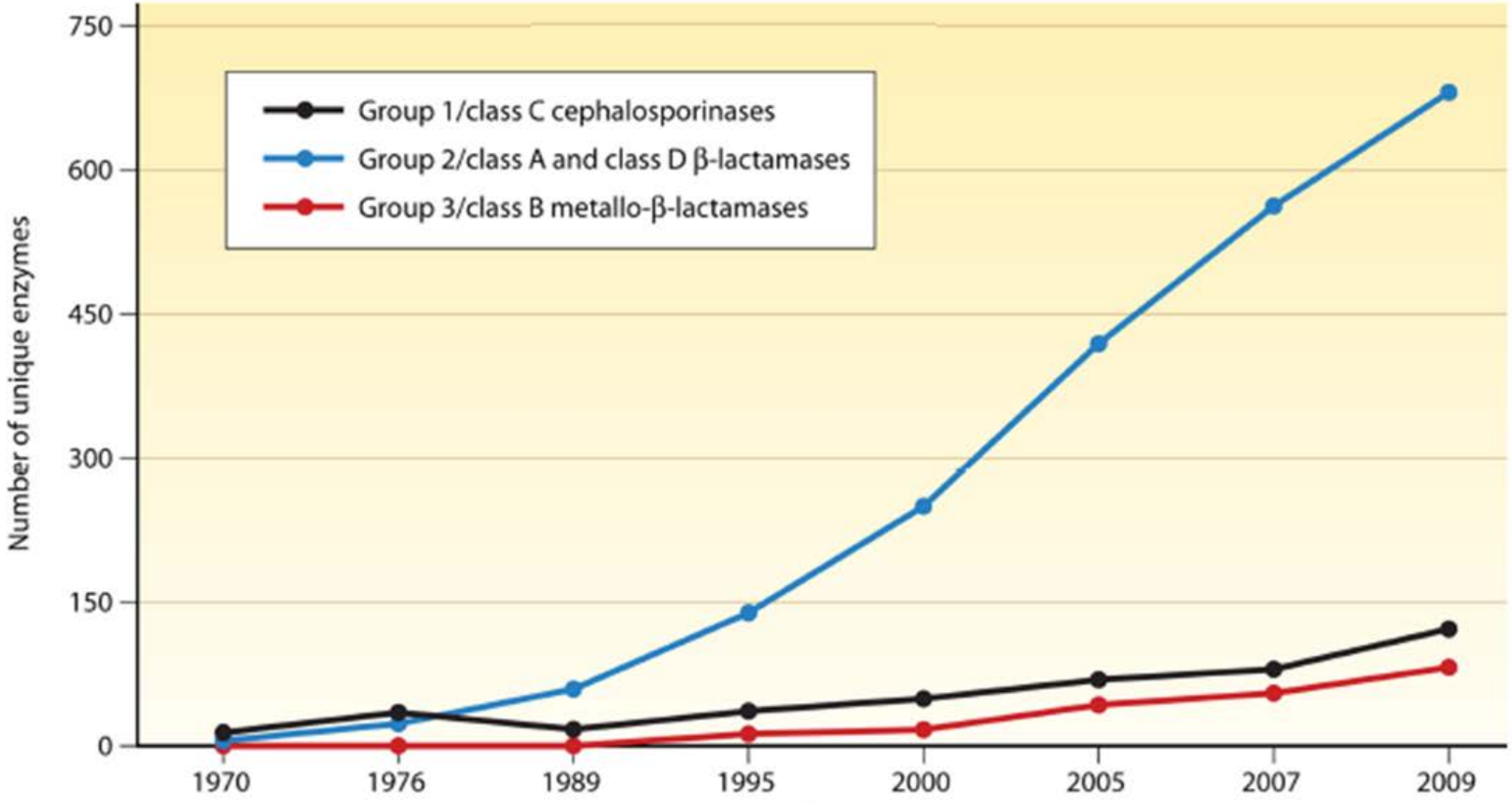


MOR	B-Lactams	Aminoglycs	Quinolones	Glycopeptides
Enzymatic Inactivation	+++	+++	-	-
Decreased Permeability	+	+	+	++
Efflux	+	+	+	-
Alteration of Target Site	++	++	+++	+++

Source: Mandells 2015.
Munoz-Price. N Engl J Med 2008;358:1271.

Identification of Beta-Lactamases

Increase in Identification 1979-2009



Increase in beta-lactamases identified 1970-2009. Based on functional groups. Molecular sequence database now maintained by NIH (2015)

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Source: Bush K, Jacoby GA. AAC 2010.

B-Lactamases

Classifications and targets

Class	Examples	Encodes Resistance to:
A (Serine)	Staph penicillinases	Penicillin, ampicillin, amoxicillin
	TEM-1; SHV-2	Penicillin, ampicillin, amoxicillin, 1st generation cephalosporins
	ESBLs	Penicillins, cephalosporins, aztreonam. Inhibited by BLIs.
	Plasmid Carbapenemases (**KPCs**, IMI)	Penicillins, cephalosporins, β-lactams / β-lactamase inhibitors, carbapenems, aztreonam
B (Zinc)	Metallo-β-lactamases (**NDM**)	Penicillins, cephalosporins, β-lactams / β-lactamase inhibitors, carbapenems. Inactive against aztreonam.
C (Serine)	**AmpC** β-lactamases	Penicillins, cephalosporins, β-lactams / β-lactamase inhibitors, aztreonam
D (Serine)	**OXA** carbapenemases	Penicillins, cephalosporins, β-lactams / β-lactamase inhibitors, carbapenems. Some subtypes **remain sensitive to 3rd/4th gen cephalosporins.**

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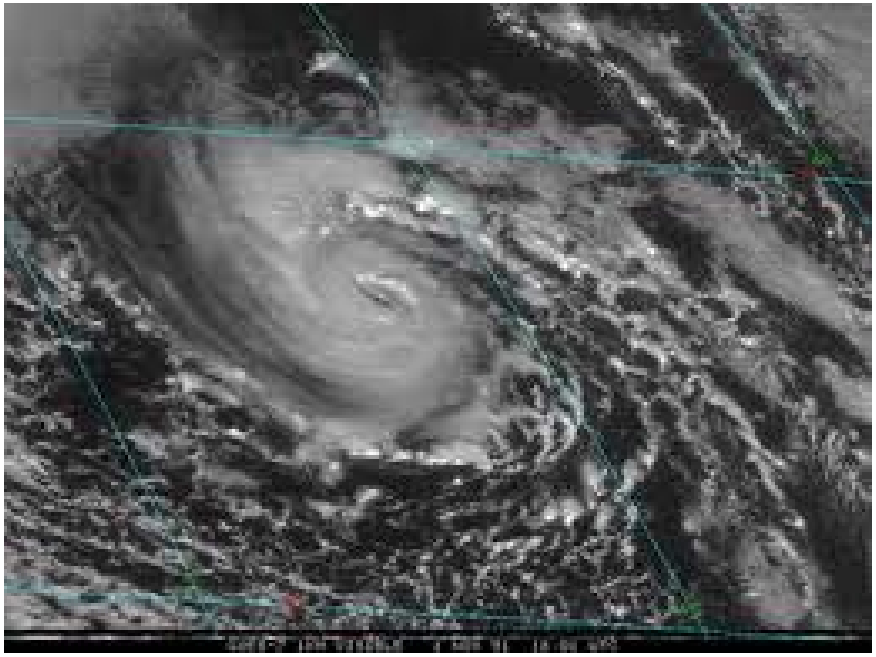
Source: Murray PR. Antimicrobial Resistance Primer. IDBR 2012.

Multi-Drug Resistance

The Perfect Storm: Focus on Carbapenem-Resistant Gram-Negatives

In reality: Bacteria express **multiple** mechanisms of drug resistance leading to MDR isolates we see in clinical practice.



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Source: NOAA.gov

Carbapenem Non-Susceptible GNs

US Hospitals (n=348). All inpatient, non-duplicate GN isolates.
July 2015 – June 2016

Regional variation

Table 3. Regional differences in carbapenem non-susceptible rates/1000 admissions in the most commonly reported pathogens

Region	States	Carb NS per 1000 Admissions (n/N) *P. aeruginosa*	Carb NS per 1000 Admissions (n/N) *K. pneumoniae*	Carb NS per 1000 Admissions (n/N) *E. coli*
2	NJ, NY, PR, VI	2.67 (1022/382,854)	1.06 (406/382,854)	0.10 (40/382,854)
3	DE, DC, MD, PA, VA, WV	1.35 (209/154,291)	0.36 (55/154,291)	0.06 (10/154,291)
4	AL, FL, GA, KY, MS, NC, SC, TN	1.79 (2493/1,393,715)	0.18 (254/1,393,715)	0.10 (141/1,393,715)
5	IL, IN, MI, MN, OH, WI	1.36 (2005/1,475,464)	0.40 (595/1,475,464)	0.05 (79/1,475,464)
6	AR, LA, NM, OK, TX	1.48 (1387/934,689)	0.10 (97/934,689)	0.07 (63/934,689)
9	AZ, CA, HI, Pacific Islands	2.03 (929/458,407)	0.45 (207/458,407)	0.08 (37/458,407)
10	AK, ID, OR, WA	0.27 (84/310,193)	0.03 (10/310,193)	0.02 (7/310,193)
1, 7, 8	Other	1.07 (153/143,178)	0.03 (4/143,178)	0.06 (8/143,178)
Overall		**1.58 (8282/5,252,791)**	**0.31 (1628/5,252,791)**	**0.07 (385/5,252,791)**

Variation by Pathogen

Table 4. Carbapenem non-susceptible rates and rates per 1000 admissions by pathogen

Pathogen	Carb NS % (n/N)	Carb NS per 1000 Admissions (n/N)
P. aeruginosa	21.9% (8282/37,733)	1.58 (8282/5,252,791)
K. pneumoniae	4.8% (1628/34,018)	0.31 (1628/5,252,791)
P. mirabilis	5.1% (847/16,545)	0.16 (847/5,252,791)
E. cloacae	6.0% (679/11,243)	0.13 (679/5,252,791)
M. morganii	15.9% (511/3209)	0.10 (511/5,252,791)
E. coli	0.4% (385/96,271)	0.07 (385/5,252,791)
E. aerogenes	7.6% (284/3755)	0.05 (284/5,252,791)
S. marcescens	3.5% (175/5013)	0.03 (175/5,252,791)
C. freundii	2.6% (95/3660)	0.02 (95/5,252,791)
Overall	6.1% (12,886/211,447)	2.71 / 1000 admissions (14,236/5,252,791)

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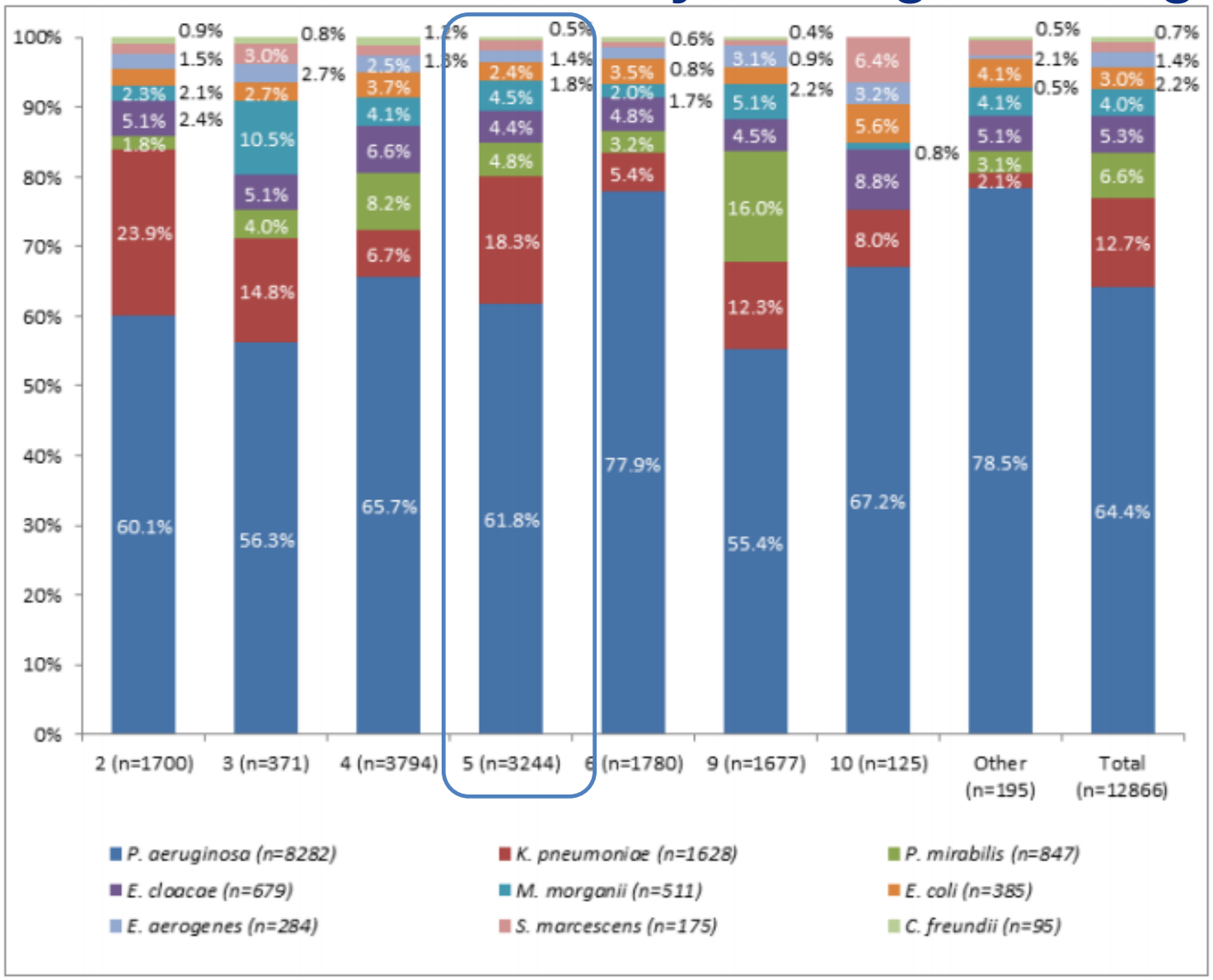
Source: McCann et al . Poster #1492. IDWeek 2016.

Carbapenem Non-Susceptible Isolate Distribution by Pathogen & Region



Source: McCann E, et al. Poster 1492. IDWeek 2016.

Carbapenem-Resistent Enterobacteriaceae (CREs)

CREs: Generic term for CR-*Enterobacteriaceae* (KPCs, MBLs and OXAs)

- KPCs: Class A
- North Carolina 1996.
- Now endemic.
- Mortality: 24-70%
- Reservoirs: LTACs
- KPC Colonization rates in Chicago LTAC: 40-50%

Table 3. Adjusted Associations Between Hospital Characteristics (Centrality and Long-Term Acute Care Hospital Sharing) and Carbapenem-Resistant *Enterobacteriaceae* Rates (per 10 000 Patient-days) Among Short-Term Acute Care Hospitals in Illinois

Hospital Characteristic	Rate Ratio	95% Confidence Interval	*P* Value
Degree centrality, by region[a]			
Chicagoland[b]	1.027	1.002–1.052	.03
Non-Chicago urban[b]	1.025	1.002–1.048	.03
Rural county[b]	1.056	1.030–1.082	<.0001
Long-term acute care hospital sharing[a]			
≥4 vs <4 patients	2.08	.85–5.08	.11

[a] Multivariable model is adjusted for each hospital's total number of beds and county type–degree centrality interaction.

[b] For degree centrality, rate ratio represents increase in carbapenem-resistant *Enterobacteriaceae* rate for each additional hospital connection.

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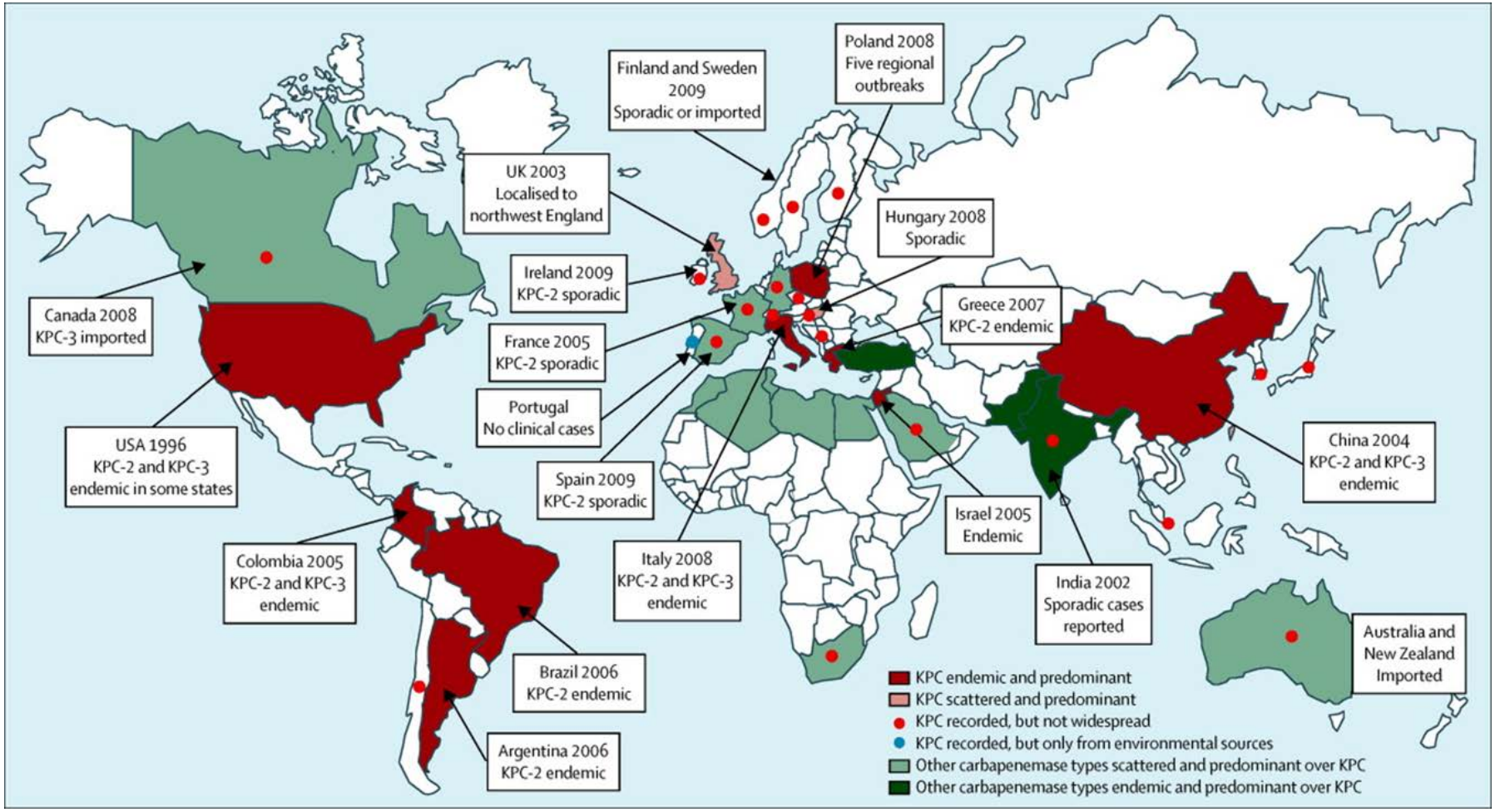
Source: Ray MR, et al. CID; 2016;83:889

KPC Carbapenemases

Growing Reports - Regional Variation / Endemic to North America



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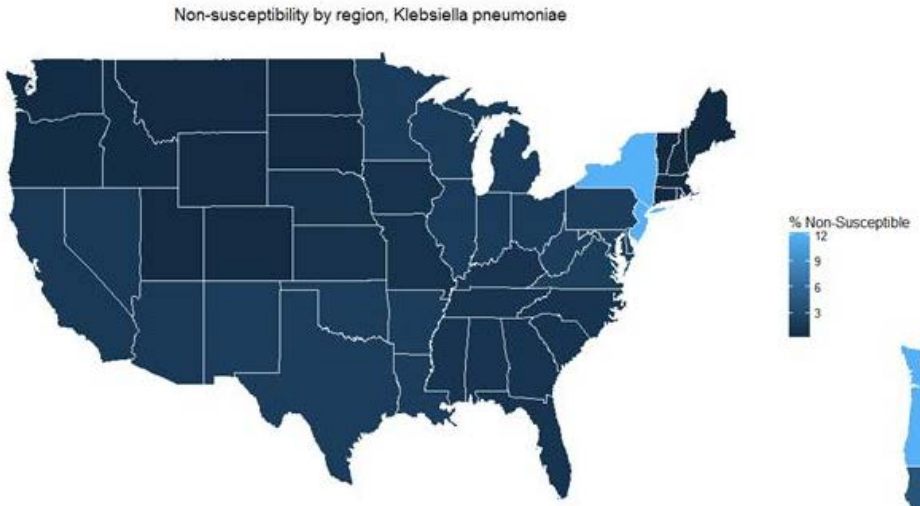
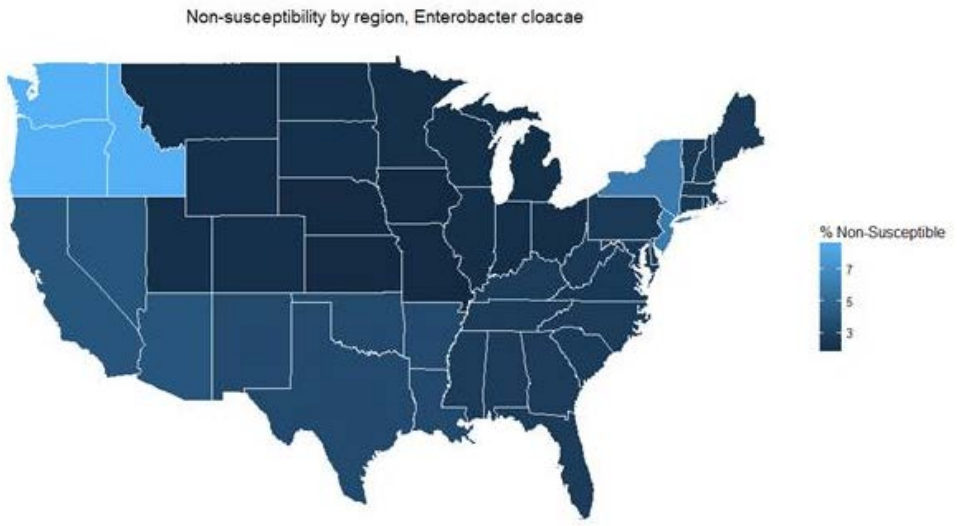
Source: Munoz-Price et al. Lancet Infectious Diseases 2013.

Regional Variation Among Species

Carbapenmase-Producing
Klebsiella pneumoniae



Carbapenmase-Producing
Enterobacter cloacae



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Source: Perez F, et al. Poster 349. IDWeek 2016.

KPC – *Klebsiella Pneumoniae* Bacteremia

Combination therapy

- Multi-centered, retrospective cohort in 3 Italian hospitals
- Patients with KPC K. pneumoniae bacteremia (n=125)
  - Treatment: Mono Rx vs Dual Rx vs Triple Drug Rx
- Outcomes: Death at 30 days
- Impact of definitive antimicrobial therapy

Agent	Doses	Percent Susceptible
Colistin	Loading Dose followed by 180-270mg/day divided Q8-12h	88%
Tigecycline	Loading Dose followed by 100-200mg/day divided Q12h	91%
Gentamicin	4-5mg/kg once daily	94%
Meropenem	2g Q8h – each dose infused over ≥3 hours	0.8% (63% MIC ≥16)

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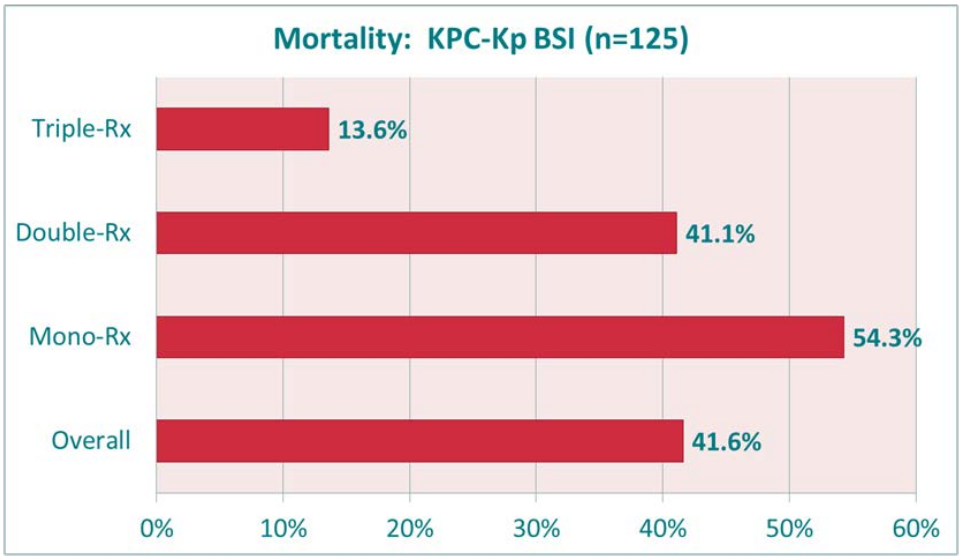
Source: CID 2012;55:943

KPC-*Klebsiella Pneumoniae* Bacteremia

Treatment	Overall Mortality
Mono-Therapy	**54.3%**
Gentamicin	80%
Tigecycline	52.6%
Colistin	50%
Double-Therapy	**41.1%**
Colistin + Gent	57%
Tige + Gent	50%
Tige + Colistin	30.4%
Triple-Therapy	**13.6%**
Tige + Gent + Mero	16.6%
Tige + Colistin + Mero	12.5%



Multivariate analysis: triple-drug regimen of ***tigecycline, colistin & meropenem*** significantly reduced the risk of death. Meropenem MICs: 63% were ≥16mg/L

November 2016: Ceftazidime/Avibactam Likely Foundation Therapy

(Carbapenemases Class A & Class D)

Monotherapy vs Combination Therapy: Unknown. Need Data.

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Source: CID 2012;55:943

New Options for MDR GNs

Ceftolozane/Tazobactam & Ceftazidime/Avibactam

Drug	Indication/Spectrum	Dosing	Adverse Events

Ceftolozane/Tazobactam (Zerbaxa™)[1]
 	
Expected Spectrum:
Carbapenem-Resistant *Pseudomonas spp.*
ESBLs
No CRE / No KPC
No ACB
	• **Complicated intra-abdominal infection (in combination with metronidazole)** caused by: *Enterobacter cloacae, E. coli, Klebsiella oxytoca, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Streptococcus salivarius*
	• **Complicated UTI (including pyelonephritis)** caused by: *E. coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa*
		• Complicated intra-abdominal infection: 1.5g Q8H over 1H for 4-14D
		• Complicated UTI (including pyelonephritis): 1.5g Q8H over 1H for 7D
		• Renal adjustments: CrCl 30-50: 750mg Q8H
		  ○ CrCl 15-29: 375mg Q8H
		  ○ HD: 750mg x1 dose then 150mg Q8H (on HD days, give dose as early as possible after HD)
		• Concern for decreased efficacy with CrCl 30-50 mL/min
		Note: Based on PK/PD data, current phase 3 trial (April 2015) is evaluating Ceftolozane/Tazobactam 3g (over 1hr) IV q8h for treatment of VAP
			• Concern for cross reactivity with beta-lactams
			• *C. difficile* associated diarrhea
			• >5%: nausea, diarrhea, headache, pyrexia

Ceftazidime/Avibactam (Avycaz™)[2]
 	
Expected Spectrum:
ESBLs
KPCs
+/- Pseudo
No NMB
Variable Ox-A
	• **Complicated intra-abdominal infections (in combination with metronidazole)** caused by: *Enterobacter cloacae, E. coli, Klebsiella oxytoca, Klebsiella pneumonia, Proteus mirabilis, Providencia stuartii*
	• **Complicated UTI (including pyelonephritis)** caused by: *E. coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus* spp., *Pseudomonas aeruginosa*
		• Complicated intra-abdominal infection : 2.5g Q8H over 2H for 5-14D (2g ceftazidime/0.5g avibactam)
		• Complicated UTI (including pyelonephritis): 2.5g Q8H over 2H for 7-14D
		• Renal adjustments: CrCl 31-50: 1.25g Q8H
		  ○ CrCl 16-30: 0.94g Q12H
		  ○ CrCl 6-15: 0.94g Q24H
		  ○ CrCl ≤5: 0.94g Q48H
		• NOTE: concern for decreased efficacy with CrCl 30-50mL/min
			• Concern for cross reactivity with beta-lactams
			• *C. difficile* associated diarrhea
			• Seizures, status epilepticus, encephalopathy, coma, neuromuscular excitability have been reported
			• >10%: nausea and vomiting, constipation, anxiety
			• >5%: increased AlkPhos, increased ALT

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Source: AHC ASP. June 2015.

Question 3

A 49yo male is admitted from a nearby long term care facility in septic shock. Patient has a history of chronic non-healing sacral ulcers and recurrent UTIs. Blood cultures from the LTAC 48hrs prior to admission are reported to as carbapenem-resistant *E.coli*. Surgery and ID consults are obtained.

Which of the following regimens may be best treatment at this time:

a) Meropenem 2g IV q8h plus Tigecycline 50mg IV q12h
b) Polymyxin B 60mg IV q12h plus Fosfomycin 3g PO daily
c) Ceftolozane/Tazobactam 3g IV q8h plus Polymyxin B 60mg IV q12h
d) Ceftazidime-Avibactam 2.5g IV q8h plus Amikacin 15mg/kg q24h

Metallo-β-Lactamases (MBLs/NDMs)

Newest MDR GN of concern: MBLs. Isolated: Southeast Asia - 2008

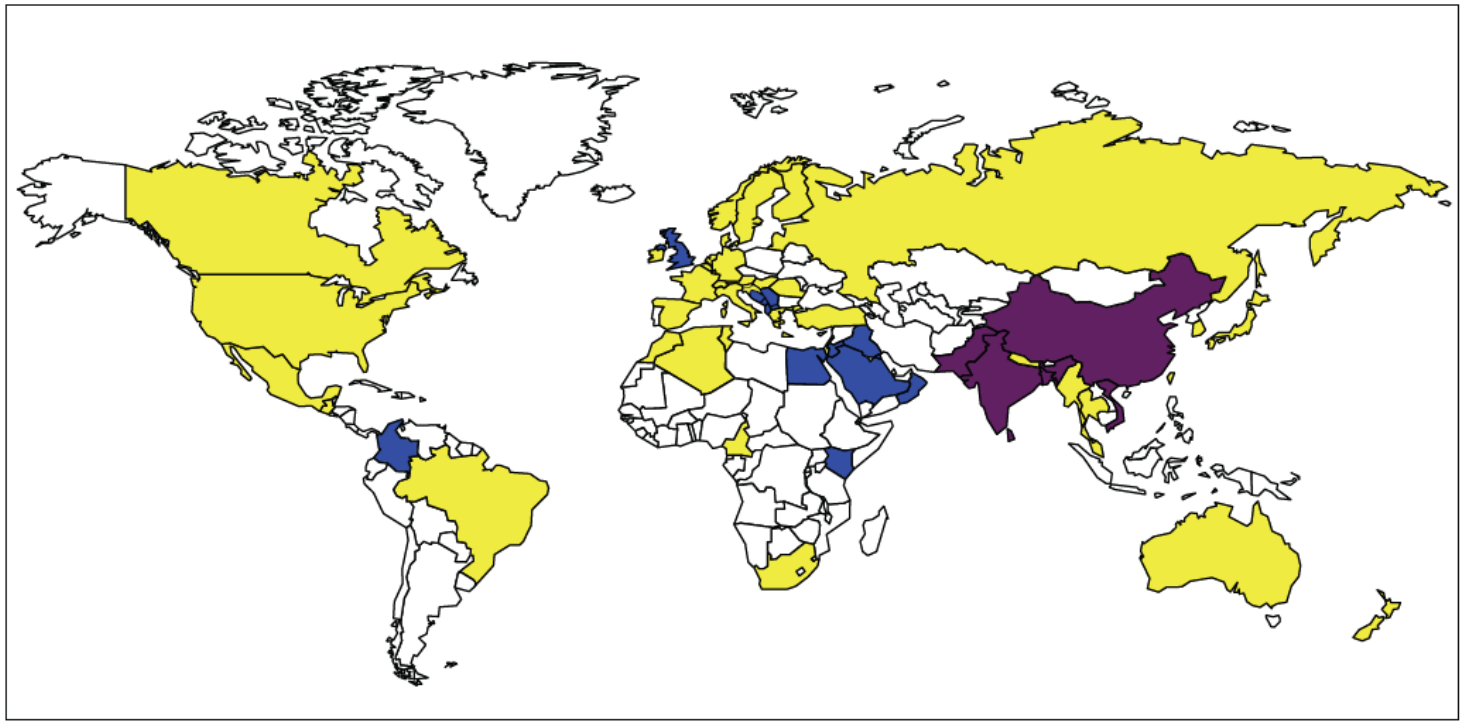

FIGURE 2: Geographical distribution of NDM producers.

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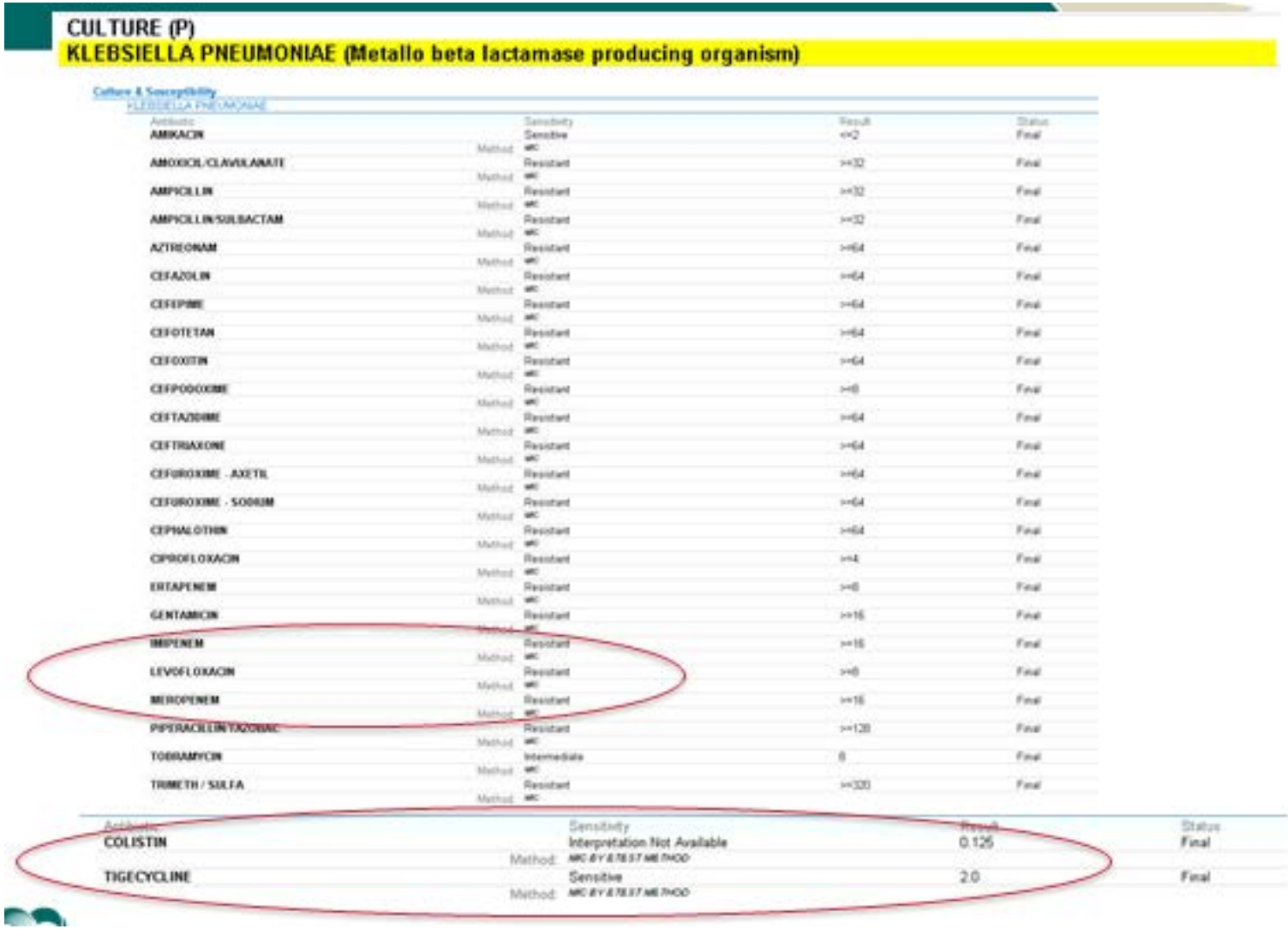
Source: Dortet et al. BioMed Res Int. 2014

NMB-Klebsiella



CULTURE (P)

KLEBSIELLA PNEUMONIAE (Metallo beta lactamase producing organism)

Culture & Susceptibility

KLEBSIELLA PNEUMONIAE

Antibiotic		Sensitivity	Result	Status
AMIKACIN		Sensitive	<=2	Final
	Method	MIC		
AMOXICIL/CLAVULANATE		Resistant	>=32	Final
	Method	MIC		
AMPICILLIN		Resistant	>=32	Final
	Method	MIC		
AMPICILLIN/SULBACTAM		Resistant	>=32	Final
	Method	MIC		
AZTREONAM		Resistant	>=64	Final
	Method	MIC		
CEFAZOLIN		Resistant	>=64	Final
	Method	MIC		
CEFEPIME		Resistant	>=64	Final
	Method	MIC		
CEFOTETAN		Resistant	>=64	Final
	Method	MIC		
CEFOXITIN		Resistant	>=64	Final
	Method	MIC		
CEFPODOXIME		Resistant	>=8	Final
	Method	MIC		
CEFTAZIDIME		Resistant	>=64	Final
	Method	MIC		
CEFTRIAXONE		Resistant	>=64	Final
	Method	MIC		
CEFUROXIME - AXETIL		Resistant	>=64	Final
	Method	MIC		
CEFUROXIME - SODIUM		Resistant	>=64	Final
	Method	MIC		
CEPHALOTHIN		Resistant	>=64	Final
	Method	MIC		
CIPROFLOXACIN		Resistant	>=4	Final
	Method	MIC		
ERTAPENEM		Resistant	>=8	Final
	Method	MIC		
GENTAMICIN		Resistant	>=16	Final
	Method	MIC		
IMIPENEM		Resistant	>=16	Final
	Method	MIC		
LEVOFLOXACIN		Resistant	>=8	Final
	Method	MIC		
MEROPENEM		Resistant	>=16	Final
	Method	MIC		
PIPERACILLIN/TAZOBAC		Resistant	>=128	Final
	Method	MIC		
TOBRAMYCIN		Intermediate	8	Final
	Method	MIC		
TRIMETH / SULFA		Resistant	>=320	Final
	Method	MIC		

Antibiotic		Sensitivity	Result	Status
COLISTIN		Interpretation Not Available	0.125	Final
	Method	MIC BY E-TEST METHOD		
TIGECYCLINE		Sensitive	2.0	Final
	Method	MIC BY E-TEST METHOD		

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MBLs/NDMs

Options for therapy

- Metallo-Beta Lactamases: Hydrolyze available carbapenems, beta-lactams, beta-lactam inhibitor combinations.
- Unable to hydrolyze Aztreonam.
- But….these organisms are truly MDR – and express multiple beta-lactamases
- In this case – Aztreonam & Ceftaz/Avi were resistant.
- **Treatment – in this case:**
  - **Aztreonam PLUS Ceftaz/Avibactam PLUS Amikacin**
- Other options…..
  - Tigecycline / Polymyxin B / High-Dose Meropenem combinations….

Options for CREs

In the pipeline

Agent	Targets	Status (10/2016)
Meropenem-Vaborbactam (RPX7009)	Class A and C (KPCs)	Phase III Trials Complicated UTI/CRE Infections
Imipenem-Relebactam	Class A and C (KPCs)	Phase III Trials PNA/Carb-resistant Infections
Plazomicin	Class A (Lacks reliable activity vs NDM)	Phase III Trials Complicated UTI/CRE Infections
Eravacycline	Class A	Phase III Trials Complicated UTI

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Thaden et al. Virulence 2016.

Question 4

True / False The most common Carbapenem-Resistant Enterobacteriaceae (CRE) observed in North America are those that harbor *Klebsiella pneumoniae* Carbapenemases (KPCs).

Partners in Stewardship

In this together

- Obvious
  - Infectious Diseases
  - Microbiology
  - Pharmacy
- Critical
  - Infection Prevention
  - Environmental Services
- Essential
  - Agriculture / Supply Chain
  - Drug Development

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Questions?

GMCCP Fall Educational Event/Business Meeting
Wednesday November 16th, 2016

Sara Revolinski, PharmD, BCPS
Antimicrobial Stewardship Coordinator
Froedtert and Medical College of Wisconsin

Claire Dysart, PharmD, BCPS
Clinical Specialist, Infectious Diseases
Zablocki VA Medical Center

Margaret Cook, PharmD, BCPS
Infectious Diseases Pharmacy Coordinator
Aurora Health Care

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