Rational Antibiotic Use

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UW Medicine

Disclosures

No conflicts of interest or relationships to disclose

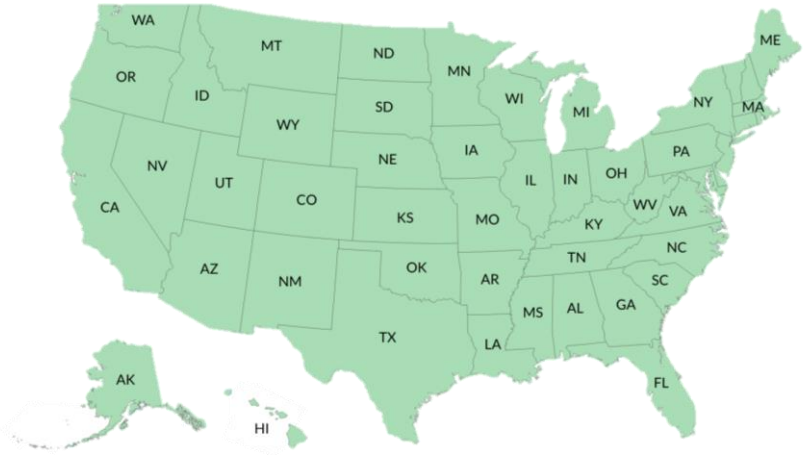
Learning Goals & Objectives

- Identify the different classes of antibiotics commonly used in clinical practice
- Become familiar with new and developing antibiotics
- Review new IDSA guidelines for ESBL-E (Extended Broad Spectrum Beta-Lactamase -Enterobacteriaceae), CRE (Carbapenem Resistant Enterobacteriaceae) and DTR-pseudomonas (Difficult-to-Treat Resistance *P.aeruginosa*)

Antibiotic Update 2023: *Variation in Use*

Prescriptions in US

- Abx Courses / yr: 300M
- Abx for Outpatients: 70%
- Abx Appropriate: 50-70%



In total, 76% of prescriptions reviewed were deemed inappropriate for the following reasons: (N=3,880)

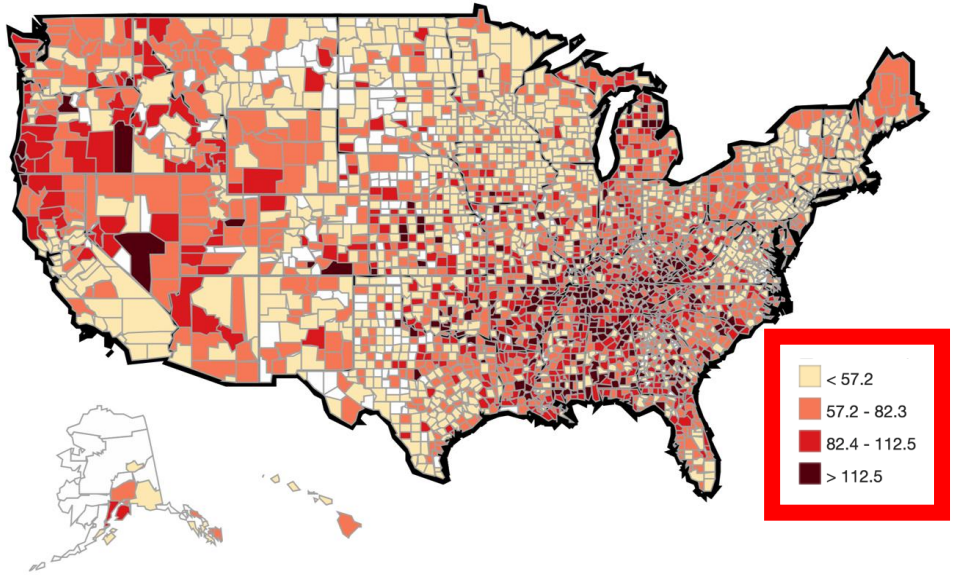
- No antibiotic was indicated (49.7% of cases);
- The wrong antibiotic was selected (12.3% of cases); and
- The wrong duration of therapy was ordered (14% of cases).

Shively *Antimicrob Agents Chemother* 2018

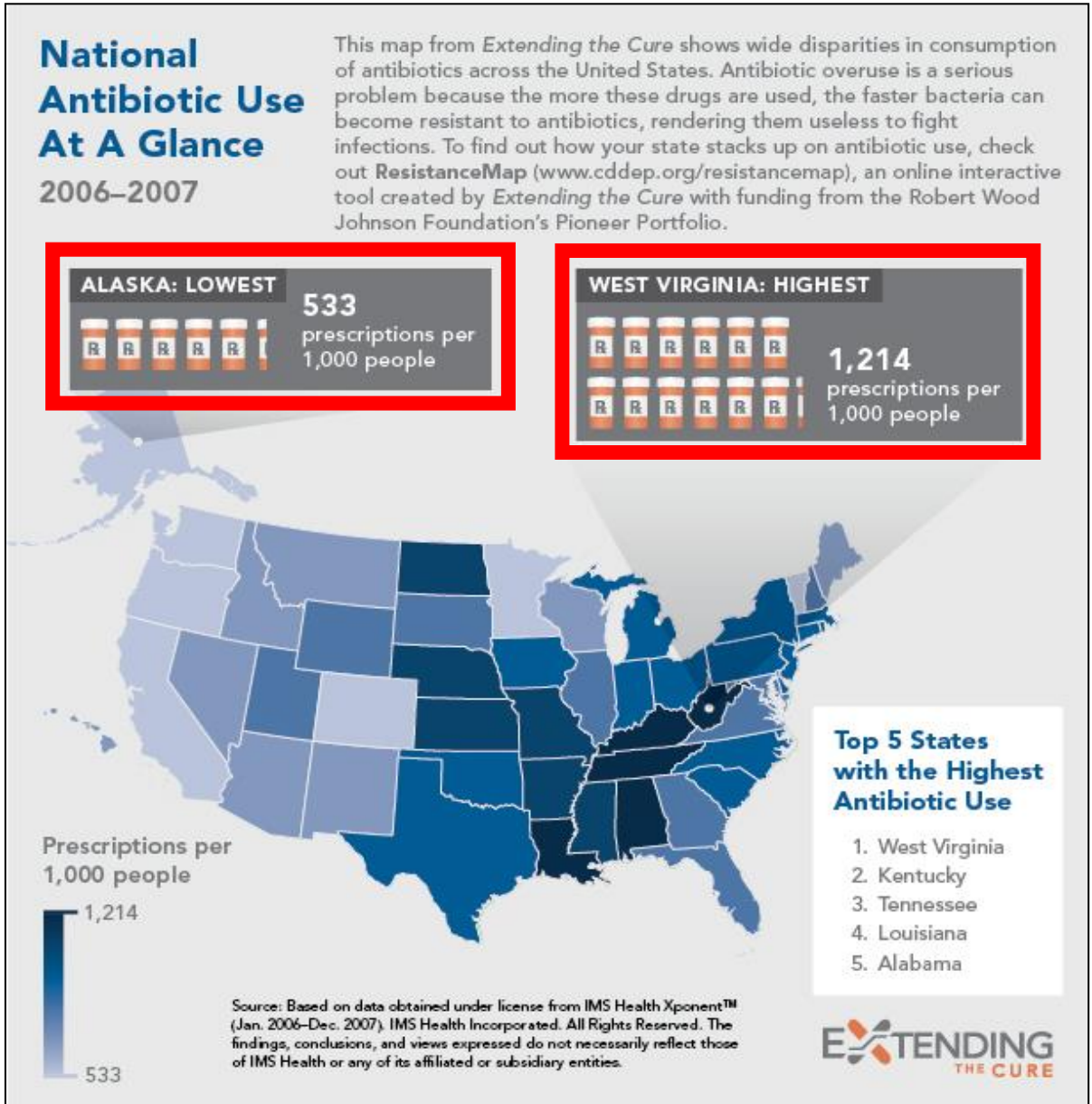
Antibiotic Update 2023: *Variation in Use*

Prescriptions in US

- Abx Courses / yr: 300M
- Abx for Outpatients: 70%
- Abx Ap
- Region

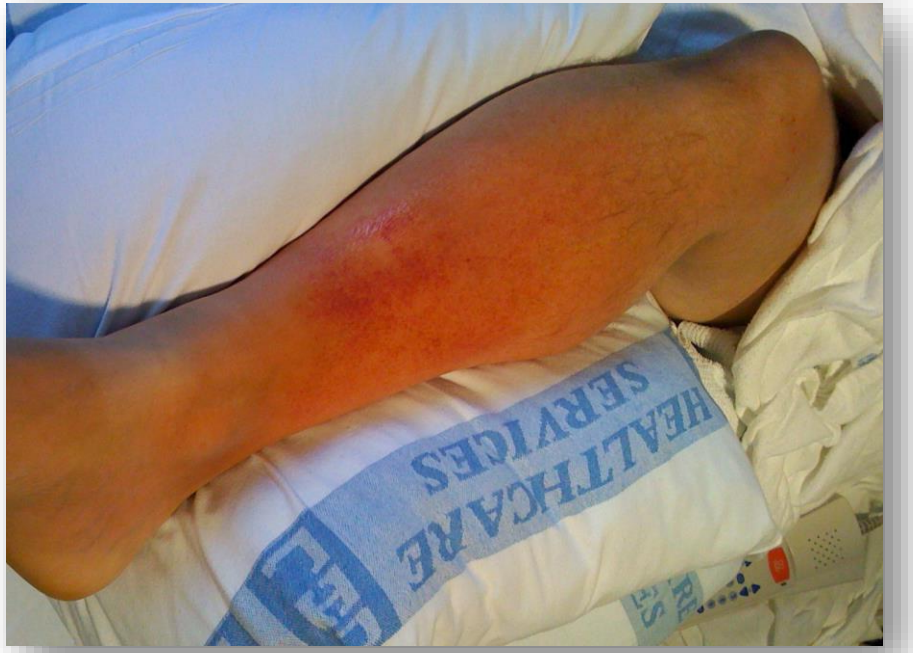


Narcotic Prescriptions per 100 persons



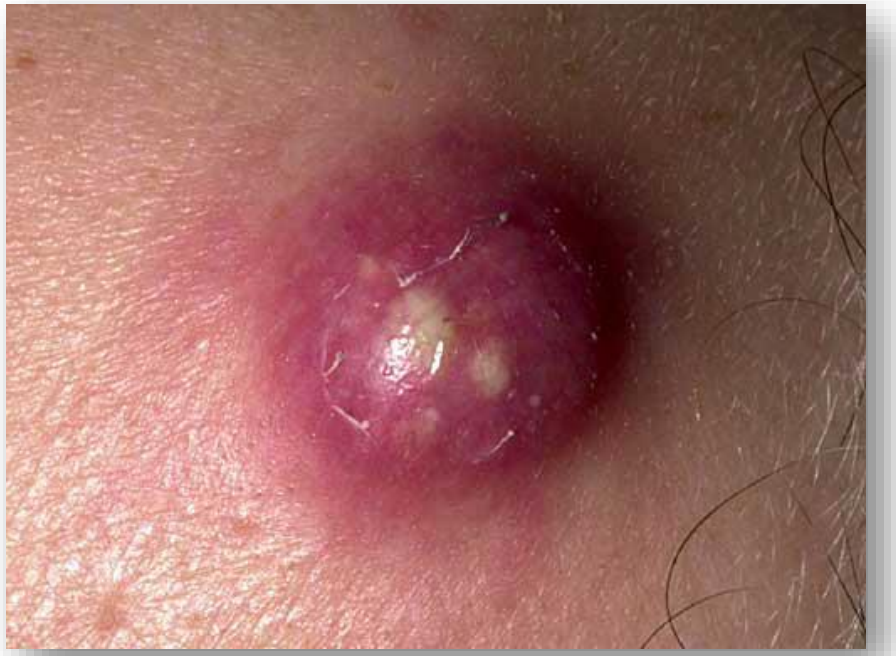
Skin & Soft Tissue Infections: *2 Main Flavors*

Cellulitis



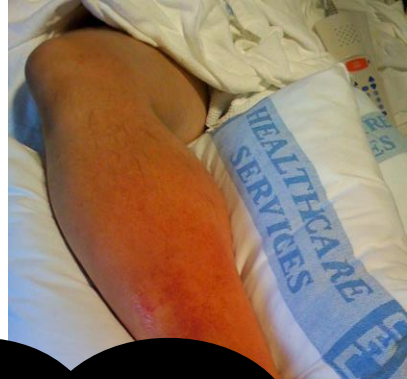
- No purulent focus
- Usually beta-hemolytic *Strep* (*S.aureus* less often)

Abscess



- Pus!
- Usually MRSA or MSSA
- (Group A Strep less often)

SSTI: *How to Cover Cellulitis?*



- 179 pts with non-cultured cellulitis
- All were treated with beta-lactams
- All had acute & convalescent st
  73% ruled in for strep
- 96% had treatment success
- CAVEAT: still reasonable to cover MRSA for "high risk" (purulence or personal MRSA history)

NOT ALL SSTI IS STAPH!

Jeng *Medicine* 2010

MANAGEMENT OF SSTIs

NONPURULENT
Necrotizing Infection /Cellulitis /Erysipelas

Severe
- ➢ **EMERGENT SURGICAL INSPECTION / DEBRIDEMENT**
  - ► Rule out necrotizing process
- ➢ **EMPIRIC Rx**
  - Vancomycin ***PLUS*** Piperacillin/Tazobactam

C & S

DEFINED Rx (Necrotizing Infections)

Monomicrobial Streptococcus pyogenes
- Penicillin ***PLUS*** Clindamycin

Clostridial sp.
- Penicillin ***PLUS*** Clindamycin

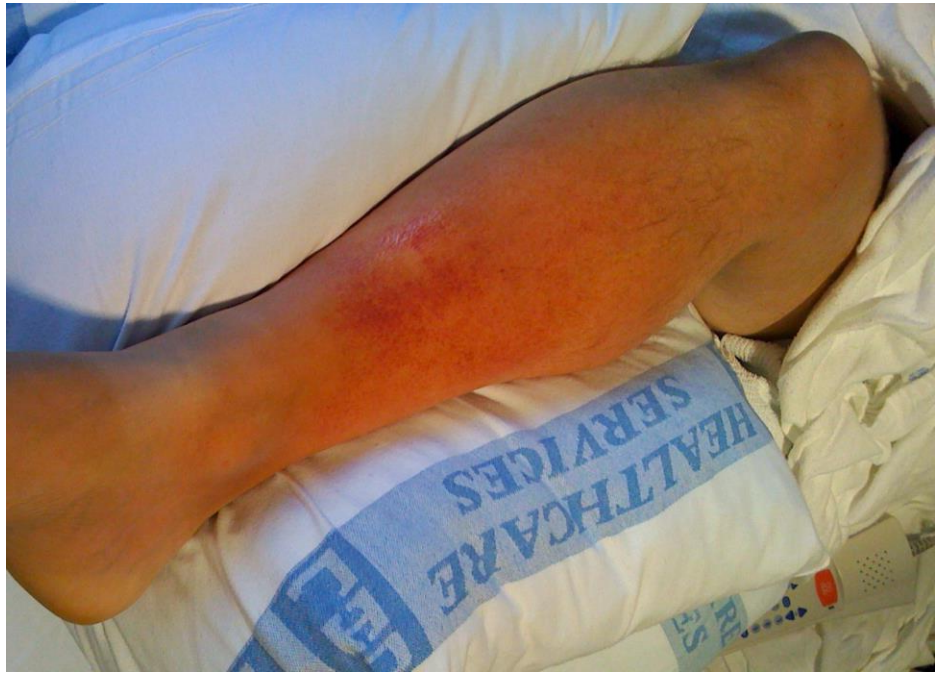
Vibrio vulnificus
- Doxycycline ***PLUS*** Ceftazidime

Aeromonas hydrophila
- Doxycycline ***PLUS*** Ciprofloxacin

Polymicrobial
- Vancomycin ***PLUS*** Piperacillin/Tazobactam

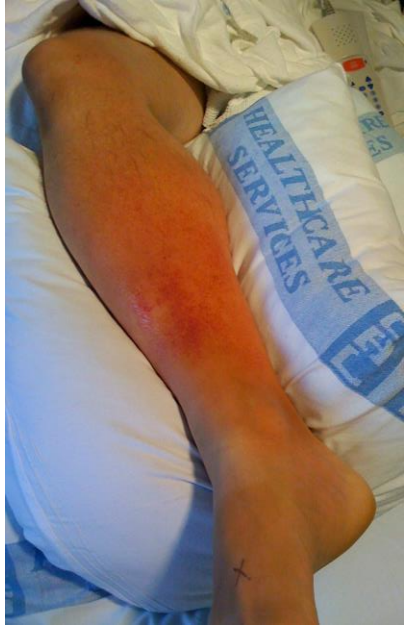
Moderate
INTRAVENOUS Rx
- Penicillin ***or***
- Ceftriaxone ***or***
- Cefazolin ***or***
- Clindamycin

Mild
ORAL Rx
- Penicillin VK ***or***
- Cephalosporin ***or***
- Dicloxacillin ***or***
- Clindamycin



Stevens *CID* 2014

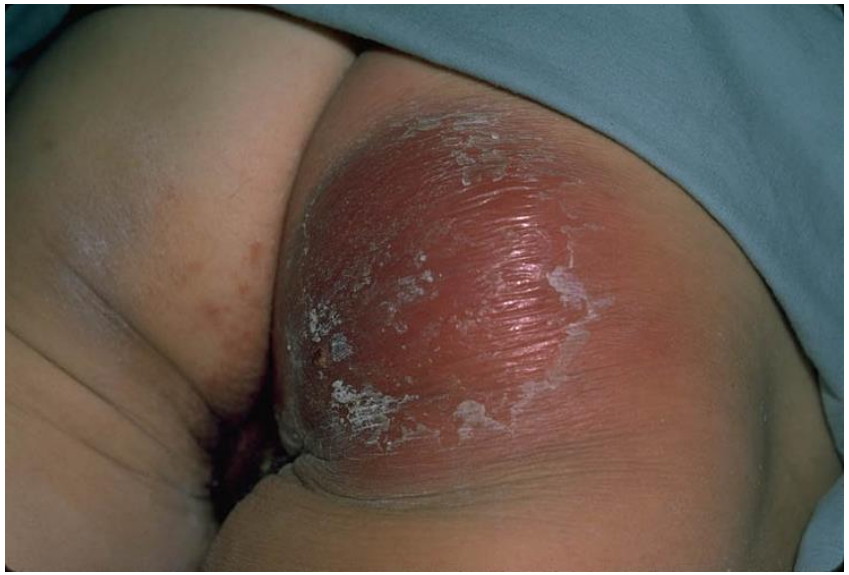
SSTI: *Prevention of Recurrence?*



- 274 pts with recurrent cellulitis
- Randomized: PCN-VK 250mg PO BID vs Placebo, followed x 3 years
- Recurrence: 22% PCN vs 37% Placebo
- HR 0.55 [0.35-0.86], p=0.01
- NNT = 5
- Recurrence rates the same once abx stopped

PCN worth considering in recurrent cases… look for other reversible factors (DM, tinea, venous stasis, etc)

Thomas *NEJM* 2013



MANAGEMENT OF SSTIs

PURULENT
Furuncle / Carbuncle / Abscess

- **Severe** → I & D, C & S → **EMPIRIC Rx**[1]
  - Vancomycin ***or***
  - Daptomycin ***or***
  - Linezolid ***or***
  - Televancin ***or***
  - Ceftaroline
- **Moderate** → I & D, C & S → **EMPIRIC Rx**
  - TMP/SMX ***or***
  - Doxycycline
- **Mild** → I & D

DEFINED Rx

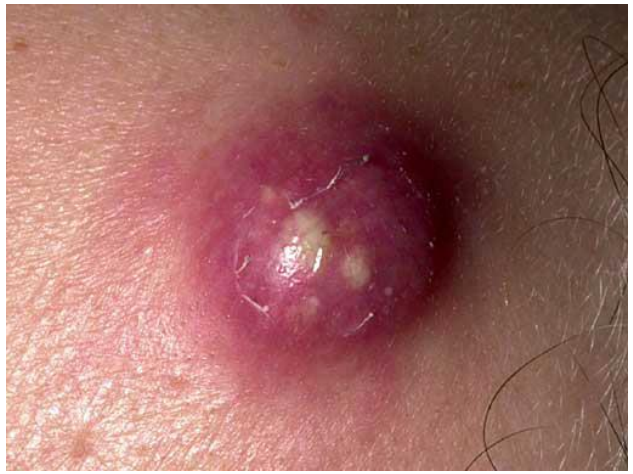
MRSA
- See Empiric

MSSA
- Nafcillin ***or***
- Cefazolin ***or***
- Clindamycin

DEFINED Rx

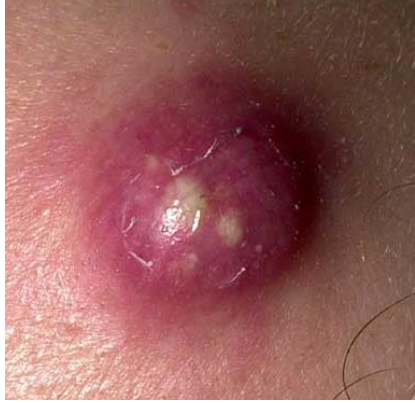
MRSA
- TMP/SMX

MSSA
- Dicloxacillin ***or***
- Cephalexin



IDSociety.org (2014)

Abscess: *Are you SURE I don't need abx?*



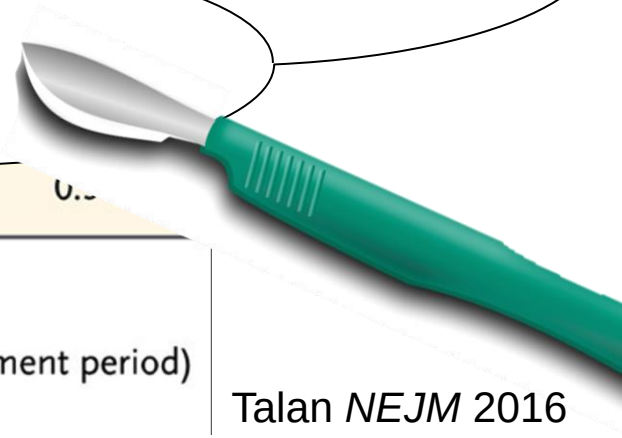
- DB-RCT: Uncomplicated abscess (all got I&D) randomized to 7 days placebo vs. TMP/SMX
- 12% better outcomes in TMP/SMX arm (both MITT & per-protocol)

I&D still gold standard for simple abscess! Slightly better cure with TMP/SMX… but at what cost?

Table 3. C…

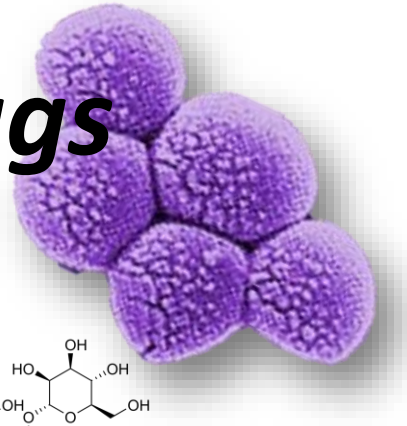
Per-protocol‡			
FDAGEEP	…(90.5)	…(–3.0 to 8.1)	0.…

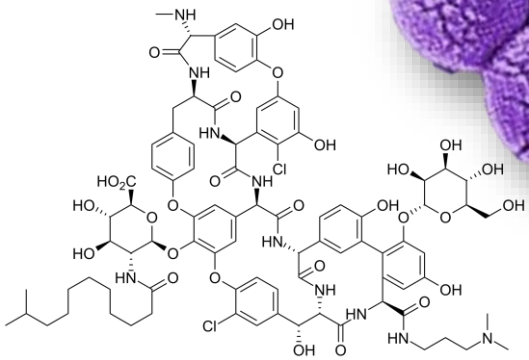
* CI denotes confidence interval.
† P values were calculated with a Wald asymptotic test of equality with a continuity correction.
‡ The primary outcome was clinical cure at the test-of-cure visit (7 to 14 days after the end of the 7-day treatment period) in the per-protocol population.



Talan *NEJM* 2016

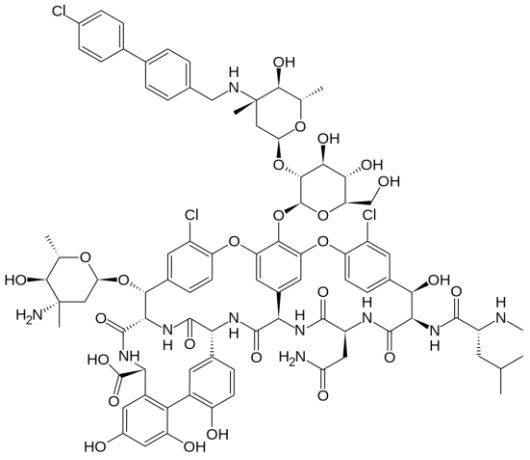
MDR Gram-Positives: *New Anti-MRSA Drugs*





- **Dalbavancin** (Dalvance)
  - ✓ Class: Lipoglycopeptide
  - ✓ Indication: gram-positive ABSSSI
  - ✓ 1.5 gm IV x 1 or 1 gm then 500 mg day 7; “$4,500 / course”
  - ✓ May elevate LFTs; dose reduce in severe liver dysfunction

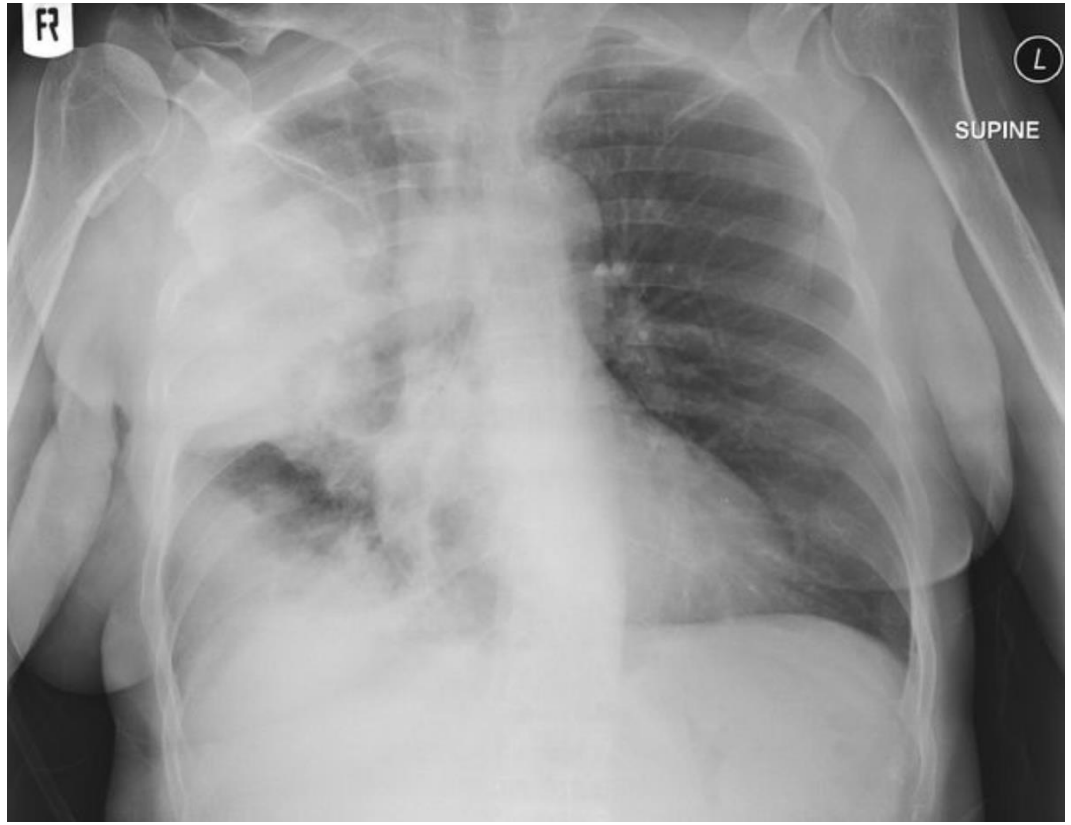
- **Oritavancin** (Orbactiv)
  - ✓ Class: Lipoglycopeptide
  - ✓ Indication: gram-positive ABSSSI
  - ✓ 1.2 gm IV x 1; “$3000 / course”
  - ✓ Falsely elevates aPTT x 5 days post-infusion



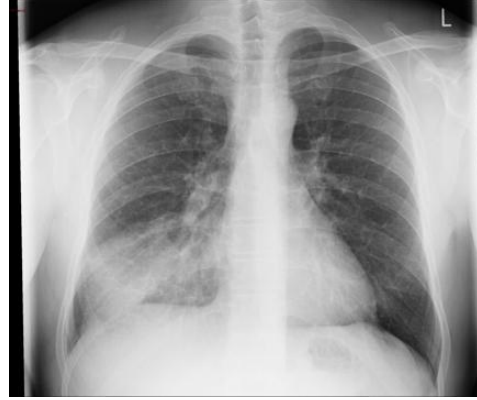
MRSA Susceptibility: *Seattle 2023*

	HMC (52%)	UWMC (35%)
Clindamycin	72%	73%
Levofloxacin	18%	20%
Doxycycline	80%	89%
TMP/SMX	90%	93%
Vancomycin	100%	100%
Linezolid	100%	100%
Daptomycin	100%	100%

Updates in ID: *Vancomycin for Pneumonia?*



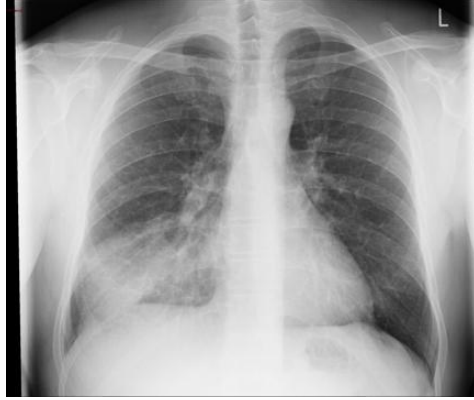
CAP: *Cover MRSA?*



- Retrospective case series (88,605 CAP pts)
- 33,632 (38%) got MRSA coverage…
- 2% had clinical MRSA infection
- aRR vanco vs standard CAP treatment:
  - ✓ 30 day mortality: 1.4 [95% CI 1.3-1.5]
  - ✓ AKI: 1.4 [95% CI 1.3-1.5]
  - ✓ CDI: 1.6 [95% CI 1.3-1.9]
  - ✓ VRE: 1.6 [95% CI 1.0-2.3]
  - ✓ GNR infection: 1.5 [95% CI 1.2-1.8]

Jones *JAMA Int Med* 2020

CAP: *Cover MRSA?*



- Retrospective case series (88,605 CAP pts)

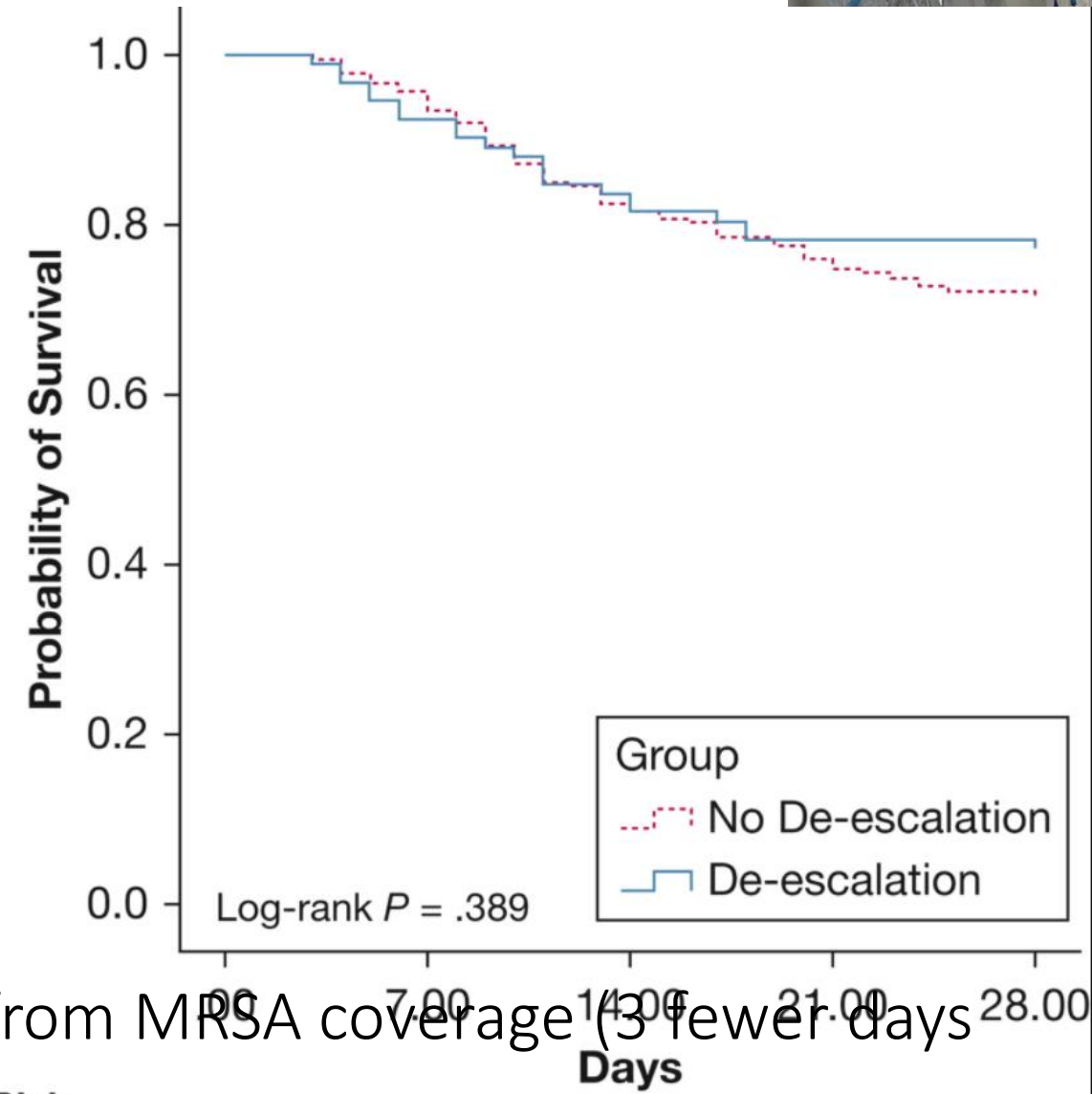
"These findings, which were robust to multiple methods of analysis, contribute to a growing body of evidence that raises questions surrounding widespread empirical use of extended-spectrum antibiotics in patients with community-acquired pneumonia."

- ✓ VRE: 1.6 [95% CI 1.0-2.3]
- ✓ GNR infection: 1.5 [95% CI 1.2-1.8]

Jones *JAMA Int Med* 2020

HAP: *Cover MRSA?*

- Retrospective case series (279 pts
- Culture negative HAP
- All got MRSA coverage… most P.ae
- 92 de-escalated off MRSA coverag



- *Impression:* No harm in de-escalating from MRSA coverage (3 fewer days in ICU… 5 fewer days in hospital)

No. at Risk					
De-escalation	92	85	77	72	71
No De-escalation	187	179	154	142	134

Cowley *Chest* 2019

CAP & VAP: *Cover for MRSA?*

- Meta-Analysis (22 studies, 5163 pts)
- Nasal swab for MRSA c/w final micro diagnosis....

			if 10% colonization	
Infection	**Sens**	**Spec**	**PPV**	**NPV**
All Pneumonia	70.9%	90.3%	44.8%	96.5%
CAP	85%	92.1%	56.8%	98.1%
VAP	40.3%	93.7%	35.7%	94.8%

- *Impressions:* No MRSA in the nose? Very unlikely to be in the lungs... if in the nose, 30-50% chance it is deeper too!

Parente *Clin ID* 2018

Updates in ID: *MRSA Colonization*

Negative MRSA Nares and Other Infections

- Retrospective cohort study across the VA, 2007-2018
- Reviewed MRSA nares and cultures within 7-days

Type of Infection	No.	Sensitivity (95% CI), %	Specificity (95% CI), %	NPV, %
All	561,325	67 (67-68)	81 (81-81)	96.5
Blood	70,185	70 (69-71)	82 (81-82)	96.5
Intra-abdominal	11,906	66 (61-71)	89 (89-90)	98.6
Wound (UE)	2,867	63 (59-67)	85 (83-86)	88.3

Mergenhagen *CID* 2020

CAP: *Ambulatory Treatment*

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

	Standard Regimen
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*[*]	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%)[†]
With comorbidities[‡] Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline[§] OR monotherapy with respiratory fluoroquinolone[‖]

Metlay JP *AJRCCM* 2019

CAP: *Inpatient Treatment, Not Severe*

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia*	β-Lactam + macrolide† or respiratory fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive

Metlay JP *AJRCCM* 2019

CAP: *Inpatient Treatment, Severe*

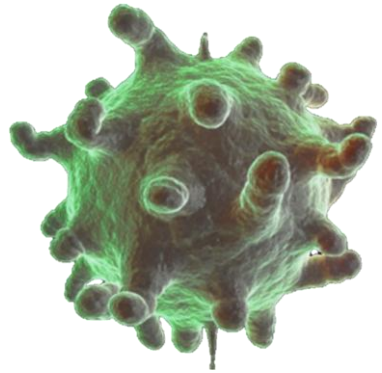
Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Severe inpatient pneumonia*	β-Lactam + macrolide† or β-lactam + fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage§ and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

Metlay JP *AJRCCM* 2019

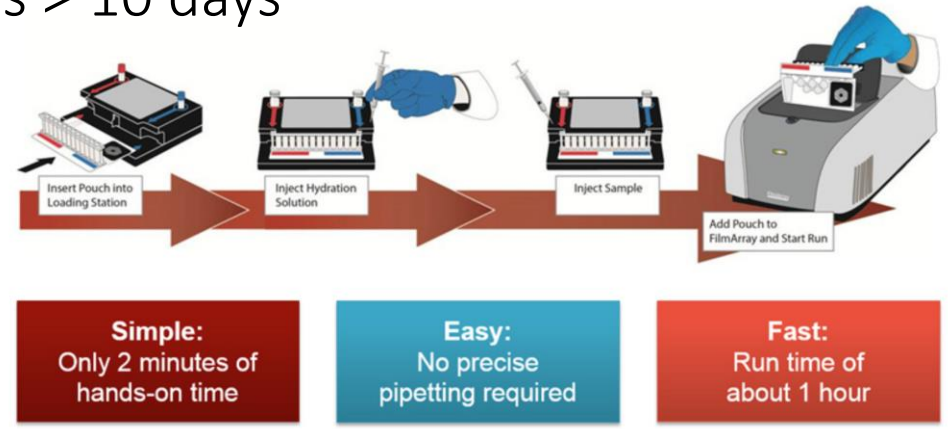
Antibiotics in 2023: *Rhinosinusitis*



American adults have 2-3 / year

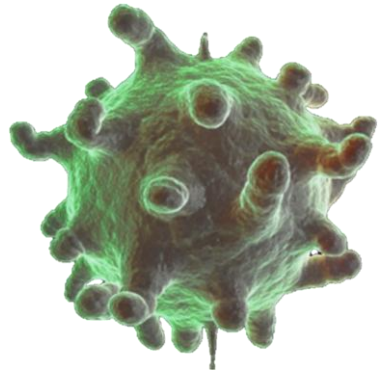
- ~98% viral (COVID-19, rhino, adeno, etc)
- 2% bacterial (*S.pneumo, H.flu, M.cat*)
- Symptomatic relief indicated **regardless** of cause
- No ironclad symptoms or signs distinguish between viral & bacterial etiologies
- Single best predictor of bacterial involvement: symptoms > 10 days
- Meta-Analysis: NNT = 15 (Young *Lancet* 2008)

Diagnostic uncertainty drives abx use!



- COVID-19 testing ubiquitous… if pts use it!
- Usually prohibitively expensive or unavailable
- Rapid detection of RSV and influenza A&B offered commercially… 1 hour turnaround time... cost ~$100

Antibiotics in 2022: *Rhinosinusitis*



Pragmatic Approach...

- Validation: “Not COVID? OK. Other viruses going around too”
- Reassurance: “Good news, no abx needed!”
- Smoking cessation helps!
- Scheduled anti-inflammatory / analgesics.
- Judicious decongestants in *select* cases.
- Consider topical steroids if h/o allergy.
- Vitamin C: A fine way to acidify your urine.
- Appropriate hygiene and infection control!
- Neti-Pot... It’s what’s for rhinosinusitis!

Fluoroquinolone Alternatives: *Sinusitis*

1st Line Empiric Abx

- Amox-Clav 875-2000 mg PO BID x 5-7 Days

2nd Line Empiric Abx

- Doxycycline 100 BID or
- Levofloxacin 500 QD or
- Moxifloxacin 400 QD

} 5-7 Days

Modified IDSA recommendations soon…?

No Longer Recommended

- Azithromycin, TMP/SMX

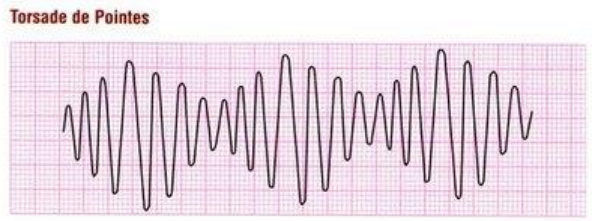
Chow 2012 IDSA Guidelines

Recurrent Rhinosinusitis: *Risk Factors*

"What's wrong with my immune system?"

- Beyond tobacco, probably nothing…
- If sino-pulmonary infections recur and ENT is out of ideas, consider ruling out:
  - ✓ Common Variable Immunodeficiency (check IgG level)
  - ✓ Cystic Fibrosis (pulmonary referral)

COPD: *Abx for Prevention?*



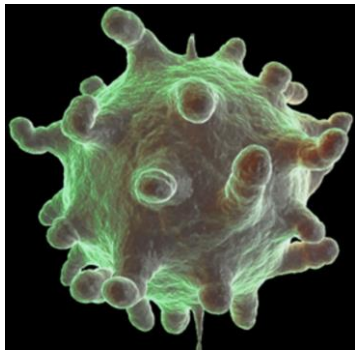
Ni et al, *PLoS One* 2015

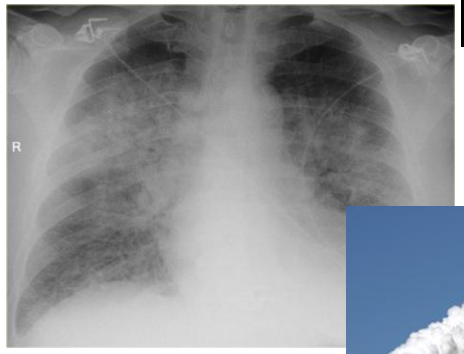
- ✓ Meta-Analysis of 1,666 pts
- ✓ Weighted RR = 0.58, 95% CI: 0.43–0.78, P < 0.01
- ✓ AE: OR = 1.55, 95%CI: 1.003–2.39, P = 0.049
- ✓ "Our results suggest 6-12 months erythromycin or azithromycin therapy could effectively reduce the frequency of exacerbations in patients with COPD. However, long-term treatment may bring increased adverse events and the emergence of macrolide-resistance. A recommendation for the prophylactic use of macrolide therapy should weigh both the advantages and disadvantages."

COPD: *Abx for Treatment?*

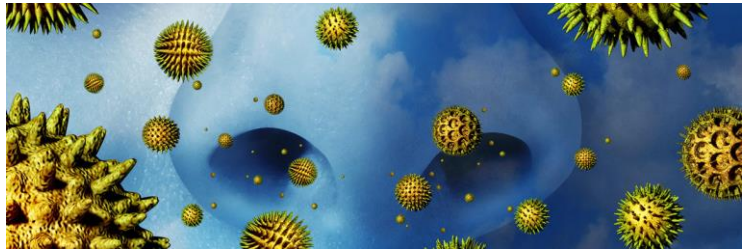
Exacerbation Triggers

- ✓ Bacterial Infection
- ✓ Viral Infection
- ✓ Smoke
- ✓ Allergens
- ✓ Pollutants
- ✓ Noncompliance
- ✓ Natural Progression
- ✓ Mimics (CHF)
- ✓ Procalcitonin endorsed by GOLD group









COPD: *Is This Bacterial?*

Common Presentations for ABECB

- ✓ Cough
- ✓ Fever
- ✓ Chest Pain
- ✓ Dyspnea
- ✓ Increased Sputum Production
- ✓ Increased Sputum Purulence

"Cardinal Symptoms" suggesting a bacterial source

GOLD Recommendations

- ✓ Abx if all 3 present
- ✓ Abx if purulent sputum plus 1 other
- ✓ Abx if admitted and ventilated

https://goldcopd.org/

COPD: ***How to Treat with Abx?***

Ambulatory

- ✓ Amox-Clav 875mg PO BID or 500mg PO TID x 5 D
- ✓ Amox 500mg PO TID x 3-14 D
- ✓ Doxy 100mg PO BID x 3-14 D
- ✓ Cefuroxime 500mg PO BID x 10 D
- ✓ Azithro 500mg PO x 1 then 250mg PO QD x 4 D
- ✓ LVX or MOXI x 5 days

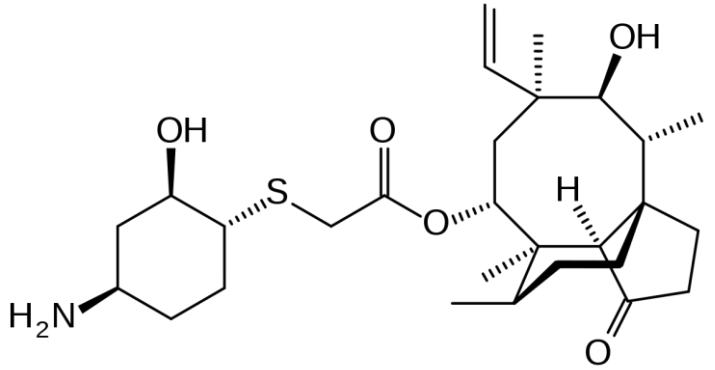
Admitted

Treat as for CAP

(ceftriaxone + [azithro or doxy]) x 5 D

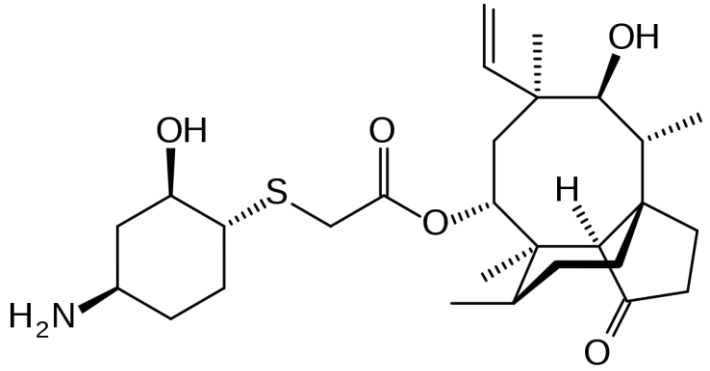
Antibiotic Update: *New Oral Pleuromutilin*

Lefamulin



- Novel Class: Pleuromutilin
- MOA: Protein synthesis blocker (50S)
- Approved for adults with CAP (no SSTI... yet)
  - ✓ *S.pneumoniae*
  - ✓ MSSA
  - ✓ *H.influenzae*
  - ✓ *Legionella pneumophila & Mycoplasma pneumoniae & Chlamydophila pneumoniae*

Antibiotic Update: *New Oral Pleuromutilin*

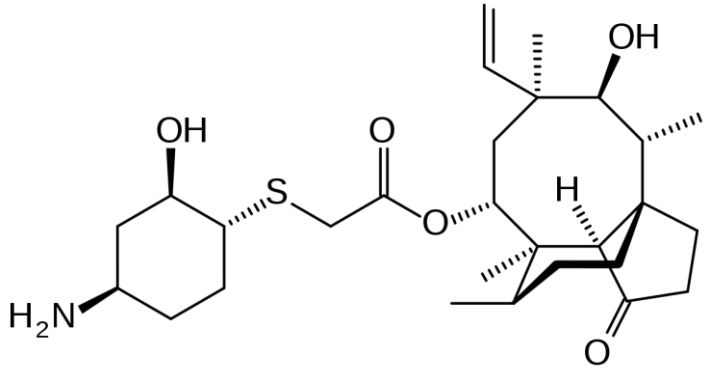


Lefamulin

- IV and PO formulations
- Dosing:
  - ✓ 150mg IV Q 12 H x 5-7 Days
  - ✓ 600mg PO Q 12 H x 5 Days
  - ✓ No adjustment for renal dysfunction

Antibiotic Update: *New Oral Pleuromutilin*

Lefamulin



- CYP3A4 substrate
- Adverse Events > 10%: Diarrhea
- Adverse Events 1-10%:
  - ✓ Hepatic enzyme elevation (2-3%)
  - ✓ Nausea (3-5%)
  - ✓ Hypokalemia (3%)
  - ✓ Insomnia (3%)
  - ✓ Vomiting (3%)
  - ✓ Headache (2%)

Cost

- ✓ IV: $205 / day
- ✓ PO: $275 / day
- ✓ Benefit coverage issues

Multidrug Resistant Gram Negatives

UW Medicine

Multi-Drug Resistant GNRs

- Extended spectrum beta-lactamase (ESBL)
- **Carbapenem Resistant Enterobacterales (CRE)**
- **Difficult to Treat Pseudomonas Aeruginosa (DTR)**
- Carbapenem Resistant Acinetobacter (CRAB)

Multitude of New Antibiotics

Newer Drugs

- Ceftolozone- tazobactam
- Ceftazidime- avibactam
- Imipenem- relebactam
- Meropenem-vaborbactam
- Cefiderocol
- Plazomicin
- Eravacycline

Older Drugs being called back to action

- Aminoglycosides
- Polymyxins
- Ampicillin/sulbactam
- Tetracyclines

Extended Spectrum β-Lactamase-Producing Enterobacterales

ESBLs

- ESBLs are enzymes that inactivate most PCNs, cephalosporins, and aztreonam
- Most commons organisms that produce ESBL are *E coli*, *K pneumoniae*, *K oxytoca*, *P mirabilis*
- Routine ESBL testing not performed in most labs
  - Ceftriaxone resistance can be used as a proxy for ESBL production

ESBLs

Type of Infection	Preferred Antibiotics	Alternative Antibiotics
Uncomplicated cystitis	Nitrofurantoin, TMP/SMX	Ciprofloxacin, Levofloxacin, carbapenems; Single dose aminoglycosides, oral Fosfomycin* (*for E coli only)
Pyelonephritis or complicated UTI	TMP/SMX, ciprofloxacin, levofloxacin	carbapenems
Non urinary tract infections	Carbapenems	

Carbapenem Resistant Enterobacterales - CRE

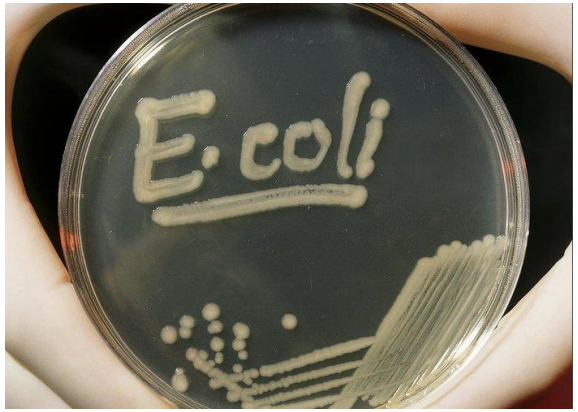
Patient Case

- 81yo Female, DM, HTN, otherwise healthy
  - Presents from LTCF with some flank pain, foul smelling urine, pain on urination
  - Fever, WBC count elevated, Cr 1.2 (baseline 0.9)
  - Hemodynamics stable, mental status normal
- Presumed urinary tract infection/pyleonephritis

…On day 3

Patient is receiving cefepime

Urine growing ***E.coli*** with following susceptibilities:



Amoxicillin R
Amox/clav R
Cefazolin R
Cefoxitin R
Ceftriaxone R
Ceftazidime R
Cefepime R
Ertapenem R
Gentamicin S
Levofloxacin R
Meropenem R
Pip/tazo R
TMP/sulfa R
Tobramycin S

What else should we test for?

What treatment should we choose?

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

THREAT LEVEL **URGENT**

13,100 Estimated cases in hospitalized patients in 2017

1,100 Estimated deaths in 2017

$130M Estimated attributable healthcare costs in 2017

Carbapenem-resistant Enterobacteriaceae (CRE) are a major concern for patients in healthcare facilities. Some bacteria in this family are resistant to nearly all antibiotics, leaving more toxic or less effective treatment options.

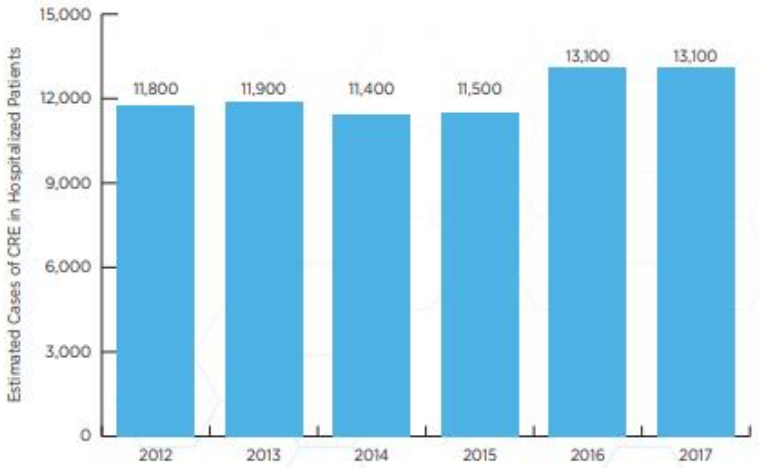
WHAT YOU NEED TO KNOW

- Patients who require devices (e.g., catheters) and patients taking long courses of some antibiotics are most at risk for CRE infections.
- CRE can carry mobile genetic elements that are easily shared between bacteria. Approximately 30% of CRE carry a mobile genetic element that can make an enzyme, which makes carbapenem antibiotics ineffective and rapidly spreads resistance that destroys these important drugs.
- Preventing CRE infections and containing the spread of carbapenem resistance is important to protect people.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

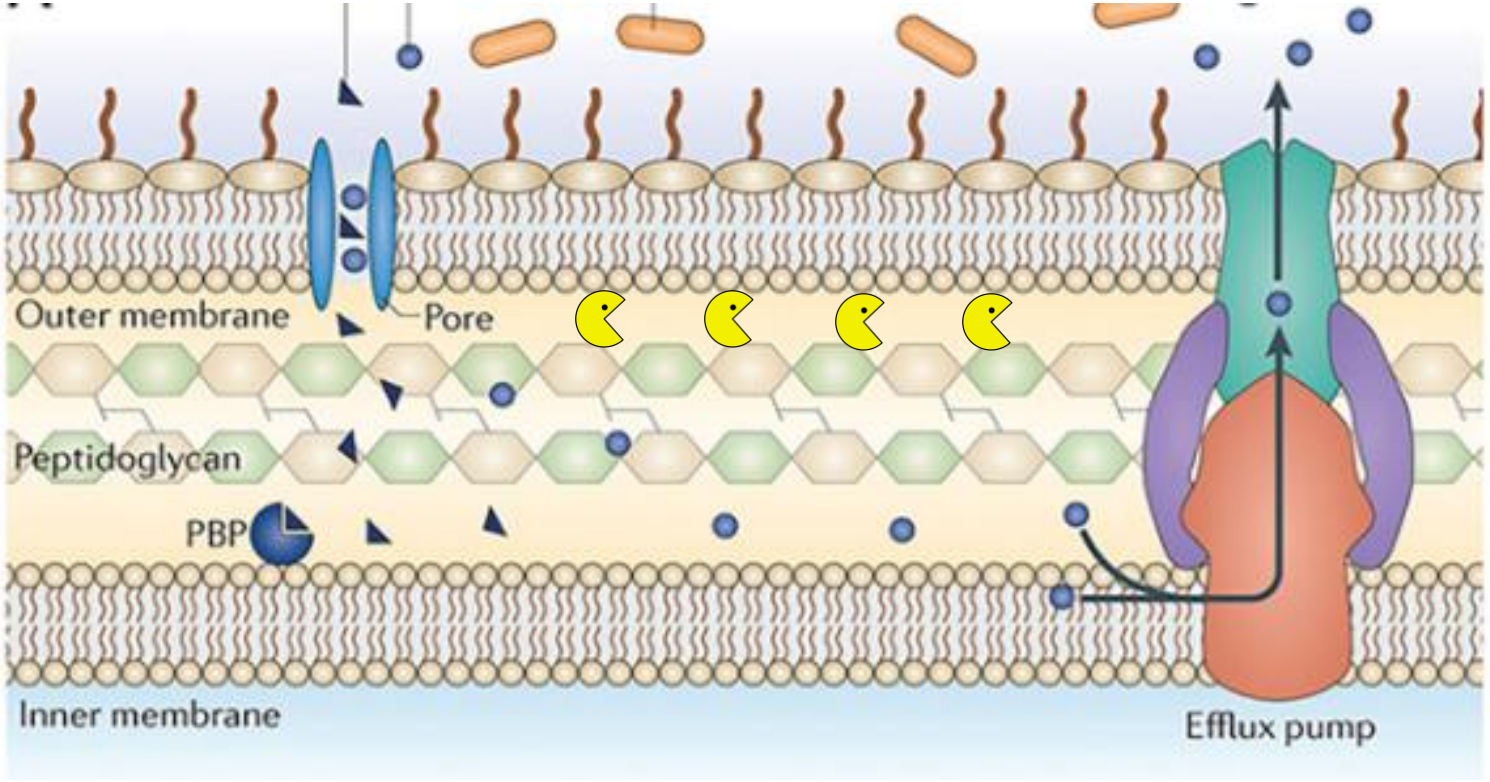
CASES OVER TIME

Containment strategies have prevented further spread of some types of CRE in the United States, but continued action is needed.



https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

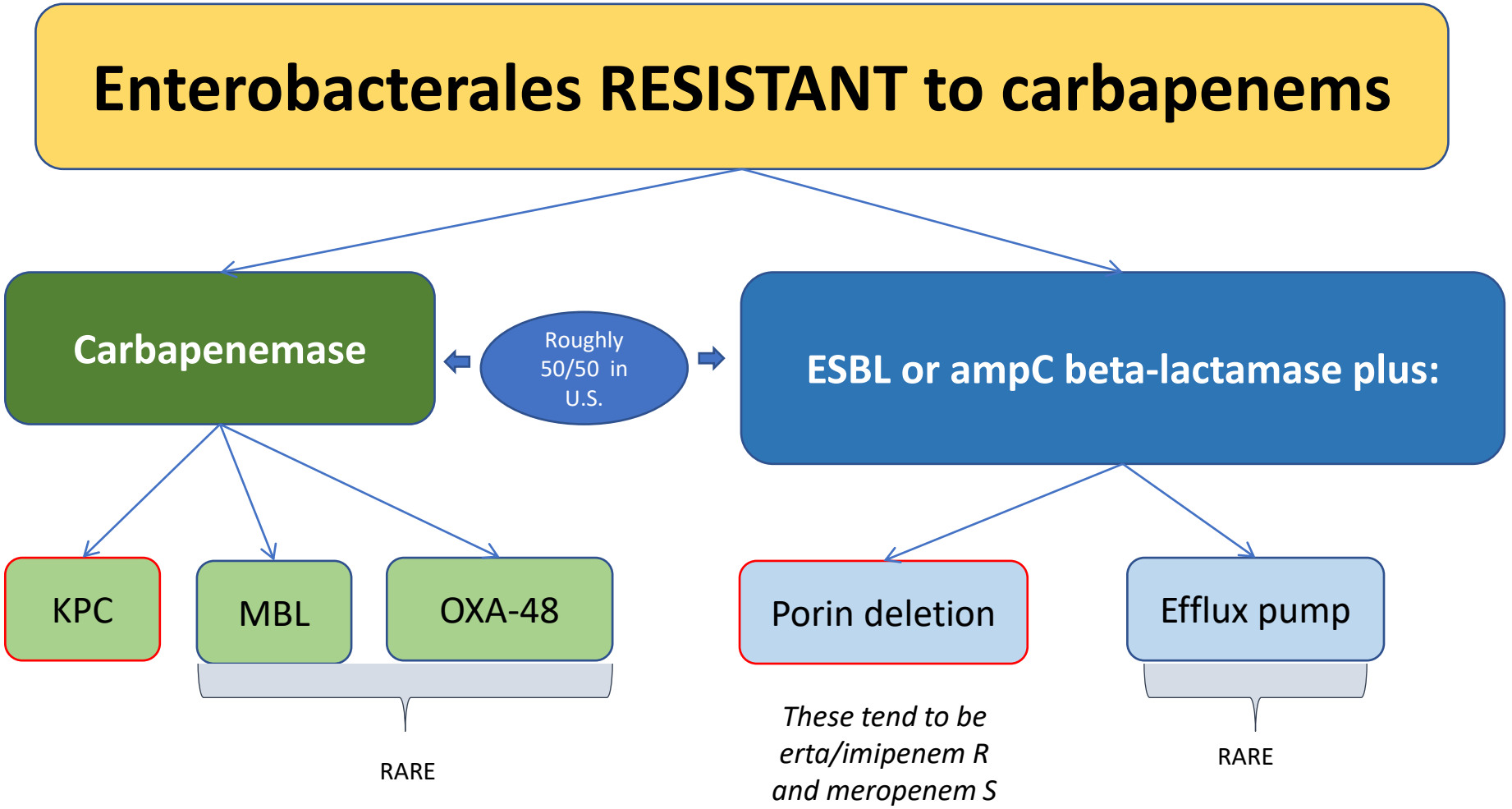
Visual of GNR Resistance



= beta-lactamase

Chellat MF. 2016. Targeting antibioticresistance. Angew Chem Int Ed Engl 55:6600–6626

Mechanism of Resistance

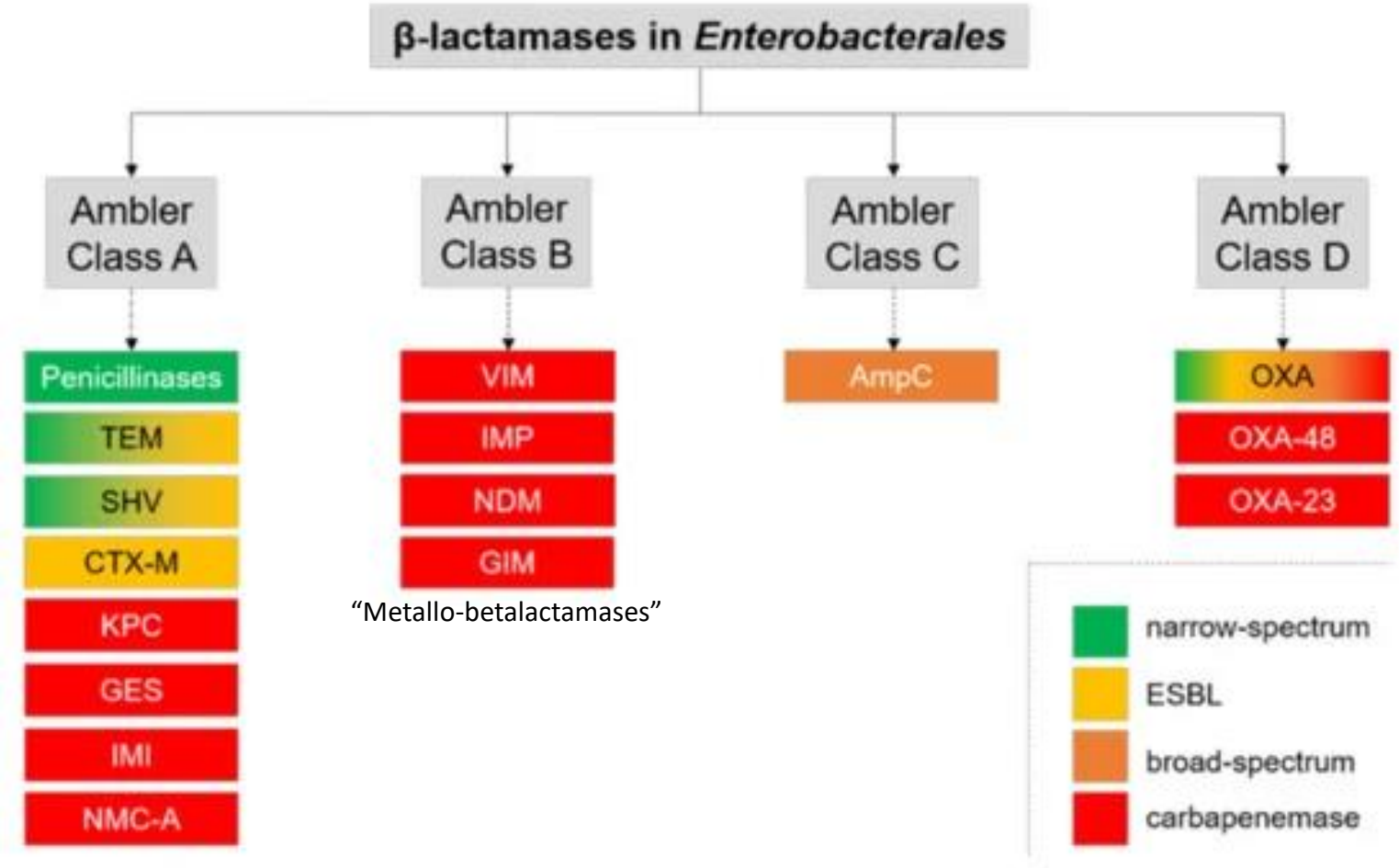


Enterobacterales Resistance

	ampC	ESBL	CRE
Location	Chromosome	Plasmid	Plasmid, Porin deletion
Bugs	“SEACHIMPK” or "HECKYES"	*E.coli, Klebsiella*	*Klebsiella, Enterobacteriaceae*
1 gen Ceph	R	R	R
2 gen Ceph	R	S	R / S
3 gen Ceph	R	R	R
4 gen Ceph	S	R / S	R
Piperacillin-tazobactam	S	S	R
Carbapenem	S	S	R
Aztreonam	R	R	R/S*

* Sensitive for Metallo-beta-lactamases only

Types of Beta-Lactamase



"Metallo-betalactamases"

Noster J, et.al. Antibiotics (Basel) . 2021 Sep 21;10(9):1140.

Testing for Resistance Type

Gram-Positive Blood Culture Test (BC-GP)

Species

Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus lugdunensis
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Enterococcus faecalis
Enterococcus faecium

Group

Streptococcus anginosus

Genus

Staphylococcus spp.
Streptococcus spp.
Micrococcus spp.+
Listeria spp.

Resistance

mecA (methicillin)
vanA (vancomycin)
vanB (vancomycin)

Gram-Negative Blood Culture Test (BC-GN)

Species

*Escherichia coli**
Klebsiella pneumoniae
Klebsiella oxytoca
Pseudomonas aeruginosa
Serratia marcescens++

Genus

Acinetobacter spp.
Citrobacter spp.
Enterobacter spp.
Proteus spp.

Resistance

CTX-M (ESBL)
IMP (carbapenemase)
KPC (carbapenemase)
NDM (carbapenemase)
OXA (carbapenemase)
VIM (carbapenemase)

The expression of the organism's resistance mechanisms is seen, in sum, in a **phenotype**

- Commonly available at most clinical micro labs
- Represents the consequence of overlapping mechanisms of resistance

Underlying drivers of resistance are encoded by genes that can be identified by various methods; the **genotype**

- Genetic testing becoming more common
- Presence of genes does not always predict level of resistance

IDSA Guidance Document - CRE

For carbapenem resistant organisms that don't have a carbapenemase (ie porin deletion + ESBL)

- Cystitis
  - Ciprofloxacin,levofloxacin
  - Trimethoprim/sulfamethoxazole
  - Nitrofurantoin
  - Meropenem
  - Single-dose of an aminoglycoside
- Infections outside the urinary tract
  - Meropenem prolonged infusion

https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

IDSA Guidance Document - CRE

For organisms that are meropenem resistant or KPC enzyme identified

- For all types of infection
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam
  - Imipenem-cilastatin-relebactam

https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

Difficult to Treat (DTR) *Pseudomonas aeruginosa*

UW Medicine

Patient Case

- 81 yo female, DM, HTN, otherwise healthy
  - Presents from LTCF with some flank pain, foul smelling urine, pain on urination
  - Fever, WBC count elevated, Cr 1.2 (baseline 0.9)
  - Hemodynamics stable, mental status normal
- Presumed Urinary tract infection/pyleonephritis

“Wild Type” *P. aeruginosa*

Pseudomonas aeruginosa

- Has a chromosomally encoded ampC enzyme
- Several efflux pumps encoded (affect across antibiotic classes)
- Porins on outer membrane that modulate molecules traveling across and can be shut off
- Intrinsic resistance to penicillins, 1st thru 3rd gen cephalosporins, ampicillin/sulbactam, amoxicillin/clavulaunate, ertapenem
- Intrinsic resistance to macrolides and tetracyclines

Alternate Reality on day 3

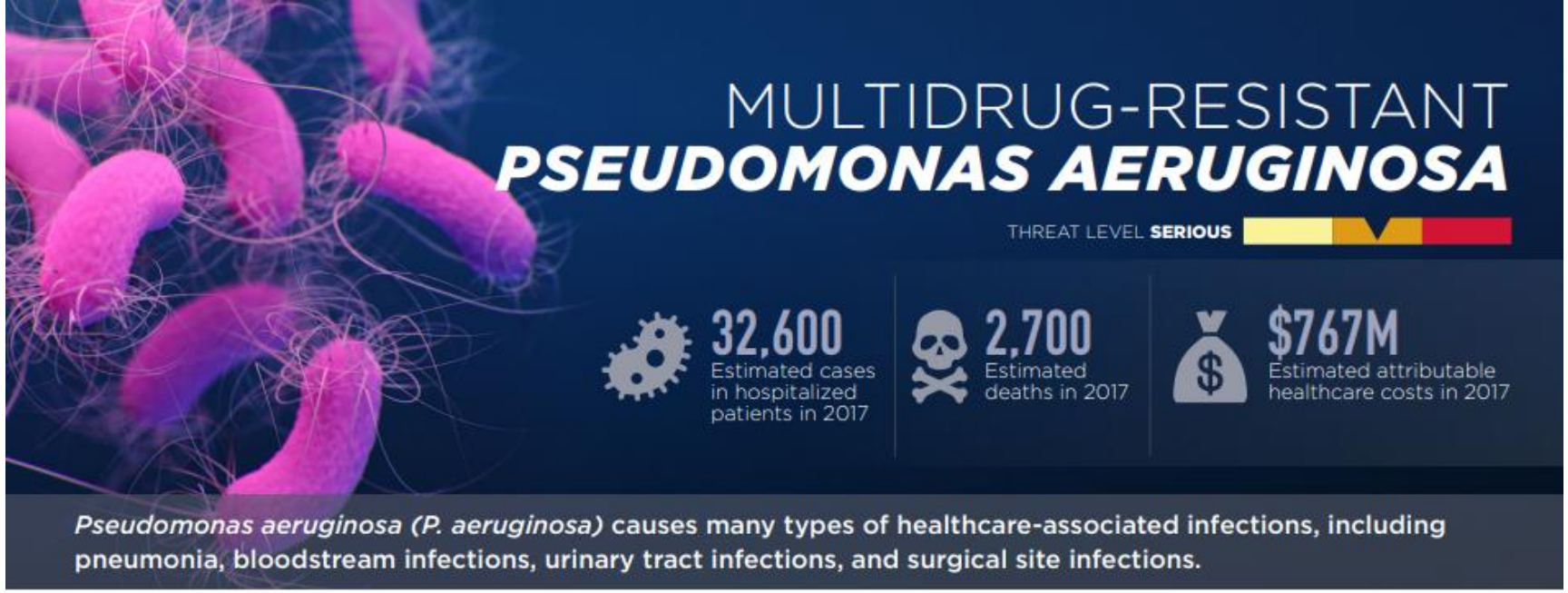
Patient is receiving cefepime

Urine growing ***P. aeruginosa*** with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

What else should we test for?

What treatment should we choose?



WHAT YOU NEED TO KNOW

- *P. aeruginosa* infections usually occur in people in the hospital or with weakened immune systems. It is particularly dangerous for patients with chronic lung diseases.
- Some types of multidrug-resistant (MDR) *P. aeruginosa* are resistant to nearly all antibiotics, including carbapenems.
- Two to 3% of carbapenem-resistant *P. aeruginosa* carry a mobile genetic element that makes a carbapenemase enzyme. This enzyme makes carbapenem antibiotics ineffective. Mobile genetic elements are easily shared between bacteria, rapidly spreading resistance that destroys these important drugs.

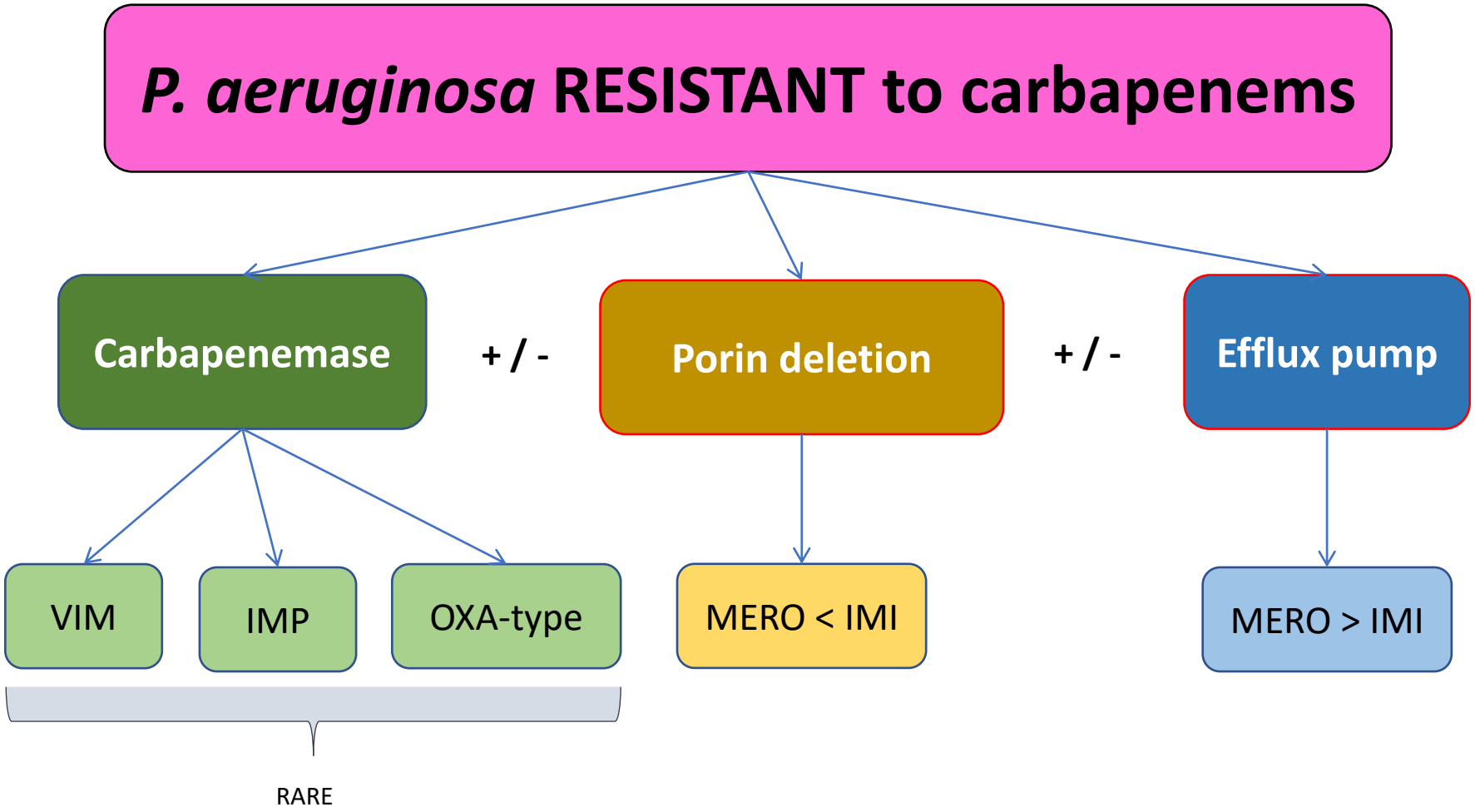
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Difficult to Treat (DTR) is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following:

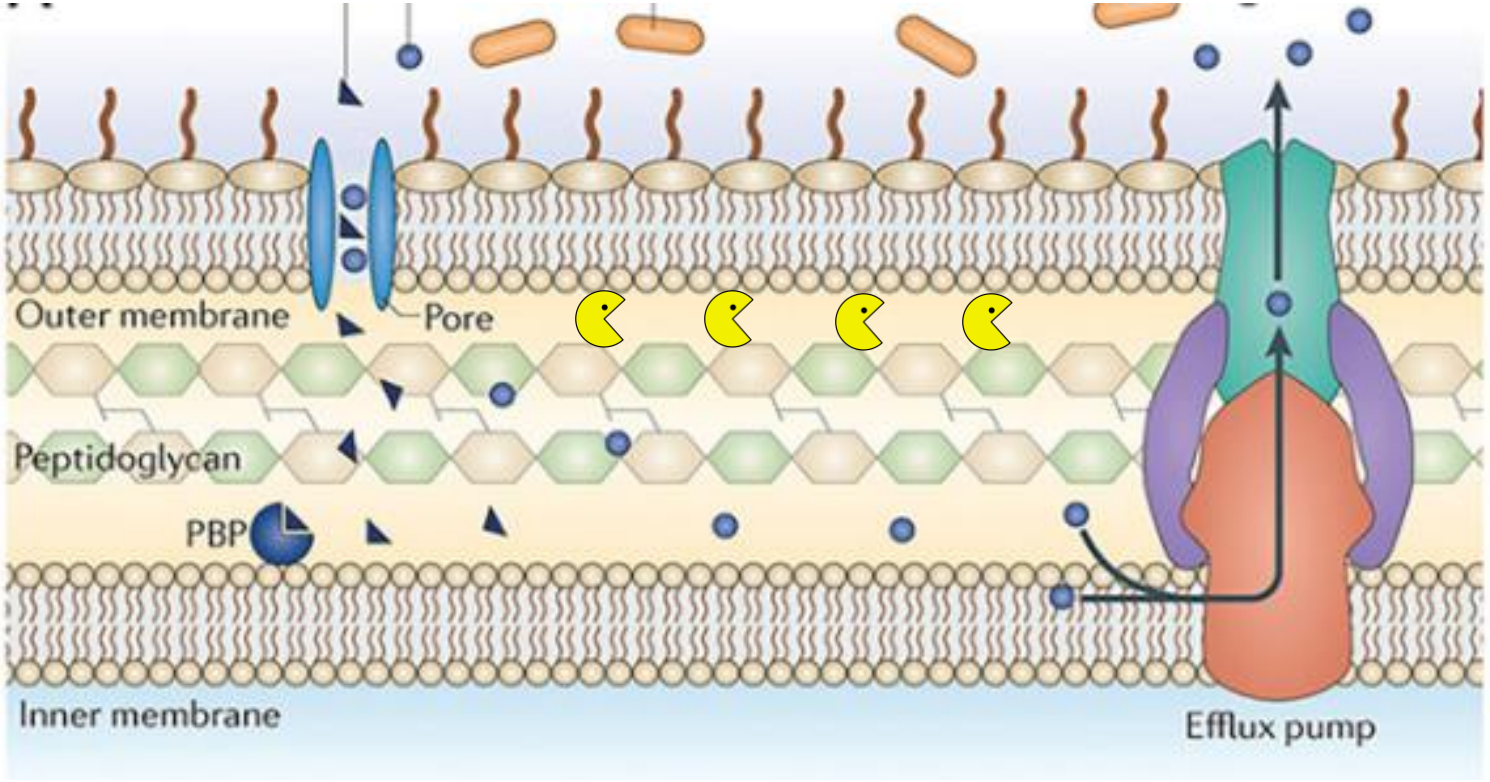
- Piperacillin-tazobactam
- Ceftazidime
- Cefepime
- Aztreonam
- Meropenem
- Imipenem-cilastatin
- Ciprofloxacin and Levofloxacin

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Mechanism of Resistance



Visual of GNR Resistance



= beta-lactamase

Chellat MF. 2016. Targeting antibioticresistance. Angew Chem Int Ed Engl 55:6600–6626

IDSA Guidance Document – DTR *Pseudomonas aeruginosa*

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (when first-line options not available/tolerated)
Cystitis	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol, or a single-dose of an aminoglycoside	Colistin
Pyelonephritis or cUTI[1]	Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol	Once-daily aminoglycosides
Infections outside of the urinary tract	Ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam	Cefiderocol Aminoglycoside monotherapy: limited to uncomplicated bloodstream infections with complete source control[2]

[1]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[2]Uncomplicated bloodstream infections include a bloodstream infection due to a urinary source or a catheter-related bloodstream infection with removal of the infected vascular catheter.

https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

Review of Drugs Used to Treat MDR GNRs

UW Medicine

Ceftolozane/tazobactam

- New ceph with *old* inhibitor which impairs variety of beta-lactamases (ESBL, ampC); ceftolozane less affected by porin deletion/efflux/ampC resistance mechanisms
- FDA Indications:
  cUTI, cIAI, HABP/VABP
- Safety:
  Similar to other beta-lactams
- Considerations:
  - ESBL activity is not uniform, especially for *K. pneumoniae*
  - Given as a prolonged infusion
  - Limited anaerobic activity
  - Growing evidence for efficacy in MDR *P. aeruginosa* infections
  - Limited use in *Acinetobacter baumannii* (OXA enzymes)
  - IV only

DTR Pseudomonas aeruginosa

Takeda S. Antimicrob Agents Chemother. 2007 Mar; 51(3): 826–830.
Van Duin D. Clin Infect Dis . 2016 Jul 15;63(2):234-41.

Ceftazidime- avibactam

- Older 3rd gen ceph with new inhibitor which impairs variety of beta-lactamases (ESBL, ampC, KPC, OXA)
- FDA Indications:
  cUTI, cIAI, HABP/VABP
- Safety:
  similar to other beta-lactams
- Considerations:
  - Avibactam is *only* an inhibitor, no intrinsic activity
  - Limited improvement in susc. in MDR *P. aeruginosa,* CRAB
  - Does not inhibit Metallo-betalactamses (classB)
  - Limited GP and anaerobic activity
  - Growing evidence for efficacy in MDR (CRE) infections
  - IV only

CRE

DTR Pseudomonas aeruginosa

Van Duin D. Clin Infect Dis . 2016 Jul 15;63(2):234-41.

Meropenem-Vaborbactam

- Old carbapenem with *new* inhibitor which impairs variety of beta-lactamases (ESBL, ampC); meropenem less affected by porin/ampC resistance mechanisms
- FDA Indications:
  cUTI
- Safety:
  similar to other beta-lactams
- Considerations:
  - Vaborbactam is *only* an inhibitor, no intrinsic activity
  - Does not inhibit OXA(class D) nor Metallo-betalactamses (classB)
  - No improvement in susceptibility in DTR *P. aeruginosa,* CRAB
  - Newer agent so less real-world clinical data
  - IV only

CRE

Petty LA. InfectDrugResist. 2018; 11: 1461–1472

Imipenem - Relebactam

- Old carbapenem with *new* inhibitor which impairs variety of beta-lactamases (ESBL, ampC); imipenem less affected by efflux/ampC resistance mechanisms
- FDA Indications:
  cUTI, cIAI, HABP/VABP
- Safety:
  similar to other beta-lactams
- Considerations:
  - Relebactam is *only* an inhibitor, no intrinsic activity
  - Does not inhibit OXA(class D) nor Metallo-betalactamses (classB)
  - Some improvement in susceptibility in DTR *P. aeruginosa* if efflux mechanisms
  - Newer agent so less real-world clinical data
  - Growing evidence for efficacy in MDR *P. aeruginosa* infections
  - IV only

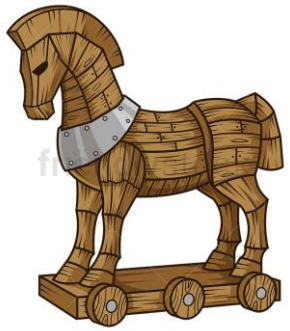
CRE

DTR Pseudomonas aeruginosa

Tompkins K. EuroJClinMicro. 2021, 40:2053-2068

Cefidericol

- New ceph with novel method of entry into cell (siderophore), structure resilient to all beta-lactamases
- FDA Indications:
  cUTI, HABP/VABP
- Safety:
  Similar to other beta-lactams
- Considerations:
  - Porin/efflux mechanisms of resistance don't impair cefidericol
  - Despite circumvention of most resistance mechanisms, bacteria can be resistant via alterations in iron transport system
  - AmpC mutations can lead to decreased susceptibility
  - Limited anaerobic activity, no GP activity
  - Concerns for poor in-vivo performance in MDR infections (did not meet clinical endpoints for efficacy)
  - Increased frequency dosing for robust renal function (q6h)
  - IV only



DTR Pseudomonas aeruginosa

CRE

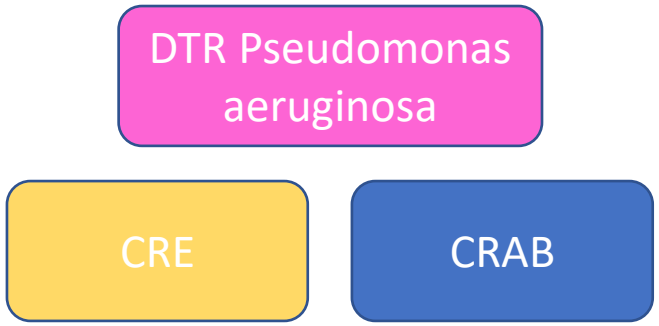
CRAB

Tamma PD. JPIDS. 2019:8(3): 251-60

Aminoglycosides

Aminoglycosides act thru interference of RNA processing at the 30s ribosomal subunit (Gentamicin, Tobramycin, Amikacin)

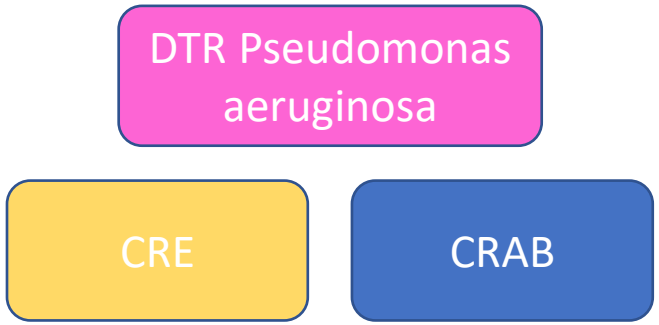
- FDA Indications:
  Most types of Gram-negative infections
- Safety:
  - Nephrotoxicity- (~15-20%); EIAD delays nephrotoxicity
  - Ototoxicity- rare but happens especially with prolonged use
  - Neurologic (muscular paralysis)
- Considerations:
  - Very broad spectrum for GNR, GP activity is only clinically accessible in combo therapy
  - Resistance occurs via efflux, inactivation, or altered target
  - Typically used in combo; monotherapy considered inferior to B-lactams (excl. urinary inf)
  - Tobramycin and amikacin tend to be broader spectrum than gentamicin
  - Renal excretion and persisting urinary levels make it an ideal urinary drug
  - Dosing has moved to EIAD in most GNR applications d/t ability to maximize peak/mic ratio and delay nephrotoxicity
  - Usefulness is further hindered by outdated susceptibility breakpoints
  - IV or inhaled



Plazomicin

New aminoglycoside with modifications that get around conventional aminoglycoside resistant mechanisms

- FDA Indications:
  cUTI
- Safety:
  similar to other aminoglycosides
- Considerations:
  - Despite its modified structure and mitigation of various mechanisms of resistance, resistance still documented
  - Showed better outcomes in cUTI (vs meropenem) due to less recurrence in sub-group analysis
  - Phase 3 study in treatment MDR infections failed due to too small of numbers
  - IV only

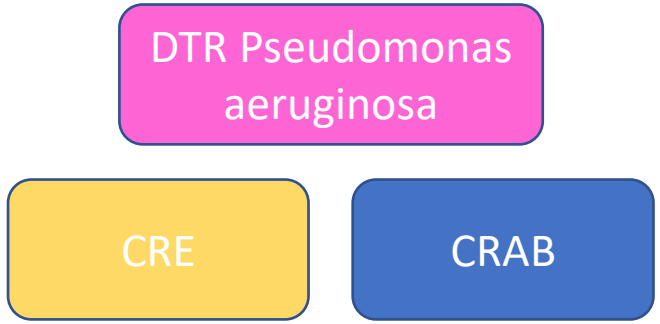


Shaeer KM. Pharmacotherapy 2019;39(1):77–93

Polymyxins

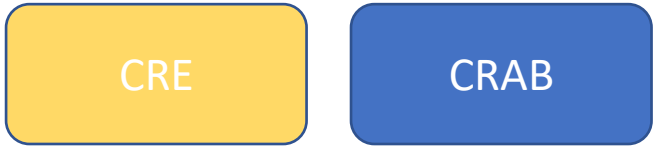
The polymyxins(colistin & polymyxinB) act thru disruption of bacterial cell membrane, binds to lipopolysaccharide (LPS)

- FDA Indications:
  Gram-negative infections
- Safety:
  Nephrotoxicity (~30% or more)
  Neurologic (parasthesias, muscular paralysis)
- Considerations:
  - Very broad spectrum for GNR, no GP or anerobic activity
  - Resistance occurs via changes in expression of target LPS
  - Typically used in combo, regrowth/ breakthrough is quick
  - PolyB is not renally excreted, but possibly less nephrotoxic
  - Colistimethate is prodrug, converts to colistin in the blood
  - Colistin drug of choice for urinary source as is eliminated there
  - IV or inhaled



Tetracyclines

- Tetracyclines act thru interference of RNA processing at the 30s ribosomal subunit (Minocycline, Tigecycline, Eravacycline)
- FDA Indications:
  - CIAI, SSTI varies by agent
- Safety:
  - GI upset is primary toxicity
- Considerations:
  - GNR susceptibility is limited in MDR infections to some CRE and CRAB
  - Resistance occurs via efflux or altered target
  - Typically used in combination; monotherapy in pneumonia and SSTI
  - Low serum concentrations relative to tissue concentrations (poor for bacteremia)
  - Urinary excretion poor and varies by agent but have successfully treated urinary sources of infection
  - IV only except minoycline



Combination Therapy?

- Three rationales for combo therapy
  - Increased activity (synergy)
  - Increase likelihood of one active agent
  - Prevent resistance from occurring
- Very little supporting evidence to engage in combination therapy
- Utilized in gray areas with very little data in the “kitchen sink” approach

Tamma PD. ClinMicroRev. 2012, 25(3):450. 2019;39(1):77–93

Phage Therapy

Bacteriophages are viruses which infect bacteria

- Very targeted/specific: certain species, subtypes of bacteria
- Bacterial killing thru, infection, replication within the bacteria, and eventual bacterial lysis
- Ubiquitous, often sourced from waste water
- Harmless to humans in direct manner

Have been developed as infection therapy

- Hindered by logistics
    - Difficult to operationalize
    - Difficult to study clinically
    - Bacteria can become resistant

Rahimi-Midani A. Antibiotics (Basel). 2021 Dec 6;10(12):1496.

CRE - Cefepime on day 3

Patient with UTI is still febrile but clinically stable

Which Drug?

- Ceftazidime- avibactam
- Ceftolozane-tazobactam
- Cefiderocol
- Meropenem-vaborbactam
- Imipenem-relebactam
- Aminoglycosides
- Plazomicin
- Polymyxins
- HD Ampicillin/sulbactam
- Eravacycline/ Minocycline/ Tigecycline

Urine growing ***E. coli*** with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

Septic CRE on day 3

Patient is deteriorating on cefepime and vancomycin,

- On vasopressors,
- Source is thought to be a pneumonia

Blood (line and peripheral) growing *E. coli* with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

Which Drug?

- Ceftazidime- avibactam
- Ceftolozane-tazobactam
- Cefiderocol
- Meropenem-vaborbactam
- Imipenem-relebactam
- Aminoglycosides
- Plazomicin
- Polymyxins
- HD Ampicillin/ sulbactam
- Eravacycline/ Minocycline/ Tigecycline

DTR PSA - Cefepime on day 3

Patient with UTI is still febrile but clinically stable

Urine growing ***P. aeruginosa*** with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

Which Drug?

- Ceftazidime- avibactam
- Ceftolozane-tazobactam
- Cefiderocol
- Meropenem-vaborbactam
- Imipenem-relebactam
- Aminoglycosides
- Plazomicin
- Polymyxins
- HD Ampicillin/ sulbactam
- Eravacycline/ Minocycline/ Tigecycline

Septic DTR PSA on day 3

Patient is deteriorating on cefepime and vancomycin,

- On vasopressors,
- Source is thought to be a pneumonia

Blood (line and peripheral) growing *P. aeruginosa* with following susceptibilities:

- Ceftazidime R
- Cefepime R
- Gentamicin S
- Levofloxacin R
- Meropenem R
- Pip/tazo R
- Tobramycin S

Which Drug?

- Ceftazidime- avibactam
- Ceftolozane-tazobactam
- Cefiderocol
- Meropenem-vaborbactam
- Imipenem-relebactam
- Aminoglycosides
- Plazomicin
- Polymyxins
- HD Ampicillin/ sulbactam
- Eravacycline/ Minocycline/ Tigecycline

Take Home Points

- Deescalate antibiotics when possible
- Longer duration of antibiotics not does equal better for many common infections
- MDR Infections pose a unique challenge
  - Dynamic landscape of resistance mechanisms
  - Each organism has its unique idiosyncrasies
- New drugs offer hope
  - They come to market with limited clinical data
  - Overlap with current drugs
  - Tend to be costly which limits empiric use
  - Resistance inevitably occurs once the drug is used

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