UWTASP

tele-antimicrobial stewardship program

Resistant Gram-negative Rods

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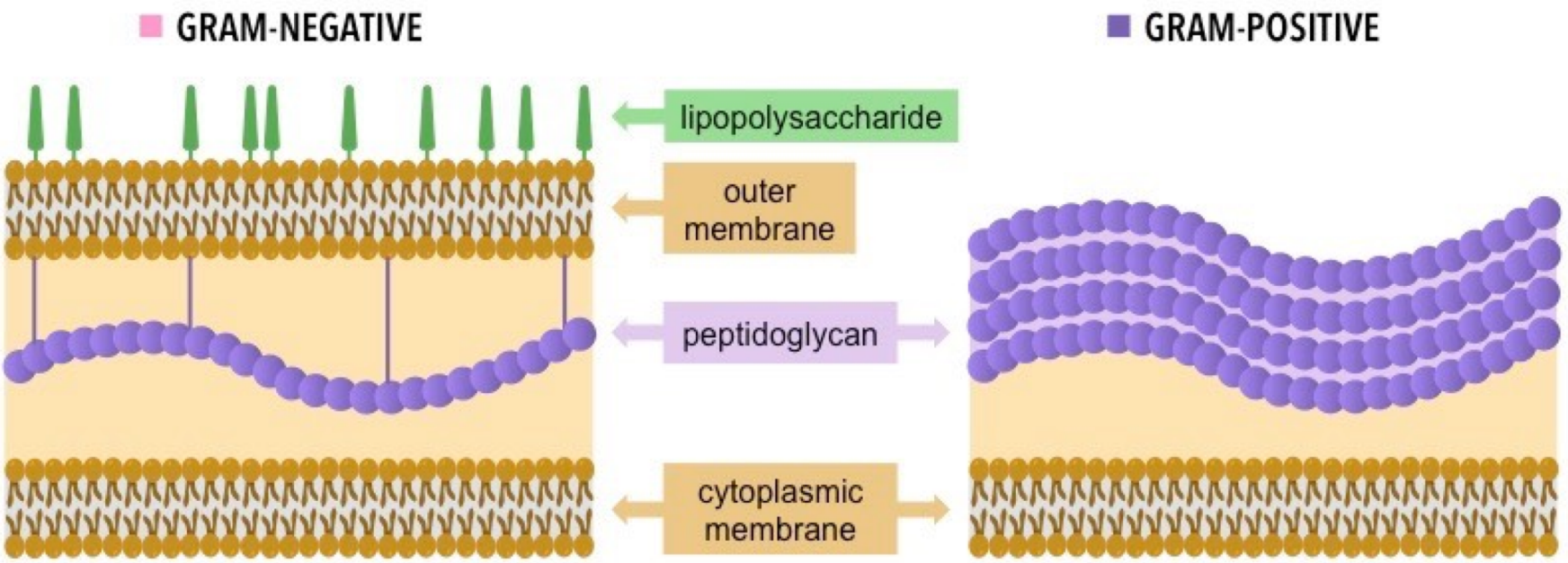
Disclosures

None

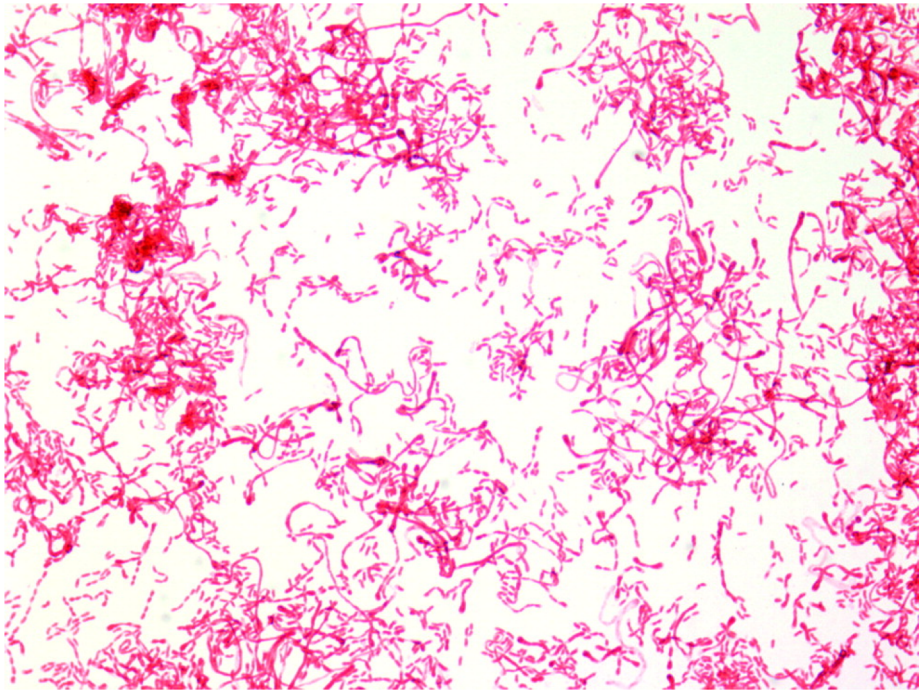
Except….

Gilead, ID WEEK 2019

Cell Envelope Review



Examples of Gram-negative rods (GNRs)

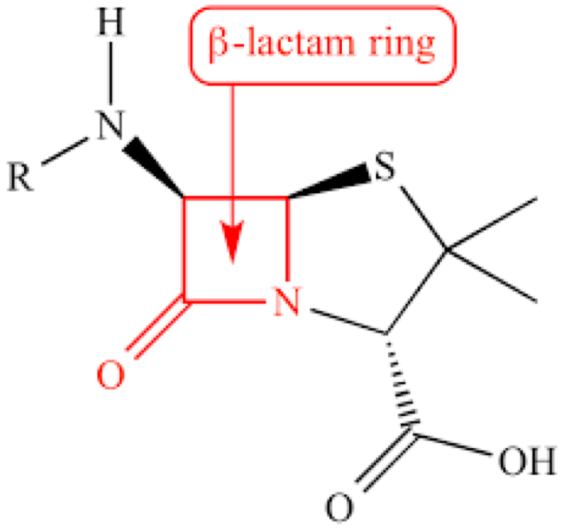


E. coli
Klebsiella spp
Pseudomonas spp
Citrobacter spp
Serratia spp
Enterobacter spp
Acinetobacter spp
Campylobacter spp
Legionella spp
Salmonella spp
Stenotrophomonas spp

the list goes on...

Beta-lactamases

- Major mechanism of gram-negative resistance
- >1000 different beta-lactamases
  - **ESBL (extended spectrum beta-lactamase)**
  - **AmpC beta-lactamase**
- Enzymes that break open the beta-lactam ring
- Encoded by either chromosomal or transferable genes on plasmids



ESBL

- Extended-spectrum beta-lactamase
- Found in ***Klebsiella* spp.*, E. coli*,** and other Enterobacteriaceae
- Types: CTX-M, TEM, SHV, OXA
- Hundreds of enzymes fall into this class
- Plasmid-encoded
- Can test for ESBL in the lab!

ESBL Review

- S to 2nd gen cephalosporins *in vitro*
- Should avoid pip/tazo; looks S *in vitro*, but not used clinically (may be OK for simple UTI)
- Cefepime – can be S or R depending on type
- **First-line therapy for serious infections = carbapenems**
- Cystitis: consider nitrofurantoin or fosfomycin
- In general if an *E. coli* or *Klebsiella* species is resistant to ceftriaxone or ceftazidime, then consider it an ESBL

	ESBL
Location	Plasmid
Bugs	*E.coli, Klebsiella*
1 gen Ceph	R
2 gen Ceph	S
3 gen Ceph	R
4 gen Ceph	S / R
Piperacillin-tazobactam	S
Carbapenem	S
Aztreonam	R

Merino Trial (2018)

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

- 379 bloodstream infections due to *E. coli* or *Klebsiella* resistant to ceftriaxone but susceptible to pip/tazo → randomized to pip/tazo or meropenem
- 30-day all-cause mortality higher with pip/tazo compared to meropenem

Wash your hands!

Meta-analysis in Lancet ID (2017): Antibiotic Stewardship programs reduced colonization and infection with ESBL organisms by 48%, and were more effective when implemented with hand hygiene interventions

Study in ICHE (2016): Hand hygiene was most effective method of controlling transmission of ESBL bugs in ICU (more than cohorting or antibiotic restrictions)

Case

80 yo F who had spine surgery with hardware placement last month. She presents with fever and a draining spinal wound, and she is admitted for washout. You order blood cultures and start ceftriaxone and vancomycin.

8 hours later, the micro lab calls you: blood cultures are growing a Gram-negative rod.

The next day

The Gram-negative rod is identified as *Enterobacter aerogenes* (now *Klebsiella aerogenes*). Sensitivities are pending. Her fevers are improving. What do you do next?

A. Continue ceftriaxone and wait for sensitivities

B. Switch to cefepime while waiting for sensitivities

C. Switch to meropenem while waiting for sensitivities

D. Add a fluoroquinolone to her regimen

Her sensis come back

Which of the following IV antibiotics is the most appropriate treatment for her *Enterobacter* bacteremia and spinal osteo?

A. Ceftriaxone

B. Meropenem

C. Cefepime

D. None of the above

ENTEROBACTER AEROGENES (NOW NAMED KLEBSIELLA AEROGENES)

	Microtiter MIC Interp	Microtiter MIC Value (mcg/mL)
Ampicillin	R	>16
Ampicillin/Sulbactam	I	16
Aztreonam	S	<=1
Cefazolin	R	>16
Cefepime	S	<=0.25
Cefotetan	R	
Ceftazidime	S	<=1
Ceftriaxone	S	<=0.25
Ciprofloxacin	S	<=0.06
Ertapenem	S	<=0.12
Gentamicin	S	<=4
Levofloxacin	S	<=0.5
Meropenem	S	<=1
Piperacillin/Tazobactam	S	<=2
Trimeth_Sulfamethoxazole	S	<=2

AmpC beta-lactamases

- Chromosomal enzymes that hydrolyze penicillins and 1st - 3rd gen cephs
- Bacteria initially appears susceptible, but becomes resistant during therapy *(particularly with third-gen cephalosporins)*
- Landmark study 1991 Chow et al
- AmpC gene becomes de-repressed via a complex pathway
- Selection for the AmpC beta-lactamase varies by the beta-lactam used and by the organism
- Beta-lactamase inhibitors do not work!
- No commercially available test for AmpC

AmpC organisms

Serratia

Enterobacter (many species, but *Enterobacter aerogenes* now called *Klebsiella aerogenes*)

Aeromonas

Citrobacter freundii

Hafnia alvei

Klebs**I**ella aerogenes

Morganella

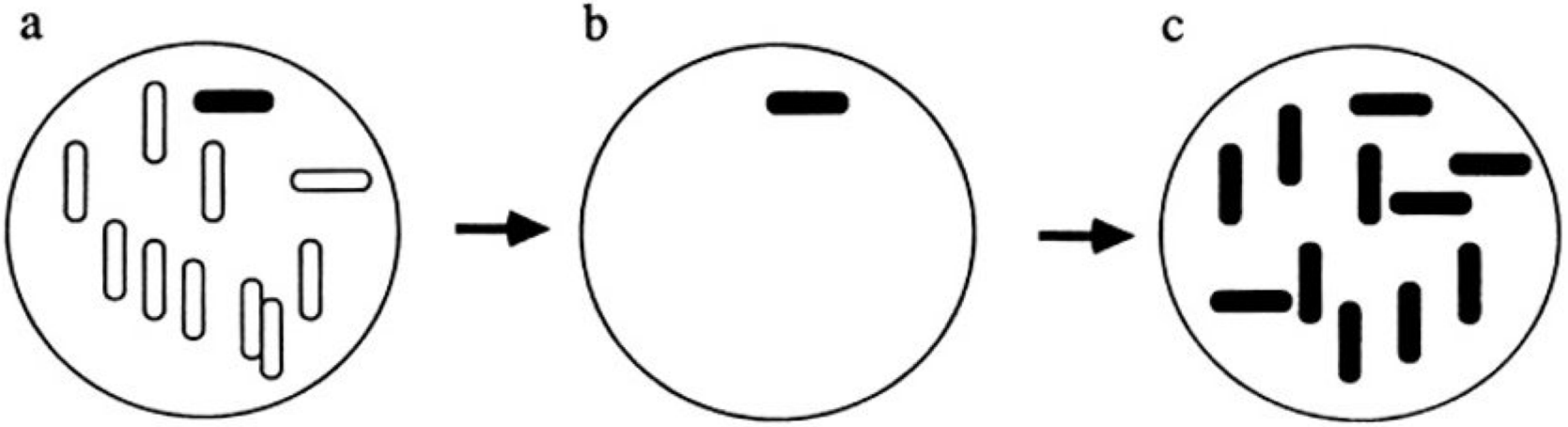
Providencia

Selection for AmpC

	Weak Inducer	Strong Inducer
Stable against hydrolysis	Cefepime	Imipenem Meropenem
Unstable against hydrolysis	Ceftriaxone Ceftazidime Piperacillin Aztreonam	Penicillin Ampicillin Amoxicillin Cefazolin

Slide courtesy of D. Black

Selection of AmpC



Ceftriaxone is able to eradicate most of the cells with repressed AmpC, but it is destroyed by AmpC and cannot eradicate the de-repressed mutant, so they multiply

Slide courtesy of Rupali Jain

After AmpC is de-repressed

	ampC	ESBL
Location	Chromosome	Plasmid
Bugs	"SEACHIMPK"	*E.coli, Klebsiella*
1 gen Ceph	R	R
2 gen Ceph	R	S
3 gen Ceph	R	R
4 gen Ceph	S	S / R
Piperacillin-tazobactam	S / R	S
Carbapenem	S	S
Aztreonam	R	R

Back to our case: 80 yo F with *Enterobacter* bacteremia

FQs & TMP/SMX are susceptible!

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Piperacillin/Tazobactam	S	<=2
Trimeth_Sulfamethoxazole	S	<=2

Avoid ceftriaxone!

Cefepime preferred over carbapenems!

Source matters!

Tamma et al (2013)

MAJOR ARTICLE

The Use of Cefepime for Treating AmpC β-Lactamase–Producing Enterobacteriaceae

Pranita D. Tamma,[1] Sonya C. T. Girdwood,[2] Ravindra Gopaul,[5] Tsigereda Tekle,[3] Ava A. Roberts,[3] Anthony D. Harris,[6] Sara E. Cosgrove,[4] and Karen C. Carroll[3]

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- Pt population: blood, BAL, or abd cultures growing *Enterobacter*, *Serratia*, or *Citrobacter*
- Compared clinical outcomes between 32 pts on cefepime and 32 matched pts on meropenem
- Conclusion: no difference in 30-day mortality or LOS

Beware of Enterobacter!

Table 1. Proportion of Microorganisms Testing Positive by Both the Cefotetan-Cloxacillin Etest and Cefotetan–Boronic Acid Disk Test for AmpC β-Lactamase Production

Organisms (n = 399)	AmpC β-Lactamase Positive, No.
Enterobacter spp (n = 213)	82 (38%)
Enterobacter cloacae (n = 131)	51
Enterobacter aerogenes (n = 77)	31
Enterobacter asburiae (n = 3)	0
Enterobacter hormaechei (n = 2)	0
Serratia marcescens (n = 86)	13 (15%)
Citrobacter spp (n = 100)	1 (1%)
Citrobacter freundii (n = 70)	1
Citrobacter koseri (n = 30)	0

- **38% of *Enterobacter* produced AmpC**
- Compared to 15% *Serratia* and 1% *Citrobacter*

Takeaways

ESBL

- Think *E. coli* and *Klebsiella* resistant to ceftriaxone
- Appears S to 2nd gen cephs (unlike AmpC)
- **Carbapenems are treatment of choice for serious infections**

AmpC

- Think SEACHIMPK! (especially Enterobacter)
- Avoid the use of first – third gen cephs, even if susceptible *in vitro*
- **Cefepime is treatment of choice for serious infections**

References

Baur et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017; 17(9):990-1001.

Chow et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 1991; 115:585–90.

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Pelat et al. Hand Hygiene, Cohorting, or Antibiotic Restriction to Control Outbreaks of Multidrug-Resistant Enterobacteriaceae. Infect Control Hosp Epidemiol 2016; 37(3):272-80.

Tamma et al. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis 2019; 69(8):1446-1455.

Tamma et al. The use of cefepime for treating AmpC β-lactamase-producing Enterobacteriaceae. Clin Infect Dis 2013; 57:781–8.