UWTASP

tele-antimicrobial stewardship program

June 25, 2019

ampC vs ESBL

UTI

We recently had a patient who grew Enterobacter cloacae complex from a urine culture.

1. Is this an ESBL and/or AmpC overproducing organism?
2. Are others putting these patients in isolation for ESBL/AmpC and/or sending this organism out for confirmation testing?
3. Are you flagging their chart as ESBL/AmpC patients?

Enterobacter cloacae complex

Drug	MIC	Interpretation
Cefazolin *(1st gen)*	>/= 64	Resistant
Cefoxitin *(2nd gen)*	>/= 64	Resistant
Ceftazidime *(3rd gen)*		Resistant
Ceftriaxone	>/= 64	Resistant
Ciprofloxacin	</= 0.25	Sensitive
Gentamicin	</= 1	Sensitive
Nitrofurantoin	64	Intermediate
Piperacillin-tazobactam	8	Sensitive
Tobramycin	</= 1	Sensitive
Trimethoprim-Sulfamethoxazole	</=20	Sensitive

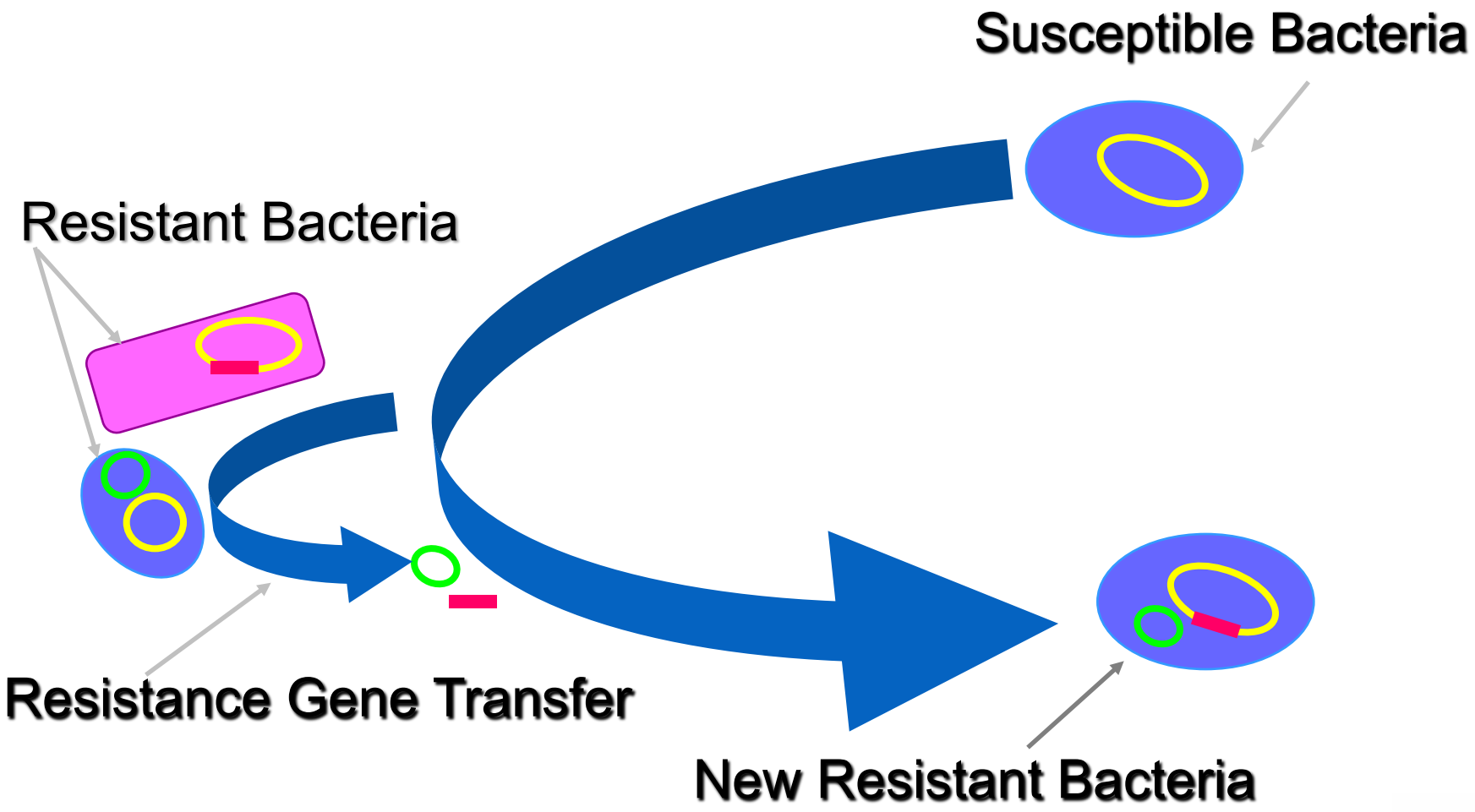
citations

Beta-Lactamases

- Inactivate these antibiotics by splitting the amide bond of the beta-lactam ring.
- Encoded by either chromosomal or transferable genes located on plasmids and transposons.
- More than 600 beta-lactamases have been described!!!!

citations

Emergence of Antimicrobial Resistance



citations

CDC

Extended Spectrum ß-Lactamases

- **Mechanism:** Drug Inactivation (Enzymes hydrolyze all ß-lactams)
- Types: CTX-M, TEM, SHV, OXA
- Usually in *Klebsiella* spp. and *E.coli… but plasmid-encoded*

citations

Laboratory Detection of ESBL

MOA	ESBL
Location	Plasmid
Inducible	*NO*
Bugs	*E.coli, Klebsiella*
1 gen Ceph	R
2 gen Ceph	S
3 gen Ceph	R
4 gen Ceph	R / S
Pip-tazo	S
Carbapenem	S
Aztreonam	R

- Commonly shows 2nd generation cephs susceptibility
- Piperacillin-tazobactam often looks susceptible in-vitro but not used clinically
- Cefepime can look either susceptible or resistance depending the type (CTX-M, SHV, TEM)
- In general if an *E.coli* or *Klebsiella* species is resistant to ceftriaxone or ceftazidime, then consider it an ESBL

citatic

ampC

- Chromosomal enzymes that hydrolyze penicillins & 1-3st generation cephalosporins
- The ampC gene is inducible via a complex pathway involving recycled cell-wall peptidoglycans.
- Selection/induction for the ampC β-lactamase varies by beta-lactam antibiotic used; stability of the antibiotic to the β-lactamase activity also varies
- Beta-lactamase inhibitors do not work against them
- No commercially available test for ampC

citations

ampC organisms

- Serratia
- Enterobacter (new: *Klebsiella aerogenes*)
- Aeromonas
- Citrobacter
- Hafnai alvei
- Indole + Proteus (vulgaris)
- Morganella
- Pseudomonas, Providencia

citations

Selection for ampC

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

Even though carbapenems are strong inducers, they are stable against hydrolysis

citations Slide courtesy of D.Black

Selection of ampC

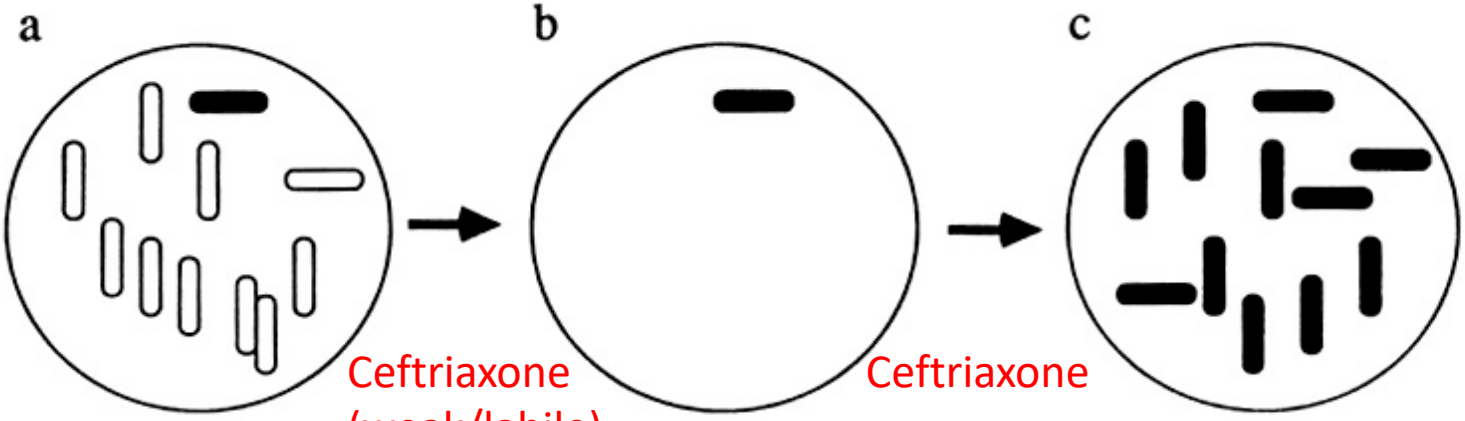


Fig. 1. Selection of a β-lactamase derepressed mutant. Stably derepressed cells are shown as ▬, inducible ones as ▭. Initially (*a*) the population contains a minority of derepressed mutants. However, (*b*) as the labile weak inducer acts, the inducible cells are killed whereas the derepressed cells survive and (*c*) grow until they dominate the microflora.

Ceftriaxone is able to eradicate most of the cells with repressed ampC BUT since it is labile to destruction by ampC it cannot eradicate the derepressed mutant and they MULTIPLY !

citations

Comparison

	ampC	ESBL	CPE
Location	Chromosome	Plasmid	Plasmid
Bugs	"SEACHIMPK"	*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	R	S	R
Carbapenem	S	S	R
Aztreonam	R	R	R/S*

* Sensitive for Metallo-beta-lactamases only

citations

Treatment of ampC

Stewardship recommends cefepime over meropenem!

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]

[1]Department of Pediatrics, Division of Infectious Diseases, [2]Department of Medicine, [3]Department of Pathology, Division of Medical Microbiology, and [4]Department of Medicine, Division of Infectious Diseases, Johns Hopkins Medical Institutions; and [5]Department of Medicine and [6]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland

- ✓ Pt population: Hospitalized patients with blood, BAL or intra-abdominal fluid growing Enterobacter spp, Serratia spp or Citrobacter spp
- ✓ Compared treatment with cefepime with matched patients treated with meropenem
- ✓ No difference in 30-day mortality or length of hospital stay
- ✓ Treatment options: depends on susceptibility
- ✓ Often cefepime or meropenem but FQs are options often

citations

Treatment of ESBL

- Carbapenems are the mainstay
  - but depends on the site of infection
  - AVOID piperacillin-tazobactam and cefepime

- Uncomplicated UTIs, depends on susceptibilities:
  - Nitrofurantoin or Fosfomycin are options

citations