UPDATES IN THE TREATMENT OF DRUG-RESISTANT ENTEROBACTERALES INFECTIONS

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DISCLOSURES

- There are no financial conflicts of interest to disclose in relation to this activity.

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LEARNING OBJECTIVES

At the conclusion of this program, pharmacist participants should be able to:

- Identify gram-negative organisms with high rates of antimicrobial resistance
- Describe resistance mechanisms of extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases
- Discuss findings of research literature describing the treatment of resistant gram-negative infections
- Select antimicrobials for a treatment regimen covering gram-negative infections

At the conclusion of this program, pharmacy technician participants should be able to:

- List two gram-negative organisms with high rates of antimicrobial resistance
- antimicrobials that can withstand resistance mechanisms by ESBL and AmpC producing Enterobacterales
- Recall place in therapy of novel antimicrobials when treating resistant bacteria
- List two antimicrobials that can withstand resistance mechansims by ESBL and AmpC producing Enterobacterales

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ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR)

- Per the CDC more than 2.8 million antimicrobial-resistant infections occur in the US annually
  - Deaths include over 35,000 patients
  - Bacteria are listed in THREE categories: urgent, serious, concerning!

Urgent

- Carbapenem-resistant *Acinetobacter*
- *Clostridioides dificile*
- Carbapenem-resistant Enterobacterales
- Drug-resistant *Neisseria gonorrhoeae*

Serious

- Drug-resistant *Campylobacter*
- ESBL-producing Enterobacterales
- Vancomycin-resistant *Enterococci*
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant *Salmonella* and *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning

- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

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Tamma PD, et al. *Clin Infect Dis*. Published online July 18, 2023
Antimicrobial resistance. Centers for Disease Control and Prevention. Updated November 23, 2021

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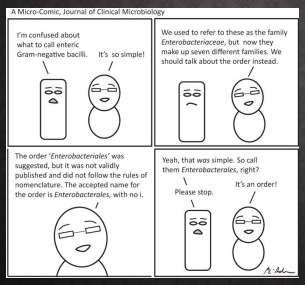
ENTEROBACTERALES VS ENTEROBACTERIACEAE



- Enterobacterales
  - Enterobacteriaceae
  - Erwiniaceae
  - Hafniaceae
  - Morganellaceae
  - Yersiniaceae
  - Budiviciaceae
  - Pectobacteriaceae

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McAdam AJ. *J Clin Microbiol*. 2020;58(2):e01888-19. Published 2020 Jan 28

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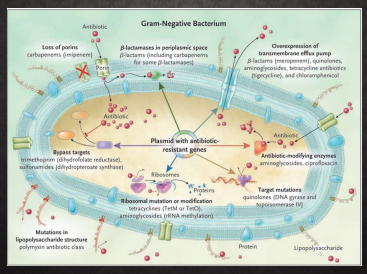
RESISTANCE IN GRAM-NEGATIVE ENTEROBACTERALES



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Peleg AY, Hooper DC. *N Engl J Med*. 2010;362(19):1804-1813

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MECHANISMS OF RESISTANCE IN GRAM-NEGATIVE ENTEROBACTERALES

- Decreased cell permeability
  - Aminoglycosides, beta-lactams, fosfomycin
- Efflux pumps
  - Fluoroquinolones, tetracyclines
- Enzymatic modification or drug degradation
  - Aminoglycosides, **beta-lactams,** fluoroquinolones, tetracyclines
- Target site modification
  - Aminoglycosides, polymyxins, fluoroquinolones, sulfamethoxazole/trimethoprim
- Target site protection
  - Fluoroquinolones, tetracyclines

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Dass. ACCP Clinical Reasoning Series in Pharmacotherapy 2023 – Part one.

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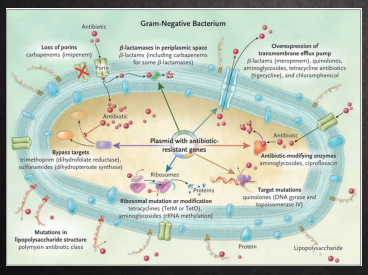
RESISTANCE IN GRAM-NEGATIVE ENTEROBACTERALES



- Decreased cell permeability
- Efflux pumps
- Enzymatic modification or drug degradation
- Target site modification

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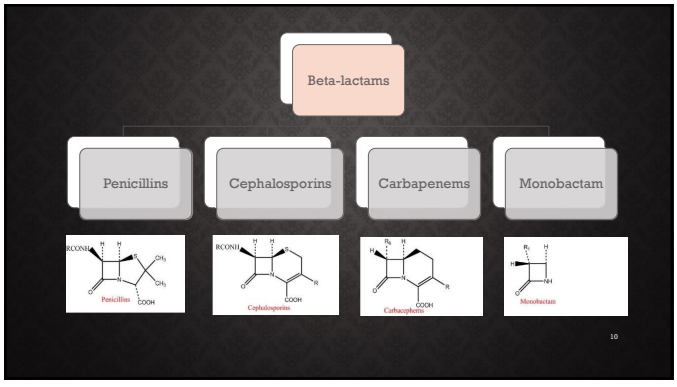

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BETA-LACTAMASES

Ambler Class (active site)	Organisms	Beta-lactamases	Substrates
A (serine)	*E. coli*, *Klebsiella* spp.	TEM-1, TEM-2, SHV-1	Ampicillin, cefazolin
	E. coli, *Klebsiella* spp.	SHV-2, CTX-M	Extended spectrum penicillins and cephalosporins
	E. coli, *Klebsiella* spp., *Enterobacter* spp.	KPC	Carbapenems
B (zinc)	*E. coli*, *Klebsiella* spp., *Enterobacter* spp.	NDM, VIM, IMP	Carbapenems
C (serine)	Plasmid: *E. coli*, *K. pneumoniae* Inducible: *E. cloacae*, *K. aerogenes*, *C. freundii*	AmpC, ACT, CMY, DHA, FOX	Penicillins and cephalosporins (1st-3rd gen)
D (serine)	*E.coli*, *Klebsiella* spp., *Enterobacter* spp.	OXA-48, OXA-50	Penicillins, cephalosporins, and carbapenems

Werth BJ. Beta-lactams . Merck Manual . September 2022. Accessed February, 2024
Dass. ACCP Clinical Reasoning Series in Pharmacotherapy 2023 – Part one.

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EXTENDED SPECTRUM BETA-LACTAMASES

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EXTENDED SPECTRUM BETA-LACTAMASES

- Increasing incidence in the United States
  - ↑ by 53% from 2012 to 2017, mainly due to higher number of community-acquired infections
- Extended spectrum beta-lactamases (ESBLs)
  - Inactivate most penicillins, cephalosporins, and aztreonam
  - Remain susceptible to carbapenems
  - Do not affect non-beta-lactams
- ESBLs are found most commonly in *E.coli, K. pneumoniae, K. oxytoca, and P. mirabilis*
  - Resistance mechanism: CTX-M enzymes, particularly CTX-M-15
  - Ceftriaxone MIC ≥2 if often used as a proxy for ESBL production

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ESBL ENTEROBACTERALES (ESBL-E) TREATMENT OPTIONS

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ESBL-E UNCOMPLICATED CYSTITIS

Preferred Therapy	Alternative Therapy	Not Suggested
Nitrofurantoin	Fluoroquinolones	Amoxicillin/ clavulanate
TMP-SMX	Carbapenems	Doxycycline
	Single dose of IV aminoglycoside	Cephamycins
	Fosfomycin (*E.coli* only)	
	Piperacillin/tazobactam or cefepime*	
	Novel beta-lactam agents^	

TMP-SMX: trimethoprim-sulfamethoxazole
*Continue if started empirically and was later identified as ESBL-E and clinical improvement occurs
^Reserve use (carbapenem resistance/drug interactions/polymicrobial infections)

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ESBL-E PYELONEPHRITIS AND COMPLICATED UTI

Preferred Therapy	Alternative Therapy	Reserved Therapy*	Not Suggested
TMP-SMX	Aminoglycosides full course	Ceftazidime-avibactam	Piperacillin-tazobactam or cefepime or cephamycins
Fluoroquinolones (cipro, levo)	Piperacillin-tazobactam	Meropenem-vaborbactam	Fosfomycin
Carbapenems (mero, imi-cil, erta)		Imipenem-cilastatin-relebactam	Nitrofurantoin
		Cefiderocol	Doxycycline

TMP-SMX: trimethoprim-sulfamethoxazole
*Reserve use (carbapenem resistance/drug interactions/polymicrobial infections)

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ESBL-E INFECTIONS OUTSIDE OF THE URINARY TRACT

Preferred Therapy	Preferred Therapy for Transition	Reserved Therapy	Not Suggested
Carbapenems*	Transition from carbapenems to oral TMP-SMX or fluoroquinolones if susceptible and criteria is met	Ceftazidime-avibactam	Piperacillin/tazobactam or cefepime or cephamycins
		Meropenem-vaborbactam	Nitrofurantoin
		Imipenem-cilastatin-relebactam	Fosfomycin
		Cefiderocol	Amoxicillin-clavulanate
			Doxycycline
			Omadacycline
			Ceftolozane-tazobactam

TMP-SMX: trimethoprim-sulfamethoxazole
*Critically ill/hypoalbuminemia: meropenem or imipenem preferred

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AMPC BETA-LACTAMASES

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AMPC BETA-LACTAMASES

- Ambler classification – Class C enzymes
- Beta-lactamase enzymes produced by several Enterobacterales
  - Function – assist with cell wall recycling
- Hydrolyze beta-lactams in the following settings:
  - Basal AmpC production
  - Increased AmpC production
    1. Inducible chromosomal gene expression (eg, *Enterobacter cloacae*)
    2. Stable chromosomal gene de-repression (eg, *Escherichia coli*)
    3. Constitutively expressed AmpC genes (eg, *Klebsiella pneumoniae*)

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Tamma PD et al. *Clin Infect Dis*. 2019;69(9):1446-1455
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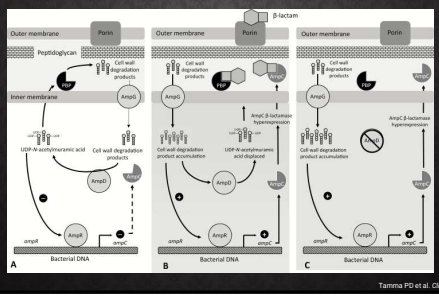
AMPC BETA-LACTAMASES



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AMPC BETA-LACTAMASE PRODUCING ENTEROBACTERALES

- Induce AmpC expression
  - Specific antibiotics can induce AmpC expression and thereby increase AmpC production
  - Increase MICs to certain antibiotics such as 3rd generation cephalosporins
  - Enterobacterales that initially show susceptibility to ceftriaxone may become resistant after a few doses of ceftriaxone
- Stable chromosomal de-repression or constitutively expressed AmpC genes
  - AmpC production is ALWAYS increased and will not test as susceptible to 3rd generation cephalosporins

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AMPC BETA-LACTAMASE PRODUCING ENTEROBACTERALES

- Commonly used acronyms to identify AmpC producers: SPACE, SPICE, OR ESCPM
  - Ignores variance within bacterial genera
  - Overly simplified
  - Old nomenclature
- Organisms at risk for AmpC production:

Moderate to High Risk	*Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*
<5% Risk	*Serratia marcescens*, *Morganella morganii*, and *Providencia spp.*

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AMPC BETA-LACTAMASE PRODUCING ENTEROBACTERALES

- Less commonly encountered organisms with inducible chromosomal AmpC genes:

Less commonly encountered organisms

- *Hafnia alvei*
- *Citrobacter youngae*
- *Yersinia enterocolitica*

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AMPC BETA-LACTAMASE PRODUCING ENTEROBACTERALES (AmpC-E)

TREATMENT OPTIONS

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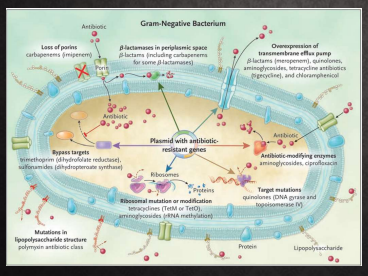
RESISTANCE IN GRAM-NEGATIVE ENTEROBACTERALES



- Decreased cell permeability
- Efflux pumps
- Enzymatic modification or drug degradation
- Target site modification

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BETA-LACTAMS: INDUCTION AND HYDROLYSIS

	Potent AmpC Inducer	Weak AmpC Inducer
Susceptible to Hydrolysis	Aminopenicillins Narrow-spectrum cephalosporins Cephamycins	Piperacillin-tazobactam Ceftriaxone Ceftazidime Aztreonam
Resistant to Hydrolysis	Imipenem	Cefepime
	Ertapenem, meropenem*	
	*Induction potential has not been formally investigated	

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MODERATE TO HIGH RISK OF INDUCIBLE AMPC-E INFECTIONS

Cefepime	• When cefepime MIC <4
Carbapenem	• When cefepime MIC ≥4 if susceptible to carbapenem
3rd generation cephalosporins	• Do NOT use for invasive infections; reasonable for uncomplicated cystitis

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MODERATE TO HIGH RISK OF INDUCIBLE AMPC-E INFECTIONS

Piperacillin-tazobactam	• Do NOT use for serious infections; reasonable for mild infections such as uncomplicated cystitis
Ceftazidime-avibactam	• Reserve use
Meropenem-vaborbactam	• Reserve use
Imipenem-cilastatin-relebactam	• Reserve use
Cefiderocol	• Reserve use
Ceftolozane-tazobactam	• Do NOT use

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LOW RISK OF INDUCIBLE AMPC-E INFECTIONS

- Low risk:
  - <5% Risk: *Serratia marcescens, Morganella morgannii,* and *Providencia spp.*
    - Use susceptibility results to guide treatment
    - Exception: high bacterial burden and limited source control → can use cefepime
- Less commonly encountered organisms with inducible chromosomal AmpC genes:
  - *Hafnia alvei*
    Citrobacter youngae
    Yersinia enterocolitica
    - Evidence is limited; Use antimicrobial susceptibility results to guide treatment
    - Exception: high bacterial burden and limited source control → can use cefepime

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DOSING GUIDANCE

Table 1. Suggested dosing of antibiotics for the treatment of antimicrobial resistant infections in adults, assuming normal renal and hepatic function[12]

Amikacin	**Uncomplicated cystitis:** 15 mg/kg IV as a single dose **Pyelonephritis or complicated urinary tract infections:** 15 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in **Supplemental Material.**
Cefepime	**Uncomplicated cystitis:** 1 gram IV every 8 hours, infused over 30 minutes **All other infections:** 2 grams IV every 8 hours, infused over 3 hours (if possible)
Ciprofloxacin	**Cystitis:** 400 milligrams IV every 12 hours or 500 milligrams PO every 12 hours **All other infections:** 400 milligrams IV every 8 hours **OR** 750 milligrams PO every 12 hours
Meropenem	**Uncomplicated cystitis:** 1 grams IV every 8 hours, infused over 30 minutes **All other infections:** 2 grams IV every 8 hours, infused over 3 hours (if possible) Additional information in **Supplemental Material.**
Ertapenem	1 gram IV every 24 hours, infused over 30 minutes
Fosfomycin	**Uncomplicated cystitis:** 3 grams PO as a single dose
Gentamicin	**Uncomplicated cystitis:** 5 mg/kg/dose IV as a single dose **Pyelonephritis or complicated urinary tract infections:** 7 mg/kg IV once; subsequent doses and dosing interval based on pharmacokinetic evaluation Additional information in **Supplemental Material.**
Imipenem-cilastatin	**Uncomplicated cystitis:** 500 mg IV every 6 hours, infused over 30 minutes **All other infections:** 500 mg IV every 6 hours, infused over 3 hours (if possible) Additional information in **Supplemental Material.**
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 hours, infused over 30 minutes Additional information in **Supplemental Material.**
Levofloxacin	750 milligrams IV/PO every 24 hours
Nitrofurantoin	**Macrocrystal/monohydrate (Macrobid®):** 100 mg PO every 12 hours **Oral suspension:** 50 milligrams PO every 6 hours
Trimethoprim-sulfamethoxazole	**Cystitis:** 160 mg (trimethoprim component) IV/PO every 12 hours **Other infections:** 8-12 mg/kg/day (trimethoprim component) IV/PO divided every 8 to 12 hours (consider maximum dose of 960 mg trimethoprim component per day) Additional information in **Supplemental Material.**

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NEW ACRONYM??

A. KA.CF.EC
B. KA.EC.CF
C. CF.EC.KA
D. CF.KA.EC
E. EC.KA.CF
F. EC.CF.KA

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QUESTIONS?

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