AmpC B-Lactamases - The Stealthy Inducible Mechanism of Resistance

Presented by: Garret Hino Jr., PharmD, BCIDP

Hawaii State Department of Health

Objectives

- Describe the mechanism of resistance for ampC B-lactamases.
- Identify moderate- to high-risk organisms that can harbor ampC B-lactamases.
- Review Infectious Diseases Society of America (IDSA) Guidelines for treatment and management of ampC B-lactamase producing organisms.
- Compare therapeutics and assess primary literature supporting utilization of select antimicrobials for ampC B-lactamase producing organisms.

AmpC B-Lactamases – Introduction and Mechanism of Resistance

Objectives

- **Describe the mechanism of resistance for AmpC B-lactamases.**
- Identify moderate- to high-risk organisms that can harbor AmpC B-lactamases.
- Review Infectious Diseases Society of America (IDSA) Guidelines for treatment and management of AmpC B-lactamase producing organisms.
- Compare therapeutics and assess primary literature supporting utilization of select antimicrobials for AmpC B-lactamase producing organisms.

Introduction – What are AmpC B-Lactamases?

- Class C serine B-lactamase enzymes (Cephalosporinases) that can rapidly hydrolyze penicillins, cephalosporins, and monobactams.
- Not significantly inhibited by B-lactamase inhibitors (i.e., clavulanate, sulbactam, tazobactam.)

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Introduction – What are AmpC B-Lactamases?

- AmpC production generally occurs by one of three mechanisms:
  - Inducible chromosomal resistance
  - Non-inducible chromosomal de-repression
  - Plasmid-mediated *ampC* gene

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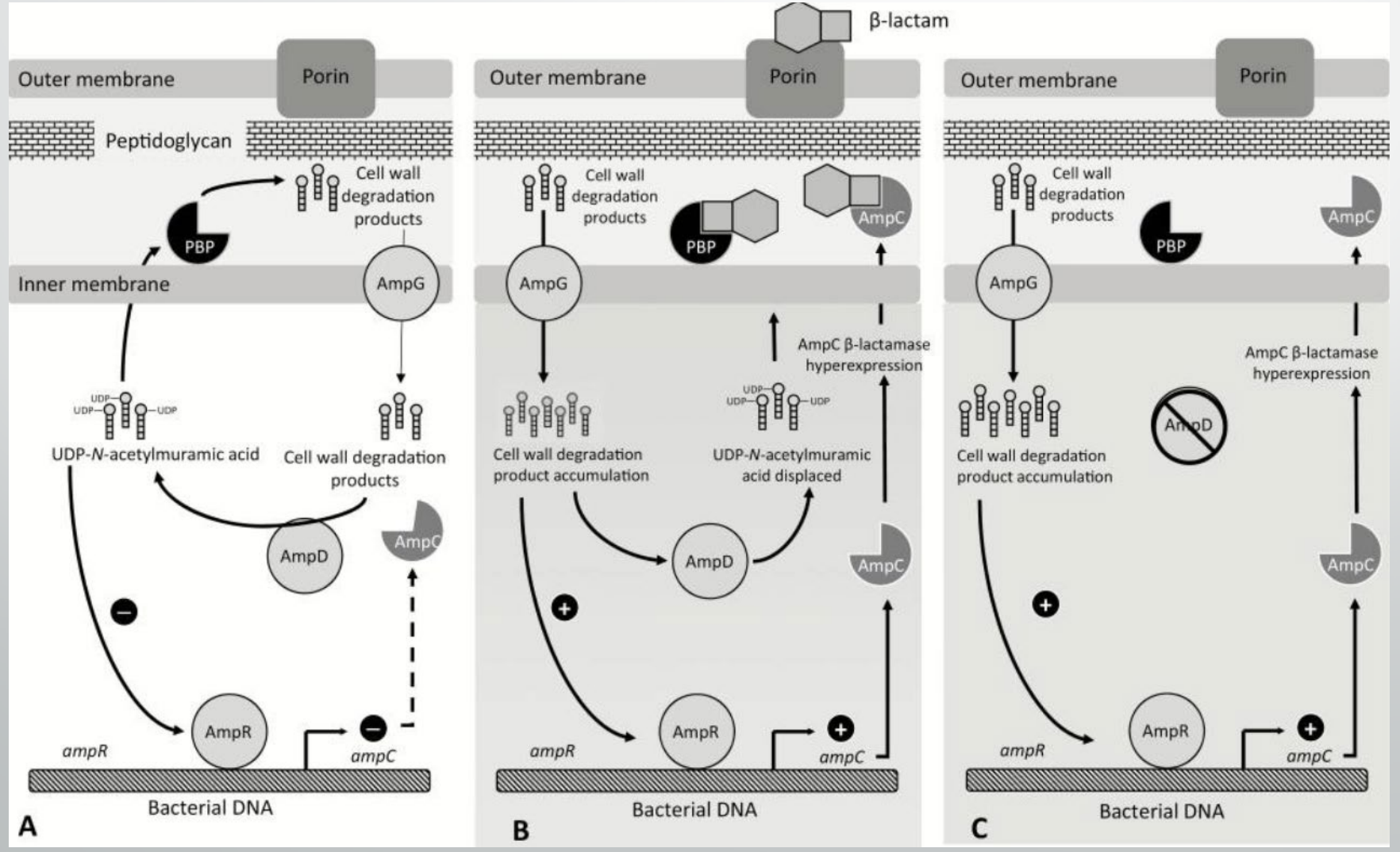
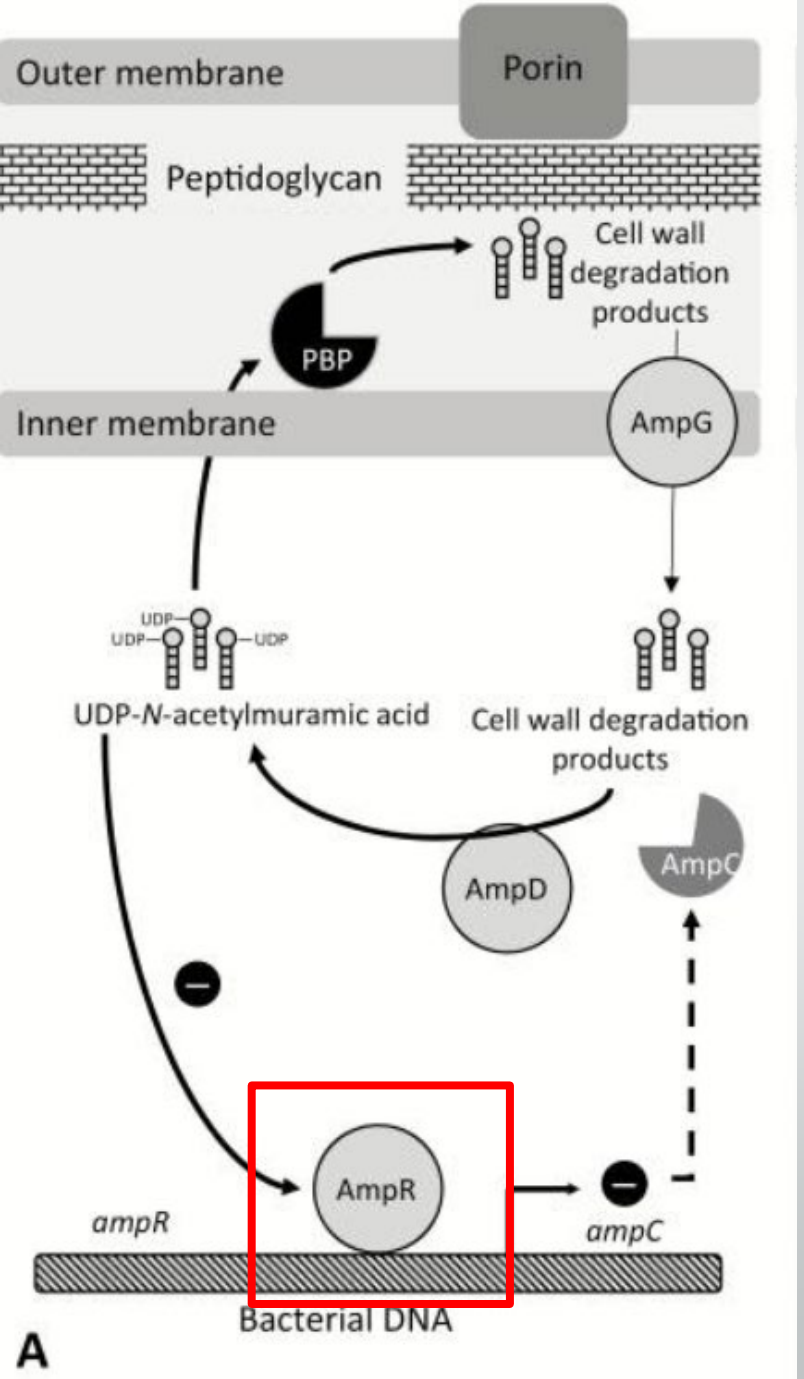
AmpC B-Lactamases – Mechanism of Resistance





- **AmpR** – Regulatory protein that inhibits AmpC B-lactamase expression

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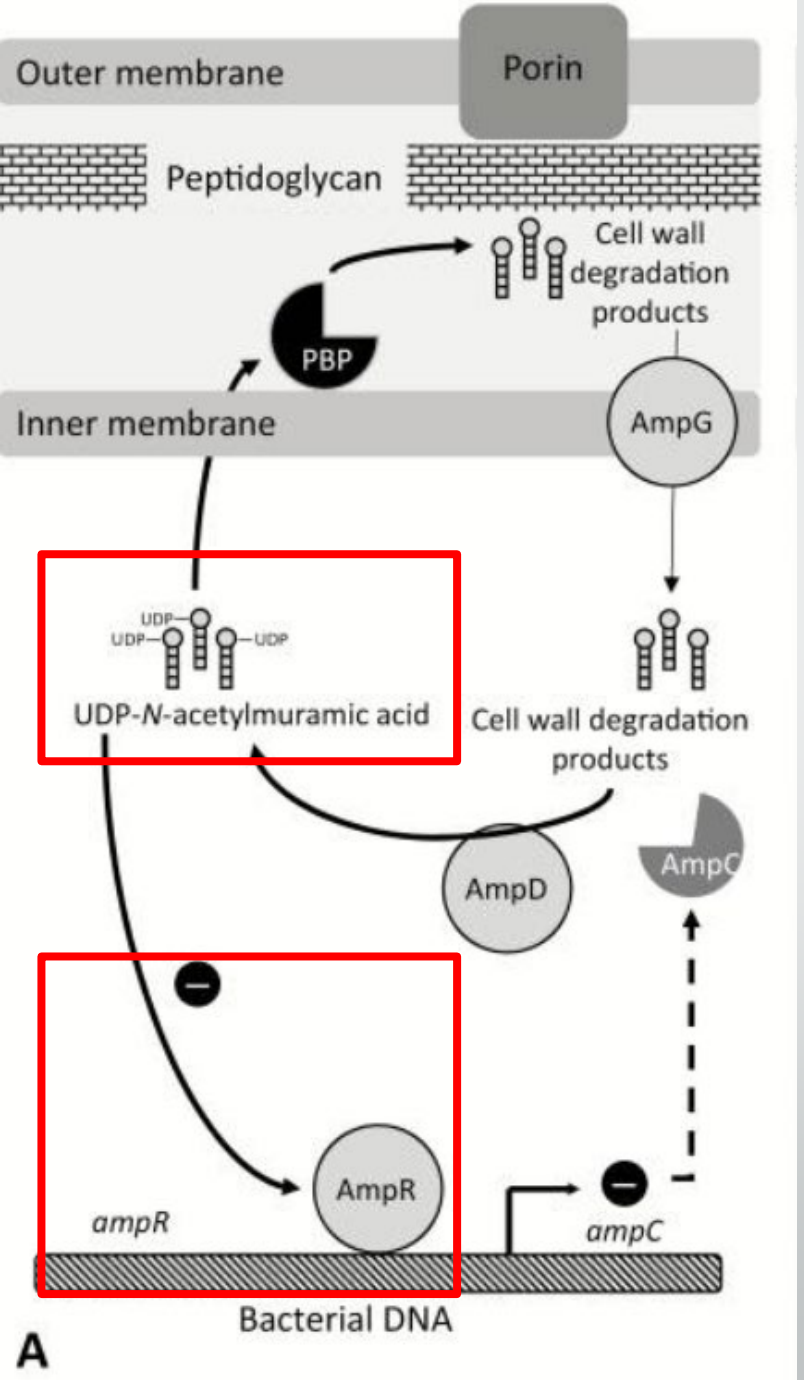

- **AmpR** = Regulatory protein that inhibits AmpC B-lactamase expression
- **Uridine diphosphate (UDP)-N-acetylmuramic acid peptides** = Negative regulator for ampC

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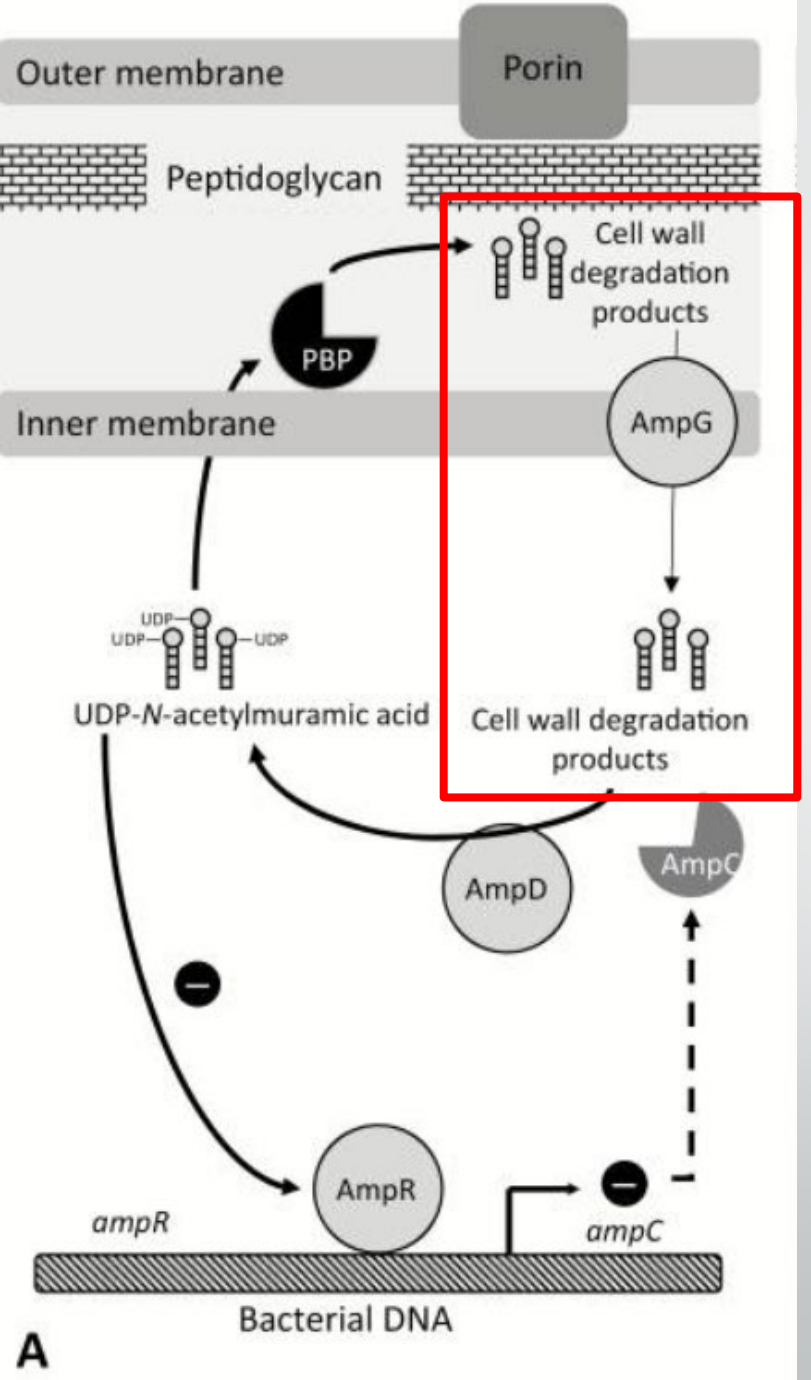

- **AmpR** = Regulatory protein that inhibits AmpC B-lactamase expression
- **Uridine diphosphate (UDP)-N-acetylmuramic acid peptides** = Negative regulator for ampC
- **AmpG** = transporter of oligopeptides into cytosol

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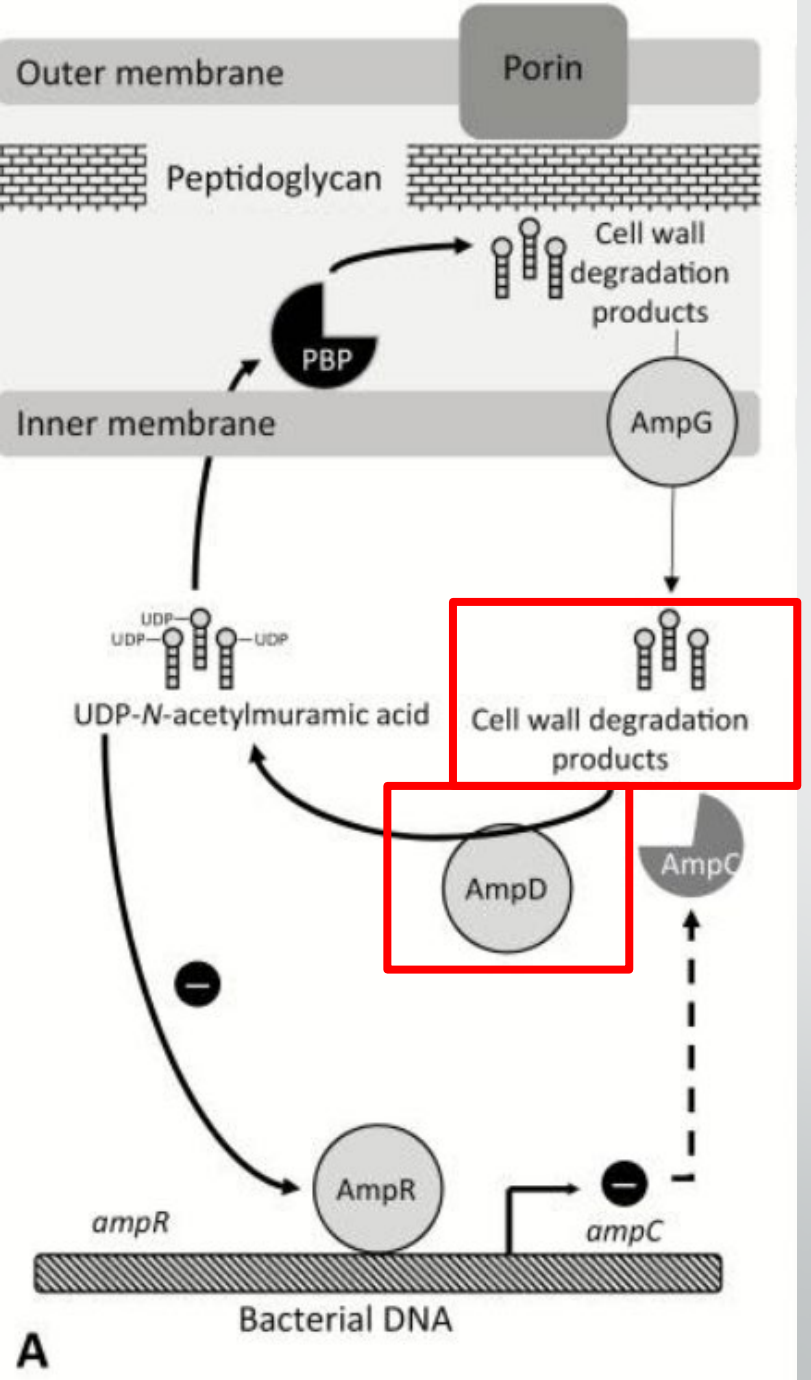

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- **Uridine diphosphate (UDP)-N-acetylmuramic acid peptides** = Negative regulator for ampC
- **AmpG** = transporter of oligopeptides into cytosol
- **AmpD** = cleaves residues off cell-wall degradation products

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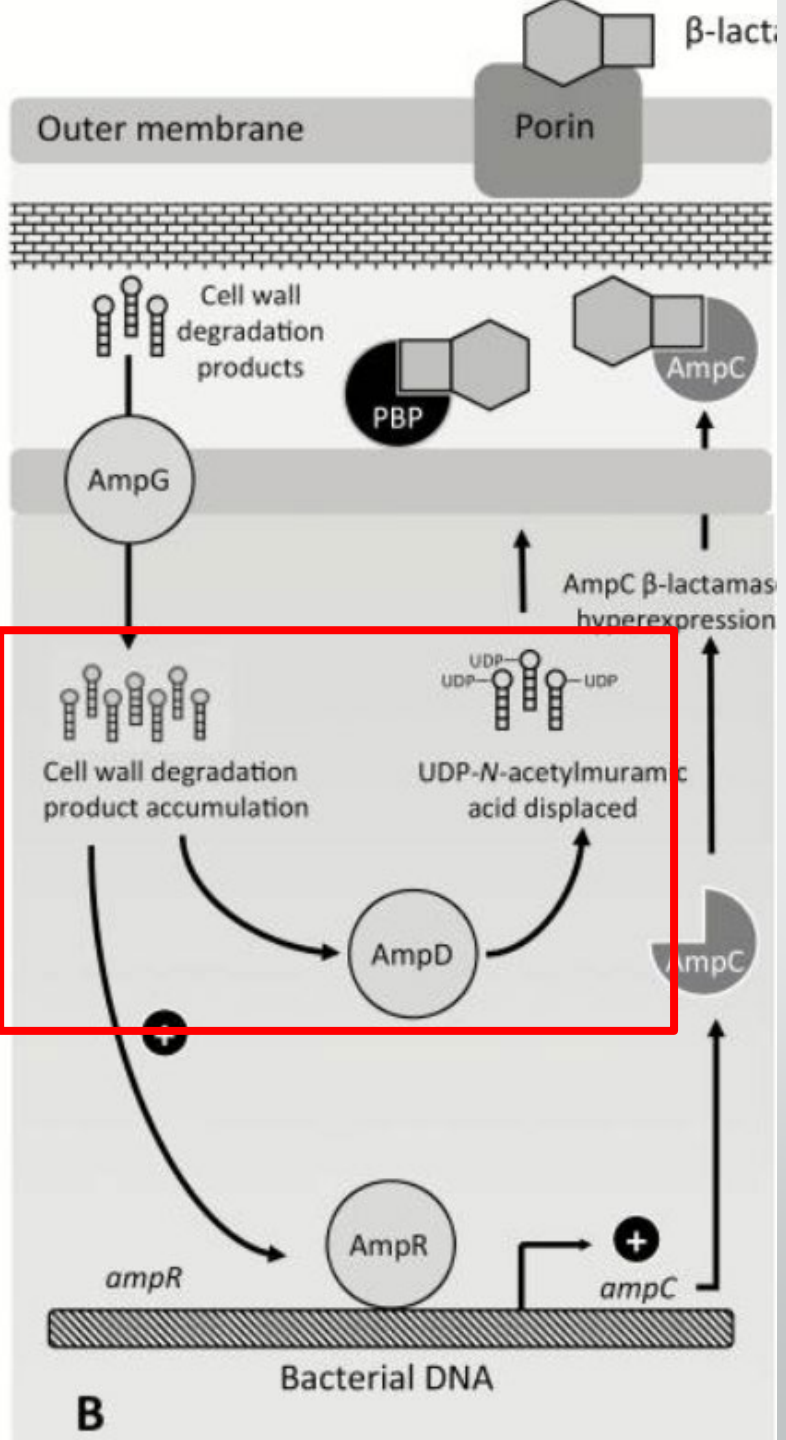
AmpC B-lactamase – Hyperexpression



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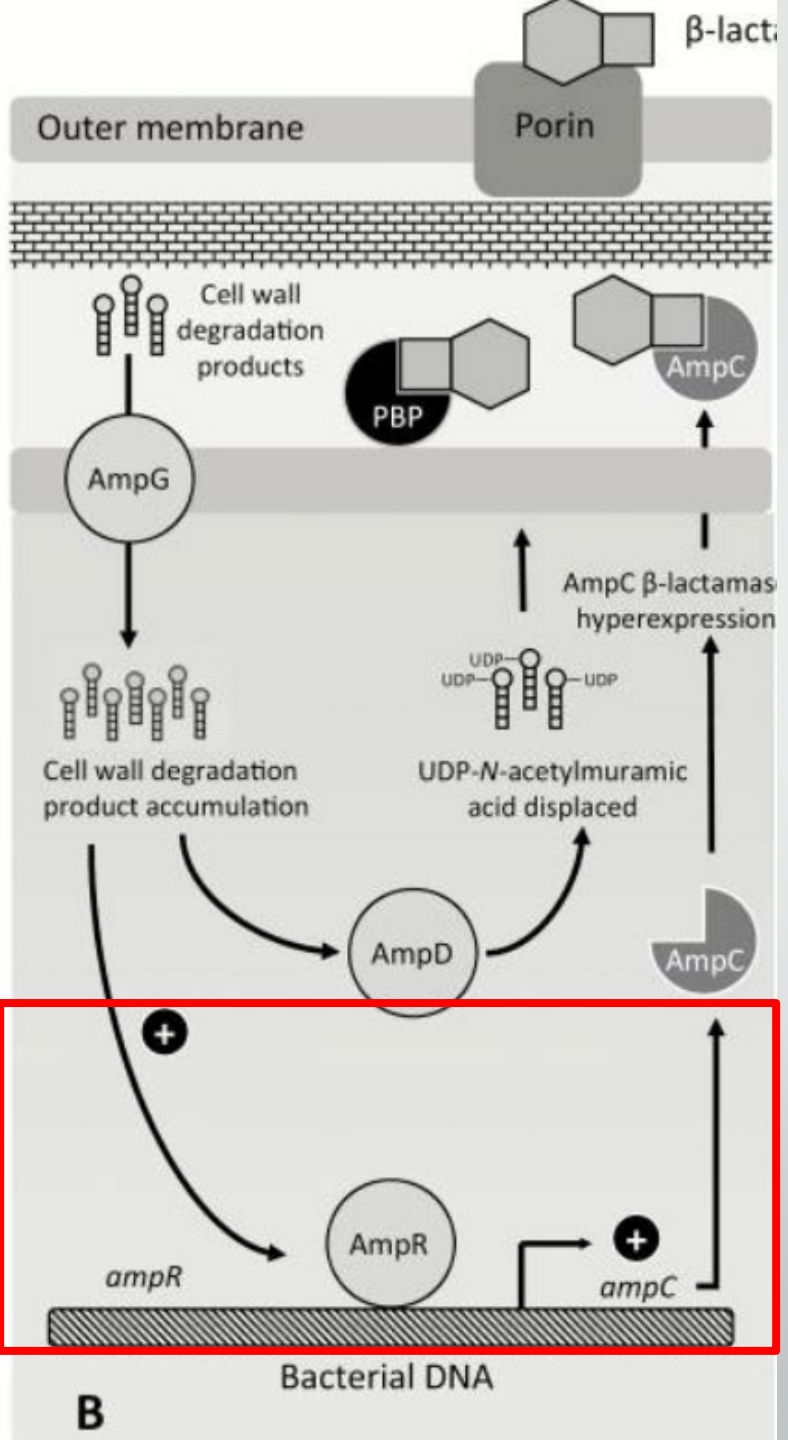

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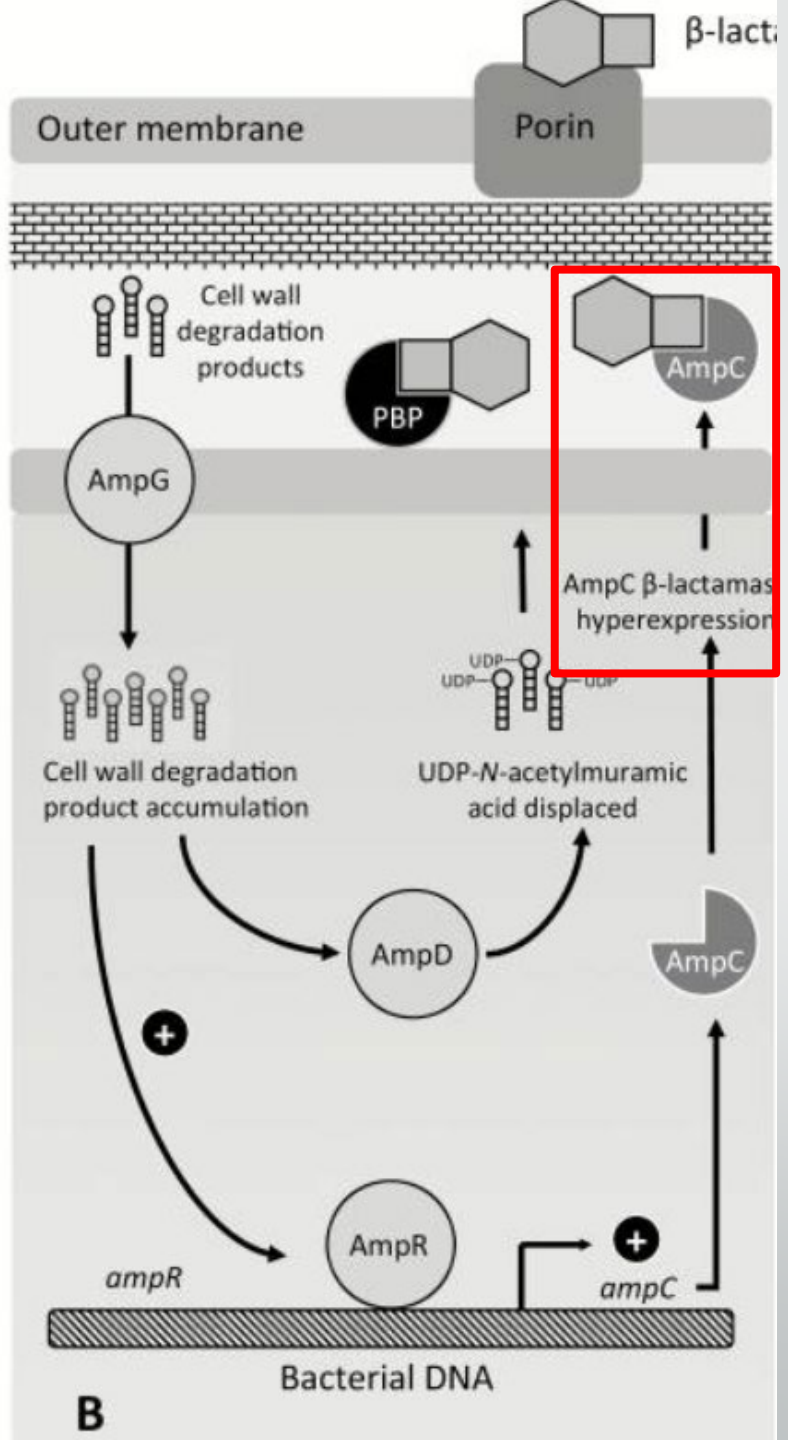

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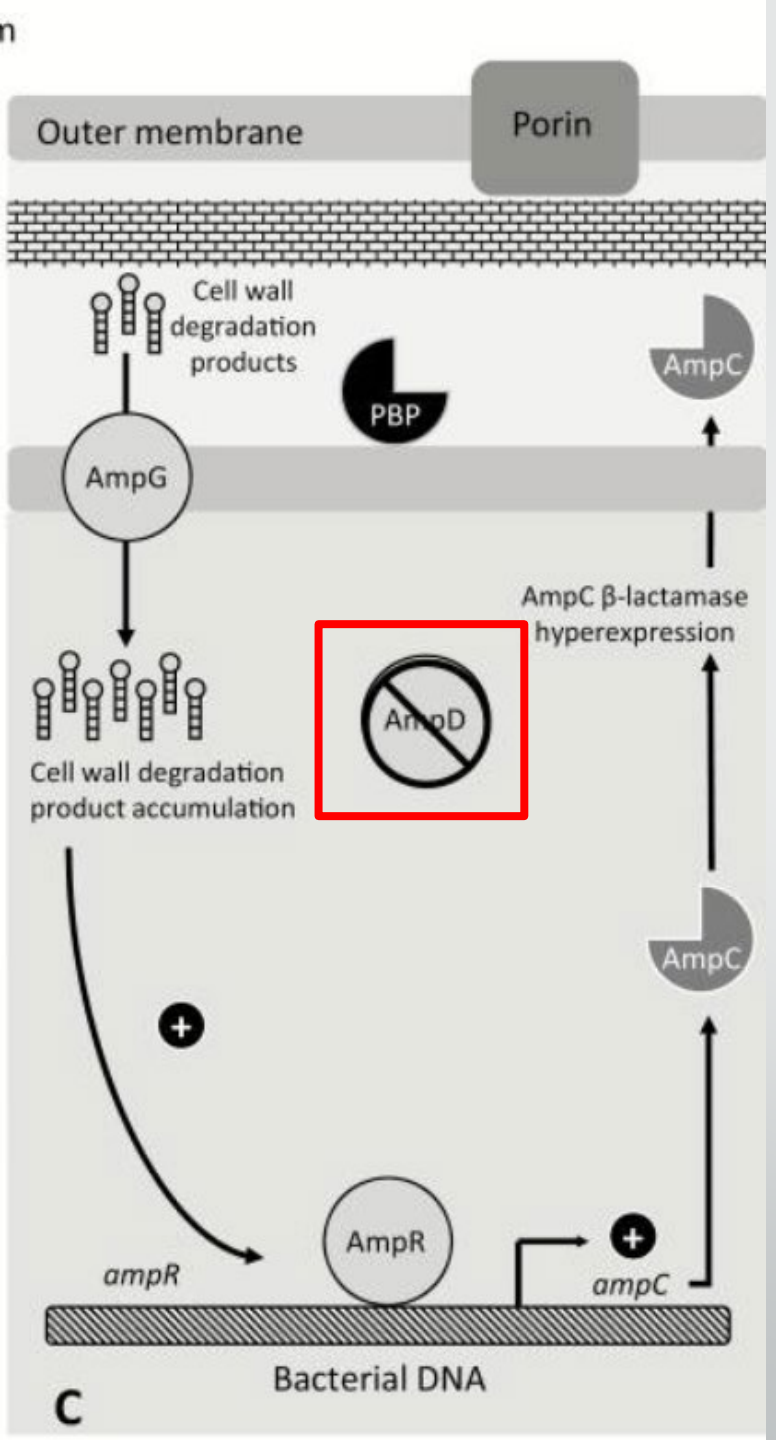
AmpC B-lactamase - Stable De-repression



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AmpC B-Lactamase – Producing Organisms

Objectives

- Describe the mechanism of resistance for AmpC B-lactamases.
- **Identify moderate- to high-risk organisms that can harbor AmpC B-lactamases.**
- Review Infectious Diseases Society of America (IDSA) Guidelines for treatment and management of AmpC B-lactamase producing organisms.
- Compare therapeutics and assess primary literature supporting utilization of select antimicrobials for AmpC B-lactamase producing organisms.

Organisms That Can Harbor AmpC B-Lactamases

- **"SPACE"** organisms
  - **S**erratia spp.
  - **P**rovidencia spp.
  - **A**cinetobacter spp.
  - **C**itrobacter spp.
  - **E**nterobacter spp.

Are the "SPACE" Organisms All Equal in Terms of AmpC Production?

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

- **Question 1:** Which Enterobacterales should be considered at moderate to high risk for clinically significant AmpC production due to an inducible *ampC* gene?

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J Antimicrob Chemother 2018; **73**: 1530–1536
doi:10.1093/jac/dky084 Advance Access publication 16 March 2018

Journal of Antimicrobial Chemotherapy

Species-specific mutation rates for *ampC* derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase

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Background: AmpC β-lactamases are encoded on the chromosomes of certain Enterobacterales and lead to clinical resistance to various β-lactams in case of high-level expression. In WT bacteria with inducible AmpC, the expression is low, but selection of stably *ampC*-derepressed mutants may occur during β-lactam therapy. Thus, for *Enterobacter* spp., *Citrobacter freundii* complex, *Serratia* spp. and *Morganella morganii* that test susceptible

Which Enterobacterales should be considered at moderate to high risk for clinically significant AmpC production due to an inducible *ampC* gene?

- *Enterobacter cloacae*
- *Klebsiella aerogenes (*previously known as *Enterobacter aerogenes*)
- *Citrobacter freundii*

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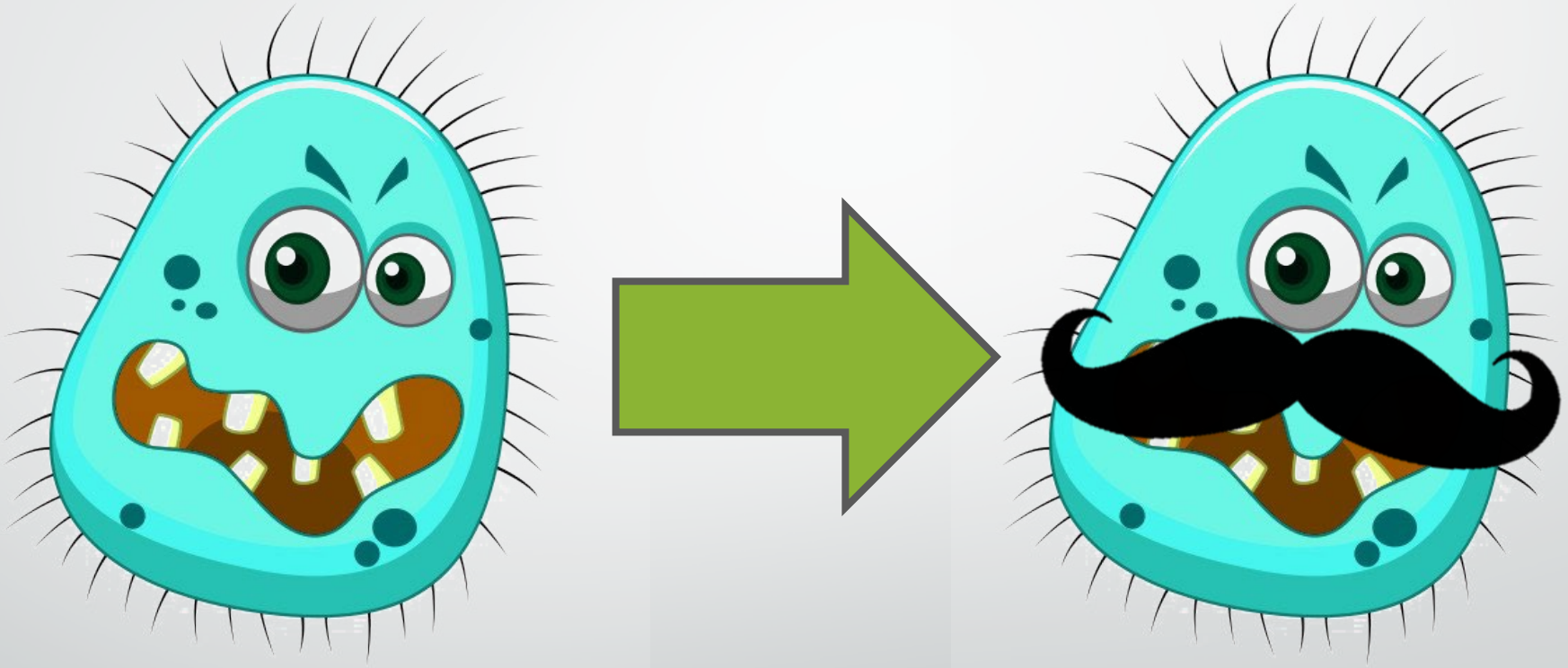
New Mnemonic? HECKYES

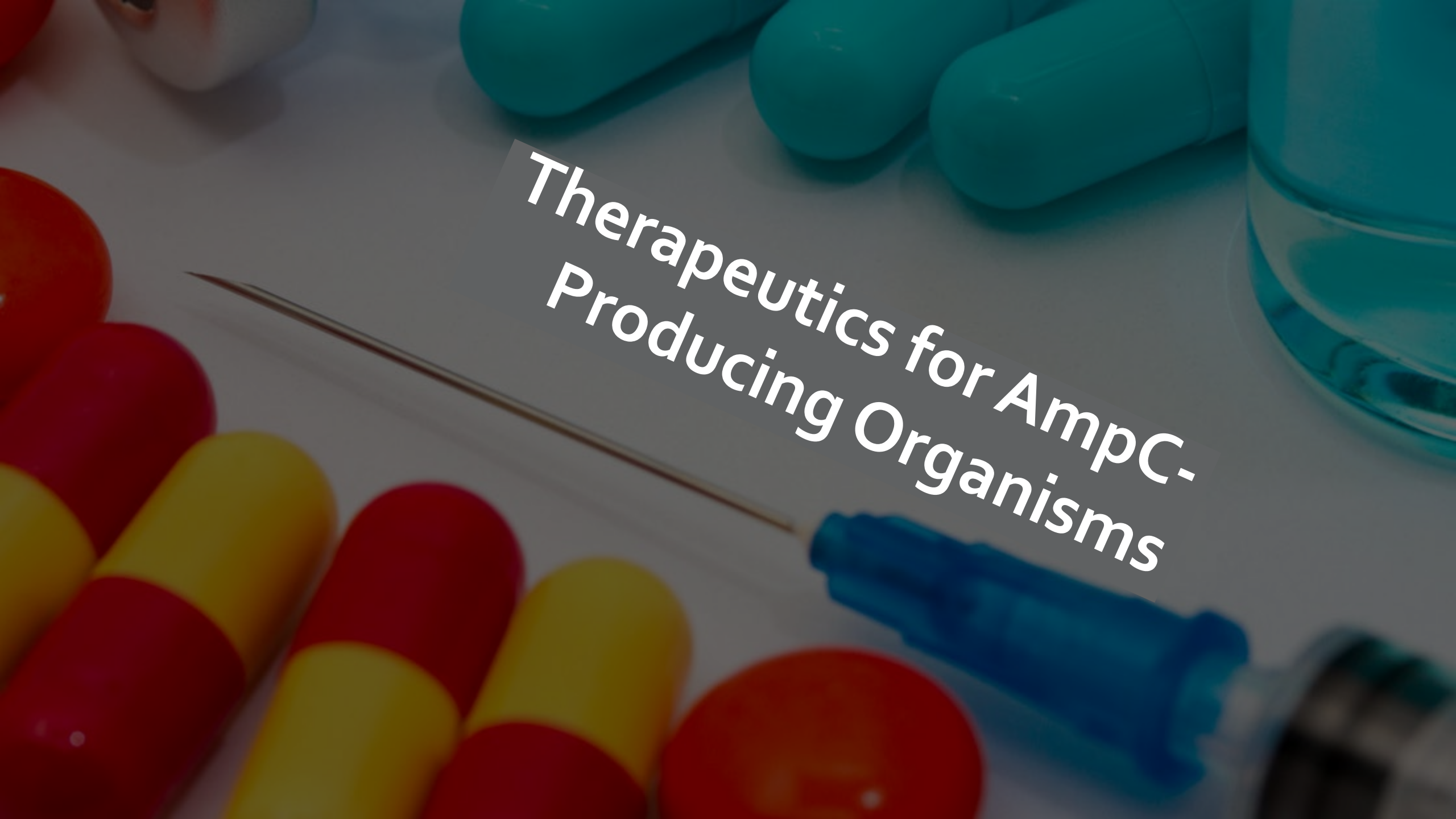
- ***H****afnia alvei*
- ***E****nterobacter cloacae*
- ***C****itrobacter freundii*
- ***K****lebsiella aerogenes* (previously known as *Enterobacter aerogenes*)
- ***YE****r****S****inia Enterocolytica*

Updates in Bacterial Nomenclature



Enterobacter aerogenes

Klebsiella aerogenes



Therapeutics for AmpC-Producing Organisms

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- **Question 2:** What features should be considered in selecting antibiotics for infections caused by organisms with moderate to high risk for clinically significant inducible AmpC production?

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Triggers for AmpC Hyperexpression

Table 1. *ampC* Induction Profile of Various Antibacterials

	Inducible (Wild-Type)	
	Strong Inducers of *ampC*	**Weak Inducers of *ampC***
Good substrates of *ampC*	Ampicillin first-generation cephalosporins, cefoxitin, cefotetan	Ceftazidime, ceftriaxone, cefotaxime, piperacillin, ticarcillin, aztreonam
Phenotype	Resistant	Susceptible
Poor substrates of *ampC*	Imipenem	Cefepime
		Meropenem
Phenotype	Susceptible	Susceptible

Macdougall C. (2011). Beyond Susceptible and Resistant, Part I: Treatment of Infections Due to Gram-Negative Organisms With Inducible β-Lactamases. The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG, 16(1), 23–30.

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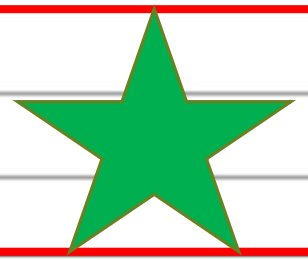

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Enterobacter cloacae
Susceptibility Panel

PHL Sample #:

Susceptibility by Broth Microdilution

Analyte/Drug	Value	Units	Results/Interpretation
Amikacin	≤8	µg/mL	Susceptible
Ampicillin	>16	µg/mL	No CLSI Interpretation
Ampicillin/Sulbactam	>16	µg/mL	No CLSI Interpretation
Aztreonam	>16	µg/mL	Resistant
Cefazolin	>16	µg/mL	No CLSI Interpretation
Cefepime	≤2	µg/mL	Susceptible
Ceftazidime	>16	µg/mL	Resistant
Ceftazidime/Avibactam	≤2	µg/mL	Susceptible
Ceftolozane/Tazobactam	8	µg/mL	Resistant
Ceftriaxone	>32	µg/mL	Resistant
Ciprofloxacin	≤0.25	µg/mL	Susceptible
Ertapenem	1	µg/mL	Intermediate
Gentamicin	≤2	µg/mL	Susceptible
Imipenem	≤1	µg/mL	Susceptible
Meropenem	≤0.5	µg/mL	Susceptible
Minocycline	8	µg/mL	Intermediate
Nitrofurantoin	64	µg/mL	Intermediate
Piperacillin/Tazobactam	>64	µg/mL	Resistant
Tetracycline	≤4	µg/mL	Susceptible
Tigecycline	≤1	µg/mL	No CLSI Interpretation
Tobramycin	≤2	µg/mL	Susceptible
Trimetho/Sulfa	≤2	µg/mL	Susceptible

Enterobacter cloacae
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Ceftazidime	>16	µg/mL	Resistant
Ceftazidime/Avibactam	≤2	µg/mL	Susceptible
Ceftolozane/Tazobactam	8	µg/mL	Resistant
Ceftriaxone	>32	µg/mL	Resistant
Ciprofloxacin	≤0.25	µg/mL	Susceptible
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- **Question 3:** What is the role of cefepime for the treatment of infections caused by Enterobacterales at moderate to high risk of clinically significant inducible AmpC production?

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What is the Role of Cefepime?

- For infections caused by organisms at moderate to high risk of clinically significant AmpC production:
  - **Cefepime is recommended** when the cefepime **MIC is ≤2 mcg/mL**.
  - **Carbapenem is recommended** when the cefepime **MIC is ≥4 mcg/mL**.

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CLSI M100-ED32:2022 Performance Standards for Antimicrobial Susceptibility Testing

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.) (Continued)											
B	Cefepime	30 µg	≥ 25	19-24	-	≤ 18	≤ 2	4-8	-	≥ 16	(28) The breakpoint for susceptible is based on a dosage regimen of 1 g administered every 12 h. The breakpoint for SDD is based on dosage regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosage regimens. See Appendix E for more information about breakpoints and dosage regimens. Also see the definition of SDD in the Instructions for Use of Tables section.

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Cefepime Therapy for Monomicrobial *Enterobacter cloacae* Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates

Nan-Yao Lee,[a,b,c] Ching-Chi Lee,[a,b,c] Chia-Wen Li,[a] Ming-Chi Li,[a] Po-Lin Chen,[a,c] Chia-Ming Chang,[a,b,c] Wen-Chien Ko[a,b,c]

Department of Internal Medicine[a] and Center for Infection Control,[b] National Cheng Kung University Hospital, Tainan, Taiwan; Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan[c]

A new category of cefepime susceptibility, susceptible dose dependent (SDD), for *Enterobacteriaceae*, has been suggested to maximize its clinical use. However, clinical evidence supporting such a therapeutic strategy is limited. A retrospective study of 305 adults with monomicrobial *Enterobacter cloacae* bacteremia at a medical center from 2008 to 2012 was conducted. The patients definitively treated with *in vitro* active cefepime (cases) were compared with those treated with a carbapenem (controls) to assess therapeutic effectiveness. The 30-day crude mortality rate is the primary endpoint, and clinical prognostic factors are assessed. Of 144 patients receiving definitive cefepime or carbapenem therapy, there were no significant differences in terms of age, sex, comorbidity, source of bacteremia, disease severity, or 30-day mortality (26.4% versus 22.2%; $P = 0.7$) among those treated with cefepime ($n = 72$) or a carbapenem ($n = 72$). In the multivariate analysis, the presence of critical illness, rapidly fatal underlying disease, extended-spectrum beta-lactamase (ESBL) producers, and cefepime-SDD (cefepime MIC, 4 to 8 μg/ml) isolates was independently associated with 30-day mortality. Moreover, those infected by cefepime-SDD isolates with definitive cefepime ther-

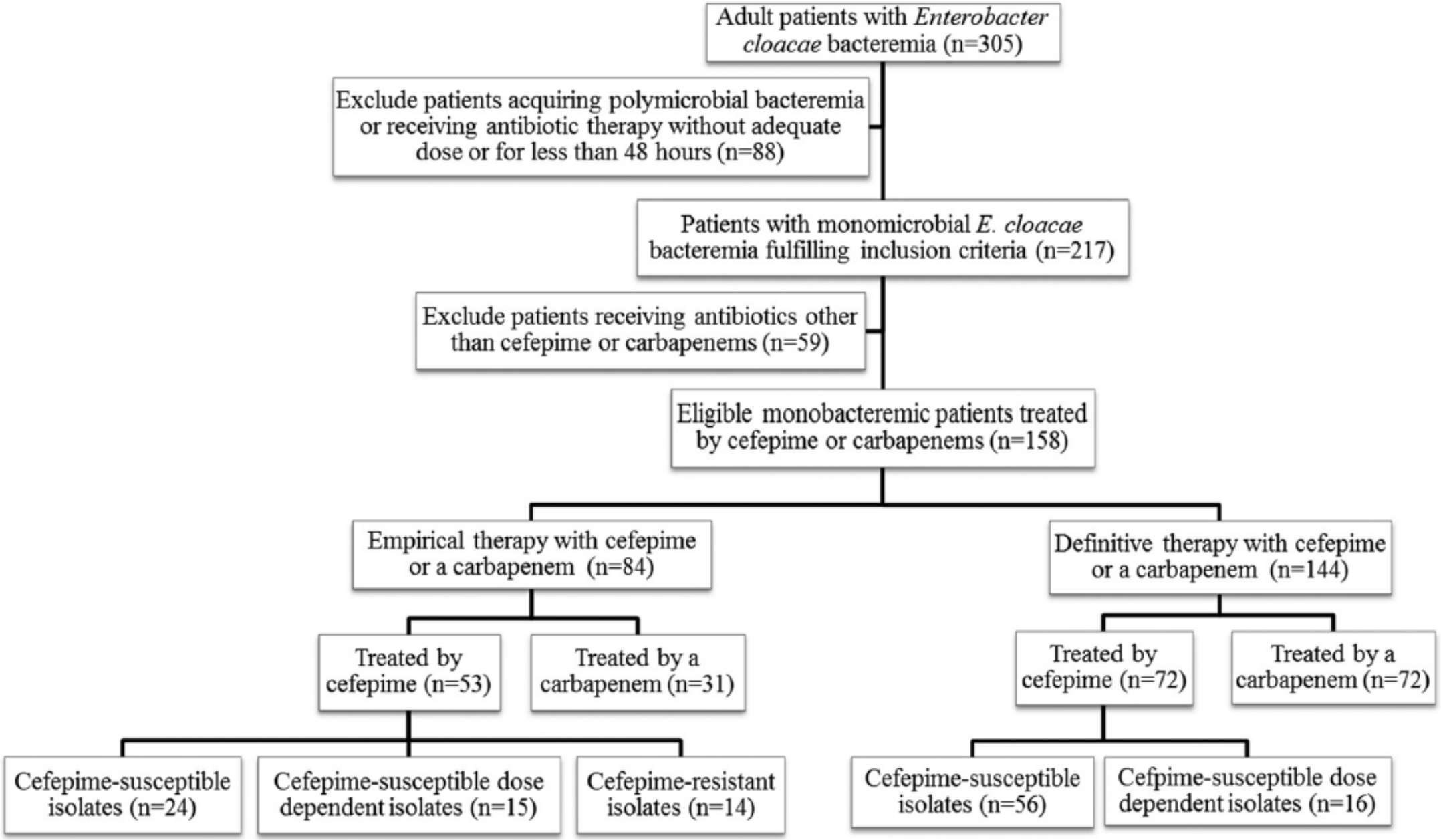
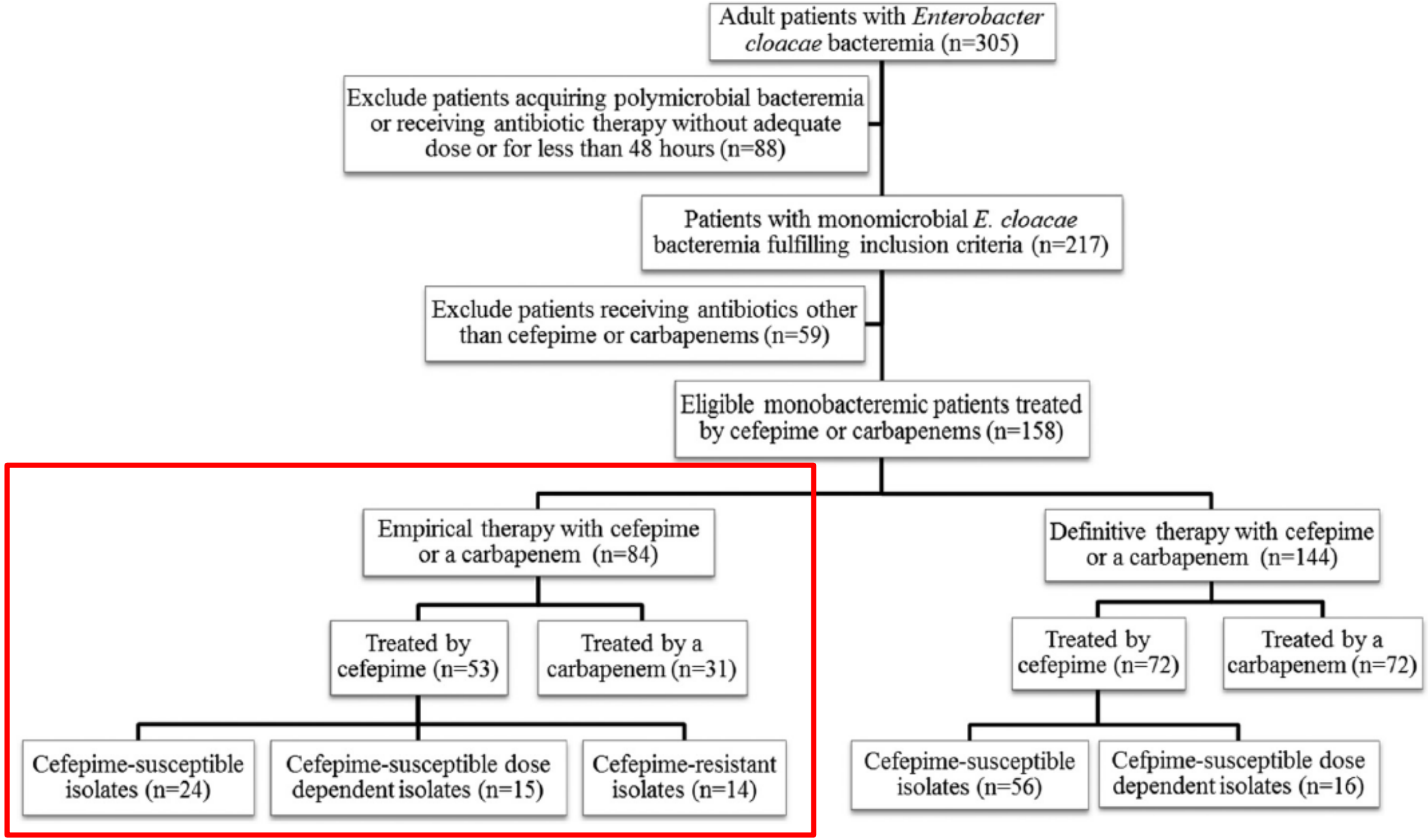


FIG 2 Study flow of the case numbers of included and excluded patients with monomicrobial *Enterobacter cloacae* bacteremia.



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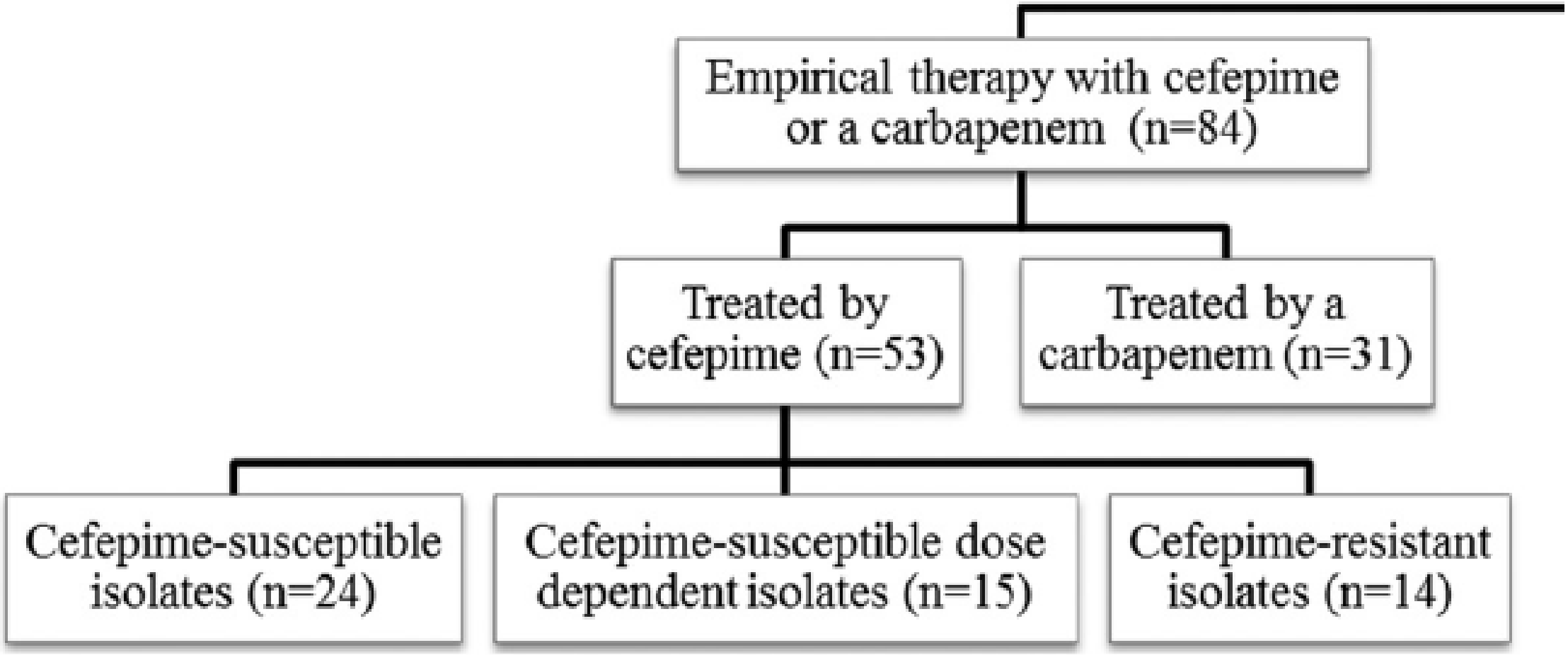
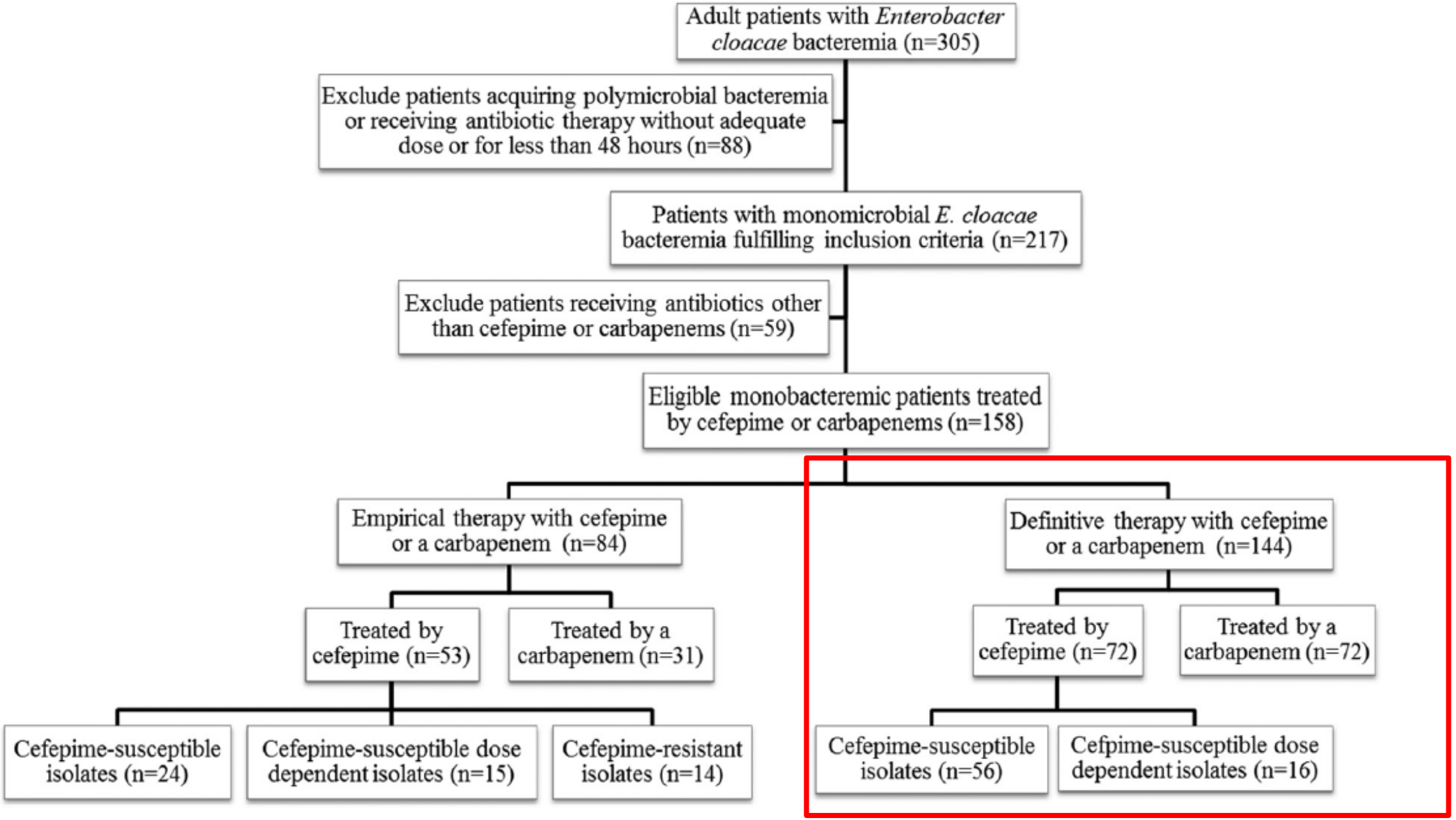

Empirical therapy with cefepime or a carbapenem (n=84)
Treated by cefepime (n=53)
Treated by a carbapenem (n=31)
Cefepime-susceptible isolates (n=24)
Cefepime-susceptible dose dependent isolates (n=15)
Cefepime-resistant isolates (n=14)



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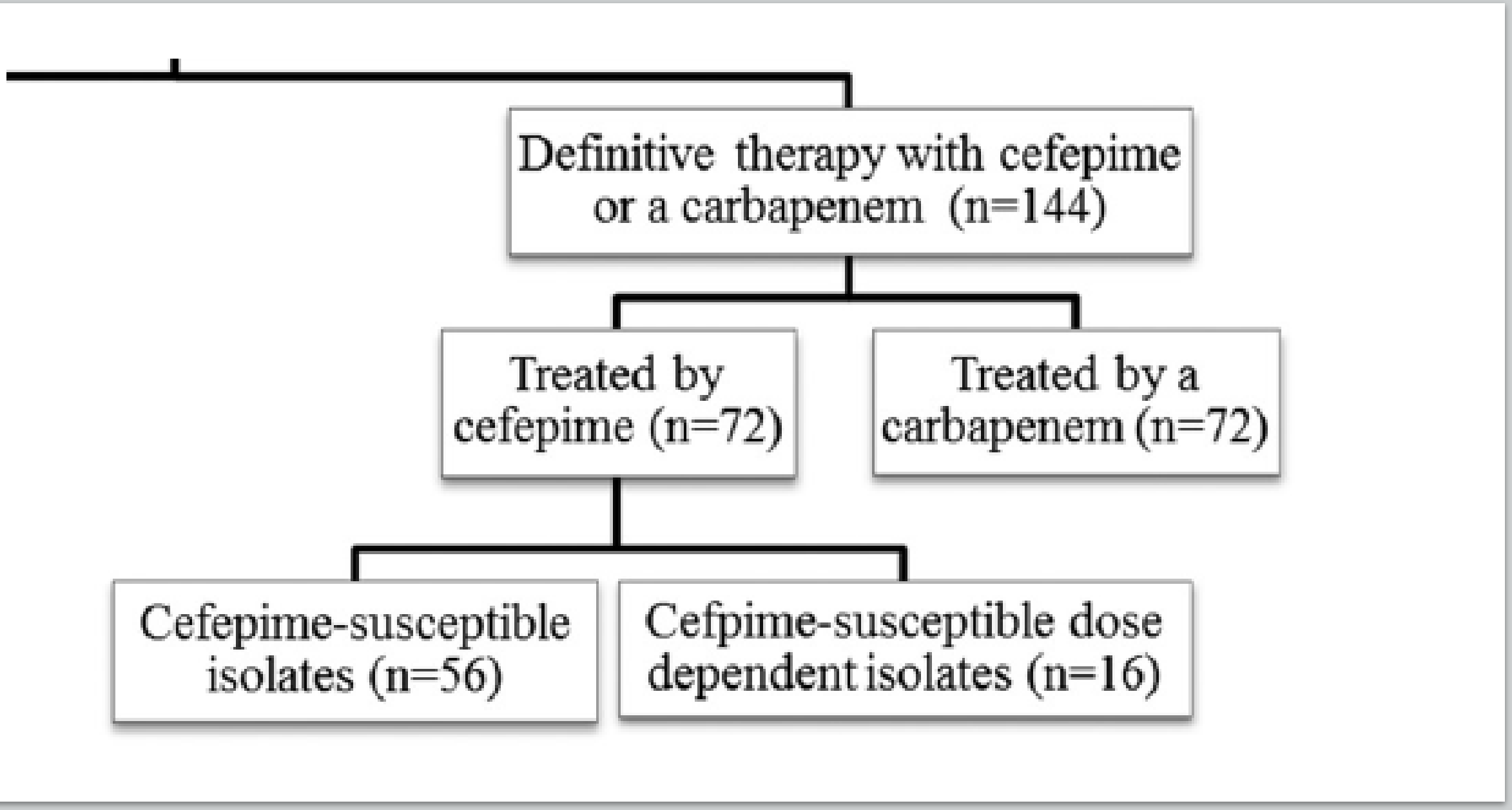
Definitive therapy with cefepime or a carbapenem (n=144)
Treated by cefepime (n=72)
Treated by a carbapenem (n=72)
Cefepime-susceptible isolates (n=56)
Cefpime-susceptible dose dependent isolates (n=16)

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

- **Question 4:** What is the role of ceftriaxone for the treatment of infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production?

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

What is the Role of Ceftriaxone ?

- For infections caused by organisms at moderate to high risk of clinically significant AmpC production:
  - Ceftriaxone (or ceftazidime) is **NOT** recommended.
  - Ceftriaxone may be a reasonable treatment option for uncomplicated cystitis when susceptibility is demonstrated.

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

- **Question 5:** What is the role of piperacillin-tazobactam for the treatment of infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production?

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

What is the Role of Piperacillin-Tazobactam?

- For infections caused by organisms at moderate to high risk of clinically significant AmpC production:
  - Piperacillin-tazobactam is **NOT** suggested for the treatment of serious infections.
  - The panel suggests caution if prescribing piperacillin-tazobactam for serious infections caused by AmpC B-lactamase producing Enterobacterales

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

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DOI 10.1186/s12879-014-0647-4

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Clinical and microbiological characteristics of bloodstream infections due to AmpC β-lactamase producing Enterobacteriaceae: an active surveillance cohort in a large centralized Canadian region

Vikas P Chaubey[1,2,8*], Johann D D Pitout[3,4,5], Bruce Dalton[2,7], Daniel B Gregson[2,3,5], Terry Ross[5] and Kevin B Laupland[1,2,3,6]

Abstract

Background: The objective of this study was to describe the clinical and microbiological characteristics of bloodstream infections (BSIs) due to AmpC producing Enterobacteriaceae (AE) in a large centralized Canadian region over a 9-year period.

Methods: An active surveillance cohort design in Calgary, Canada.

Results: A cohort of 458 episodes of BSIs caused by AE was assembled for analysis. The majority of infections were of nosocomial origin with unknown sources. *Enterobacter* spp. was the most common species while BSIs due to *Serratia* spp. had a significant higher mortality when compared to other AE. Delays in empiric or definitive antibiotic therapy were not associated with a difference in outcome. However, patients that did not receive any empiric antimicrobial therapy had increased mortality (3/5; 60% vs. 57/453; 13%; p = 0.018) as did those that did not receive definitive

Table 3 *Empiric, first adequate and definitive antimicrobial choice and associated 30-day case-fatality

Empiric antibiotic choice	Case fatality rate	First adequate antibiotic choice	Case fatality rate	Definitive antimicrobial therapy	Case fatality rate
Antibiotics with activity against AmpC-producing Enterobacteriaceae					
Aminoglycoside	7/52 (13%)	Aminoglycoside	10/80 (13%)	Aminoglycoside	15/132 11%)
Beta-lactam/Beta-lactamase inhibitor combination	15/131 (11%)	Beta-lactam/Beta-lactamase inhibitor combination	16/137 (12%)	Beta-lactam/Beta-lactamase inhibitor combination	10/22 (45%)
Carbapenem	0/16 (0%)	Carbapenem	3/31 (9.7%)	Carbapenem	5/45 (11%)
Cefepime	1/3 (33%)	Cefepime	1/5 (20%)	Cefepime	1/4 (25%)
Cefoxitin	0/1 (0%)	Cefixime	0/10 (0%)	Cefotaxime	0/2 (0%)
Ceftazidime	1/15 (6.7%)	Ceftazidime	0/10 (0%)	Ceftazidime	0/1 (0%)
Ceftriaxone	11/85 (13%)	Ceftriaxone	12/97 (12%)	Ceftriaxone	1/7 (14%)
Cefuroxime	1/5 (20%)	Colistin	0/1 (0%)	Colistin	0/1 (0%)
Colistin	0/1 (0%)	Fluoroquinolone	16/106 (15%)	Fluoroquinolone	30/231 (13%)
Fluoroquinolone	10/76 (13%)	TMP/SMX	0/9 (0%)	TMP/SMX	0/14 (0%)
TMP/SMX	2/14 (14%)				

Enterobacter Species Susceptibilities on Table 1

Table 1 Clinical and microbiological characteristics of bloodstream infections due to AmpC-producing Enterobacteriaceae in the Calgary Zone *(Continued)*

2006	24 (9.4%)	6 (8.2%)	5 (9.8%)	5 (13%)	7 (23%)	0 (0%)
2007	31 (12%)	7 (9.6%)	10 (20%)	2 (5.1%)	2 (6.7%)	0 (0%)
2008	46 (18%)	10 (14%)	7 (14%)	4 (10%)	4 (13%)	0 (0%)
Susceptibility testing (percentage susceptible)						
Ciprofloxacin	248/255 (98%)	71/73 (97%)	47/50 (94%)	36/38 (95%)	24/30 (80%)	10/10 (100%)
Gentamicin	251/255 (99%)	72/73 (99%)	45/50 (90%)	34/38 (90%)	23/30 (77%)	10/10 (100%)
Piperacillin-tazobactam	203/255 (80%)	69/73 (95%)	46/50 (92%)	38/38 (100%)	29/30 (97%)	7/10 (70%)
TMP/SMX	242/255 (95%)	73/73 (100%)	39/50 (78%)	31/38 (82%)	19/30 (63%)	10/10 (100%)
Tobramycin	251/255 (99%)	64/73 (88%)	45/50 (90%)	33/38 (87%)	26/30 (87%)	10/10 (100%)
Imipenem	255/255 (100%)	73/73 (100%)	50/50 (100%)	38/38 (100%)	30/30 (100%)	10/10 (100%)

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CLINICAL THERAPEUTICS

Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC β-Lactamase-Producing *Enterobacteriaceae*

Lucy Cheng,[a] Brian C. Nelson,[b] Monica Mehta,[b] Nikhil Seval,[a] Sarah Park,[a] Marla J. Giddins,[a] Qiuhu Shi,[c] Susan Whittier,[d] Angela Gomez-Simmonds,[a] Anne-Catrin Uhlemann[a]

Department of Medicine, Division of Infectious Diseases, Columbia University Medical Center, New York, New York, USA[a]; NewYork-Presbyterian Hospital, New York, New York, USA[b]; New York Medical College, Valhalla, New York, USA[c]; Department of Pathology and Cell Biology, Clinical Microbiology Laboratory, Columbia University Medical Center, New York, New York, USA[d]

ABSTRACT *In vivo* induction of AmpC beta-lactamases produces high-level resistance to many beta-lactam antibiotics in *Enterobacteriaceae*, often resulting in the need to use carbapenems or cefepime (FEP). The clinical effectiveness of piperacillin-tazobactam (TZP), a weak inducer of AmpC beta-lactamases, is poorly understood. Here, we conducted a case-control study of adult inpatients with bloodstream infections (BSIs) due to *Enterobacter*, *Serratia*, or *Citrobacter* species from 2009 to 2015 to assess outcomes following treatment with TZP compared to FEP or meropenem

Received 8 February 2017 **Returned for modification** 25 February 2017 **Accepted** 15 March 2017

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TABLE 3 Clinical outcomes, according to treatment category

Outcome	No. (%) of patients with outcome in:							
	Overall cohort comparison				Propensity score-matched cohort comparison			
	TZP (n = 88)	FEP/MEM (n = 77)	P value	OR (95% CI)	TZP (n = 41)	FEP/MEM (n = 41)	P value	OR (95% CI)
30-Day mortality	9 (10)	9 (12)	0.96	1.16 (0.44, 3.09)	6 (15)	3 (7)	0.33	0.50 (0.13, 2.0)
Persistent bacteremia	14 (16)	10 (13)	0.66		8 (20)	4 (10)	0.26	
7-Day mortality	1 (1)	3 (4)	0.34		0	1 (2)	0.99	
Treatment escalation	12 (14)	8 (10)	0.63		6 (15)	6 (15)	1	

Open Forum Infectious Diseases

MAJOR ARTICLE

Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)

Adam G. Stewart,[1,2] David L. Paterson,[1,2] Barnaby Young,[3,4,5] David C. Lye,[3,4,5,6] Joshua S. Davis,[7,8] Kellie Schneider,[7] Mesut Yilmaz,[9] Rumeysa Dinleyici,[9] Naomi Runnegar,[10] Andrew Henderson,[1,10] Sophia Archuleta,[6,11] Shirin Kalimuddin,[12,13] Brian M. Forde,[1,14,15] Mark D. Chatfield,[1] Michelle J. Bauer,[1] Jeffrey Lipman,[1,16,17] Tiffany Harris-Brown,[1] and Patrick N. A. Harris[1,18]; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

[1]University of Queensland, UQ Centre for Clinical Research, Brisbane, Australia, [2]Infectious Diseases Unit, Royal Brisbane and Women's Hospital, Brisbane, Australia, [3]National Centre for Infectious Disease, Singapore, [4]Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore, [5]Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, Singapore, [6]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [7]Infectious Disease Department, John Hunter Hospital, Newcastle, Australia, [8]Menzies School of Health Research, Darwin, Australia, [9]Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Istanbul Medipol, Turkey, [10]Infection Management Services, Princess Alexandra Hospital, Brisbane, Australia, [11]Division of Infectious Diseases, Department of Medicine, National University Hospital, National University Health System, Singapore, [12]Department of Infectious Diseases, Singapore General Hospital, Singapore, [13]Program in Emerging Infectious Diseases, Duke–National University of Singapore Medical School, Singapore, [14]School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, Australia, [15]Australian Infectious Diseases Research Centre, University of Queensland, Brisbane, Australia, [16]Intensive Care Services, Royal Brisbane and Women's Hospital, Brisbane, Australia, [17]Scientific Consultant, Nimes University Hospital, University of Montpellier, Nimes, France, and [18]Central Microbiology, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia

Background. Carbapenems are recommended treatment for serious infections caused by AmpC-producing gram-negative bacteria but can select for carbapenem resistance. Piperacillin-tazobactam may be a suitable alternative.

Analysis	Primary Outcome, No./Total No. (%)		Risk Difference, % (2-Sided 95% CI)	*P* Value
	PTZ	Meropenem		
Primary analysis	11/38 (29)	7/34 (21)	8.4 (–11 to 28)	.41
Per-protocol analysis	8/32 (25)	6/32 (19)	6.2 (–14 to 26)	.55
Subcomponents of the primary outcome				
Death	0/38 (0)	2/34 (6%)	5.9 (–13 to 2)	.13
Clinical failure	8/38 (21)	4/34 (12)	9.3 (–8 to 26)	.29
Microbiological failure	5/38 (13)	0/34 (0)	13.2 (2 to 24)	.03
Microbiological relapse	0/38 (0)	3/34 (9)	8.8 (–18 to 1)	.06
Subgroup analyses				
Infecting species				
Enterobacter spp	5/18 (28)	1/14 (7)	20.7 (–4 to 45)	.14
Other	6/14 (43)	6/14 (43)	0.0 (–28 to 28)	1.0
Urinary tract vs non–urinary tract source				
Urinary tract	1/8 (12)	1/6 (17)	–4.2 (–42 to 33)	.83
Non–urinary tract	10/30 (33)	6/28 (21)	11.9 (–11 to 35)	.31
Infection				
Healthcare-associated	11/35 (31)	5/24 (21)	10.6 (–12 to 33)	.37
Non–health care associated	0/3 (0)	0/3 (0)	…	
Appropriate empirical antibiotic therapy				
Appropriate	10/35 (29)	7/33 (21)	7.4 (–13 to 28)	.48
Inappropriate	1/3 (33)	0/1 (0)	33.3 (–20 to 87)	.50
Immunocompromise				
Present	1/6 (17)	1/5 (20)	–3.3 (–49 to 43)	.89
Absent	10/32 (31)	6/29 (21)	–10.5 (–11 to 32)	.35
qSOFA ≥2				
Yes	2/9 (22)	2/9 (22)	0.0 (–38 to 38)	1.0
No	9/29 (31)	5/25 (20)	11.0 (–12.0 to 34)	.36
Total duration of study drug				
<5 d	6/20 (30)	2/17 (12)	18 (–7 to 43)	.18
≥5 d	5/18 (28)	5/17 (30)	–16 (–32 to 28)	.91

Abbreviations: CI, confidence interval; PZT, piperacillin-tazobactam; qSOFA, quick Sequential Organ Failure Assessment.

Analysis	Primary Outcome, No./Total No. (%)		Risk Difference, % (2-Sided 95% CI)	*P* Value
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Healthcare-associated	11/35 (31)	5/24 (21)	10.6 (–12 to 33)	.37
Non–health care associated	0/3 (0)	0/3 (0)	…	
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Absent	10/32 (31)	6/29 (21)	–10.5 (–11 to 32)	.35
qSOFA ≥2				
Yes	2/9 (22)	2/9 (22)	0.0 (–38 to 38)	1.0
No	9/29 (31)	5/25 (20)	11.0 (–12.0 to 34)	.36
Total duration of study drug				
<5 d	6/20 (30)	2/17 (12)	18 (–7 to 43)	.18
≥5 d	5/18 (28)	5/17 (30)	–16 (–32 to 28)	.91

Abbreviations: CI, confidence interval; PZT, piperacillin-tazobactam; qSOFA, quick Sequential Organ Failure Assessment.

Revisiting This Recommendation:

- For infections caused by organisms at moderate to high risk of clinically significant AmpC production:
  - Piperacillin-tazobactam is **NOT** suggested for the treatment of serious infections.
  - The panel suggests caution if prescribing piperacillin-tazobactam for serious infections caused by AmpC B-lactamase producing Enterobacterales

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

- **Question 6:** What is the role of newer β-lactam and β-lactam-β-lactamase inhibitor combinations for the treatment of infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production?

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

What is the Role of Newer B-Lactam and B-Lactam-B-Lactamase Inhibitor Combinations?

- Panel suggests these agents be **preferentially reserved** for treating infections caused by organisms exhibiting carbapenem resistance.

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

What is the Role of Newer B-Lactam and B-Lactam-B-Lactamase Inhibitor Combinations?

- The following agents that have in-vitro activity against AmpC B-lactamase producing organisms:
  - Ceftazidime-avibactam (AVYCAZ®)
  - Meropenem-vaborbactam (VABOMERE®)
  - Imipenem-cilastatin-relebactam (RECARBRIO™)
  - Cefiderocol (FETROJA®)

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

- **Question 7:** What is the role of non-β-lactam therapy for the treatment of infections caused by Enterobacterales at moderate to high risk for clinically significant inducible AmpC production?

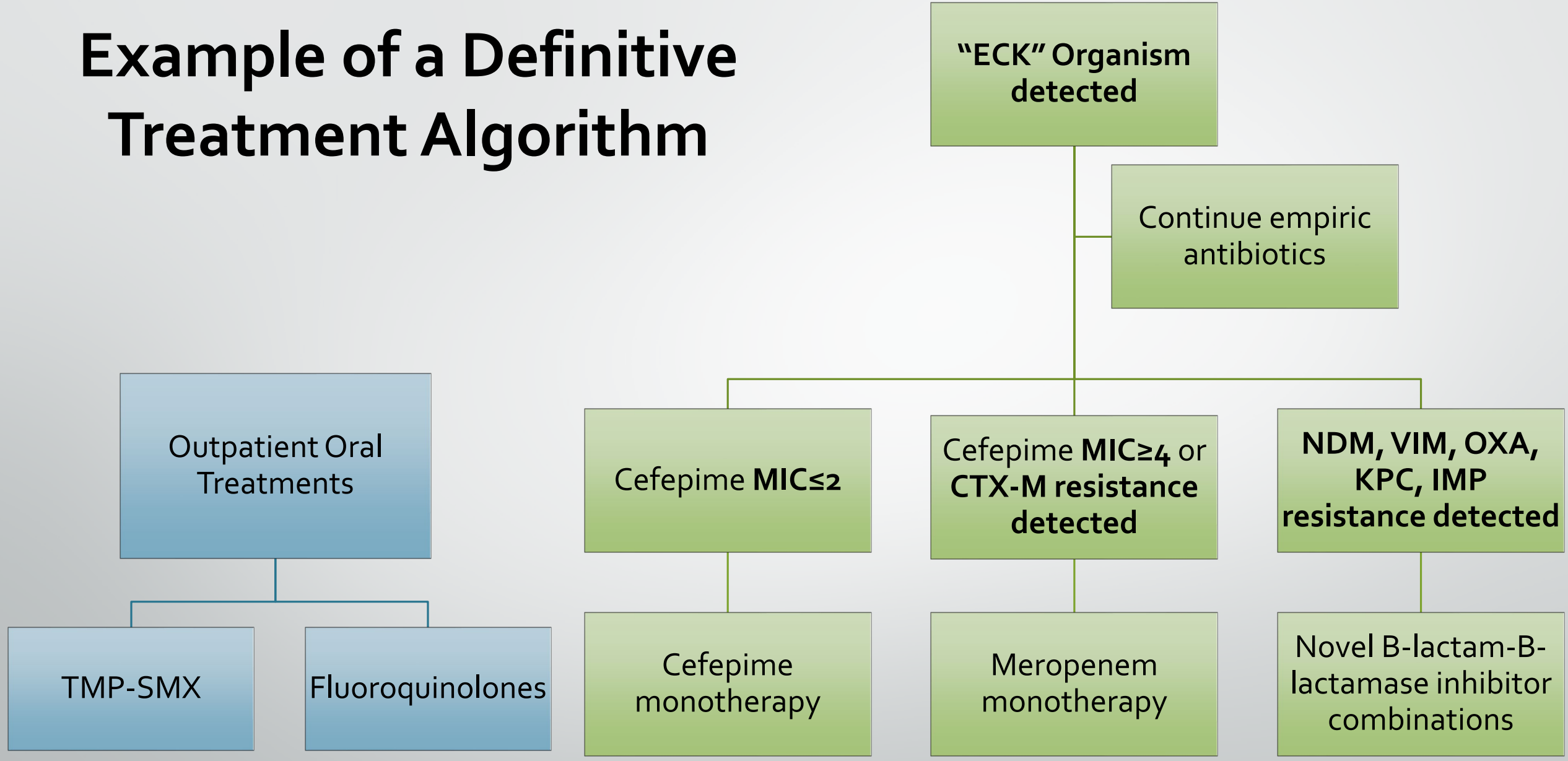
Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

What is the Role of Non-B-Lactam Therapy?

- TMP-SMX or fluoroquinolones can be considered for the treatment of invasive infections either intravenously or as oral step-down therapy.
- TMP-SMX and fluoroquinolones are **NOT** substrates for AmpC hydrolysis

Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, ciab1013. Advance online publication. https://doi.org/10.1093/cid/ciab1013

Example of a Definitive Treatment Algorithm



Summary

- "SPACE" → "H**ECK**YES"
- Ceftriaxone and ceftazidime are **NOT** recommended
- Zosyn should be used with caution for definitive therapy
- Cefepime and meropenem are both stable against AmpC B-lactamases


Mahalo for
listening!
Questions?