University Medical Center New Orleans
LCMC Health

Comparing the Efficacy of Weak Inducers and Good Substrates to Standard of Care to Treat AmpC Bacteremia

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Disclosure

The speaker, planners, and individuals in position to control content have no relevant financial relationships to disclose

Abbreviations

Abbreviation	Definition
AmpC-E	AmpC β-lactamase-producing *Enterobacterales*
CRE	Carbapenem-resistant *Enterobacterales*
ESBL	Extended spectrum β-lactamase
IDSA	Infectious Diseases Society of America
HECK Yes	*Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes, Yersinia enterocolitica*
SPACE/SPICE	*Serratia, Providencia/Pseudomonas, Acinetobacter*/Indole-positive *Proteus, Citrobacter, Enterobacter*

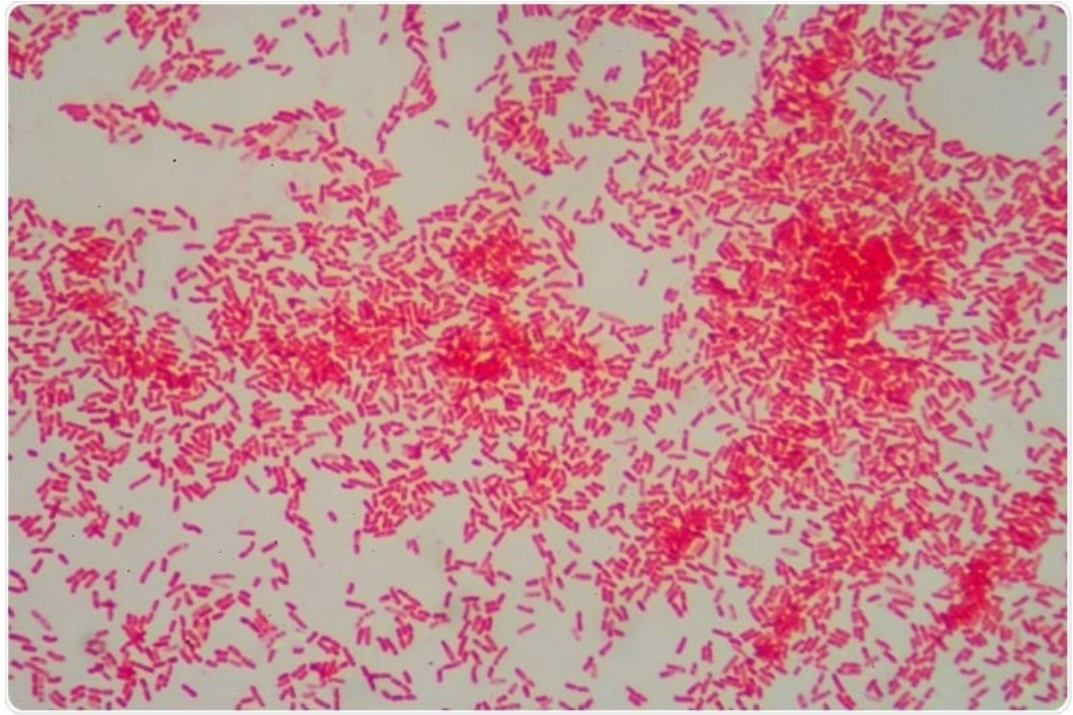
Abbreviation	Definition
AMR	Antimicrobial resistance
FUBC	Follow-up blood culture
3GC	Third-generation cephalosporin
CRO	Ceftriaxone
FQ	Fluroquinolone
SMX/TMP	Sulfamethoxazole/trimethoprim
TZP	Piperacillin/tazobactam
WIGS	Weak inducer, good substrate
WIPS	Weak inducer, poor substrate

Objectives

1. Recall differences in therapy between Gram-positive and Gram-negative bacteremia
2. Describe resistance patterns of AmpC and common AmpC β-lactamase-producing *Enterobacterales* (AmpC-E)
3. Assess the current Infectious Diseases Society of America (IDSA) recommendations on infections caused by AmpC-E
4. Evaluate the effectiveness of different antibiotics for the treatment of AmpC bacteremia

Gram-Negative Bacteremia

- Presence of viable bacteria in the bloodstream
  - 33-43% due to a Gram-negative organism
  - *Enterobacterales sp.*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
- Gram-negative vs Gram-positive
  - Higher rates of septic shock
  - Higher rates of mortality
  - Longer hospital length of stay
- Considerations for treatment
  - Duration of therapy
  - Antimicrobial resistance (AMR)



Alexandraki I, Palacio C. Crit Care. 2010;14(3):161.
Holmes CL, et al. Clin Microbiol Rev. 2021;34(2):e00234-20.

Duration of Therapy: Bacteremia

	Gram-negative	Gram-positive (*S. aureus*)
Duration		
Uncomplicated	≥ 7 days	2 – 4 weeks
Complicated	10-14 days	6 – 8 weeks
Day 0 of therapy	Initiation of appropriate antibiotics	Date of first negative blood culture

Tamma PD, et al. Clin Infect Dis. 2019;69(8):1446-1455

Antimicrobial Resistance (AMR): A Global Crisis

World Health Organization (WHO)

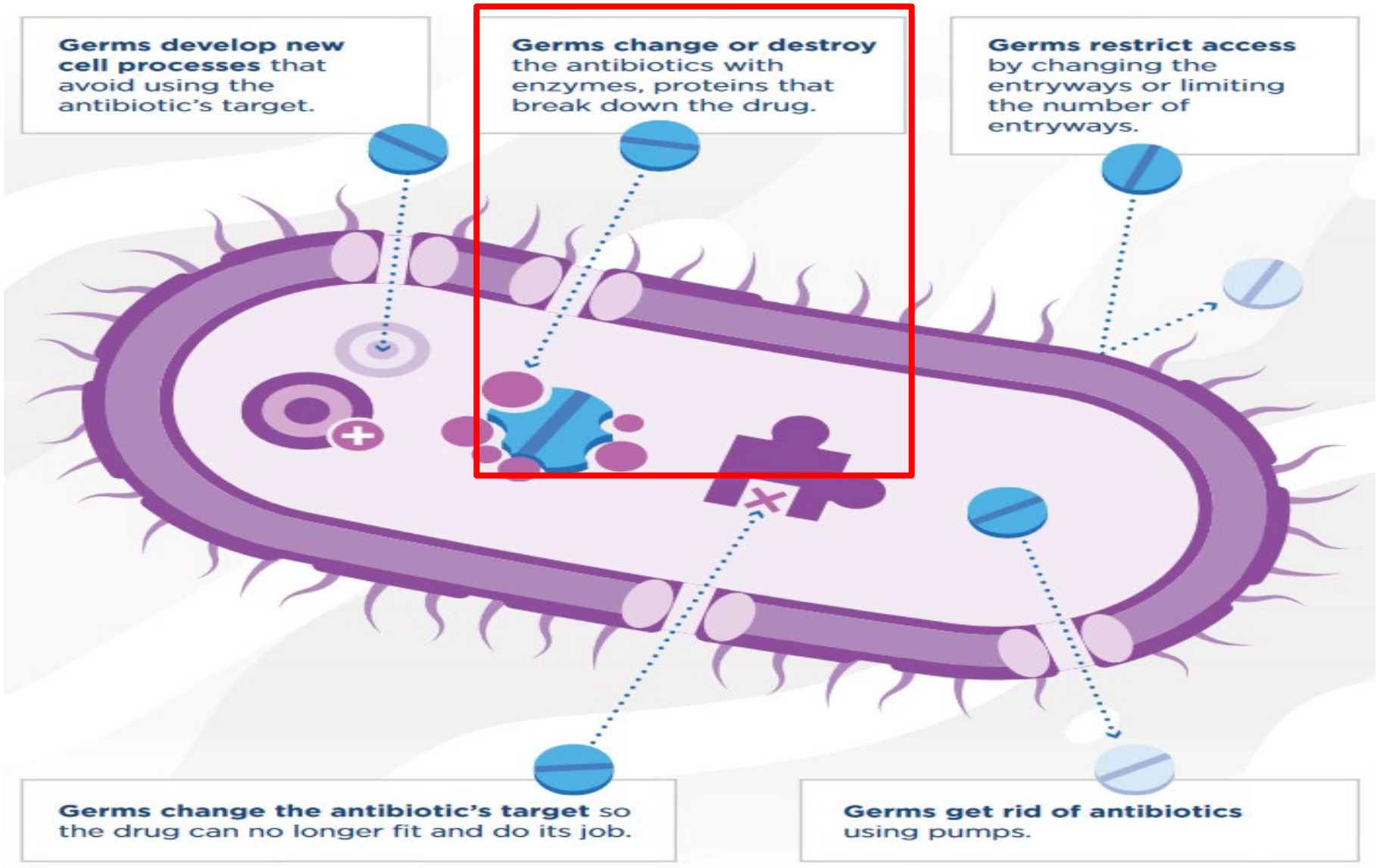
- One of the top ten global public health threats facing humanity
- Due to misuse and overuse of antimicrobials

Centers for Disease Control and Prevention (CDC)

- Antibiotic Resistance Threats in the United States (2019)
  - Over 2.8 million infections
  - Over 35,000 deaths
- Most urgent and serious threats are Gram-negative organisms

CDC. Antibiotic Resistance Report. 2019
WHO. Antimicrobial Resistance. 2021

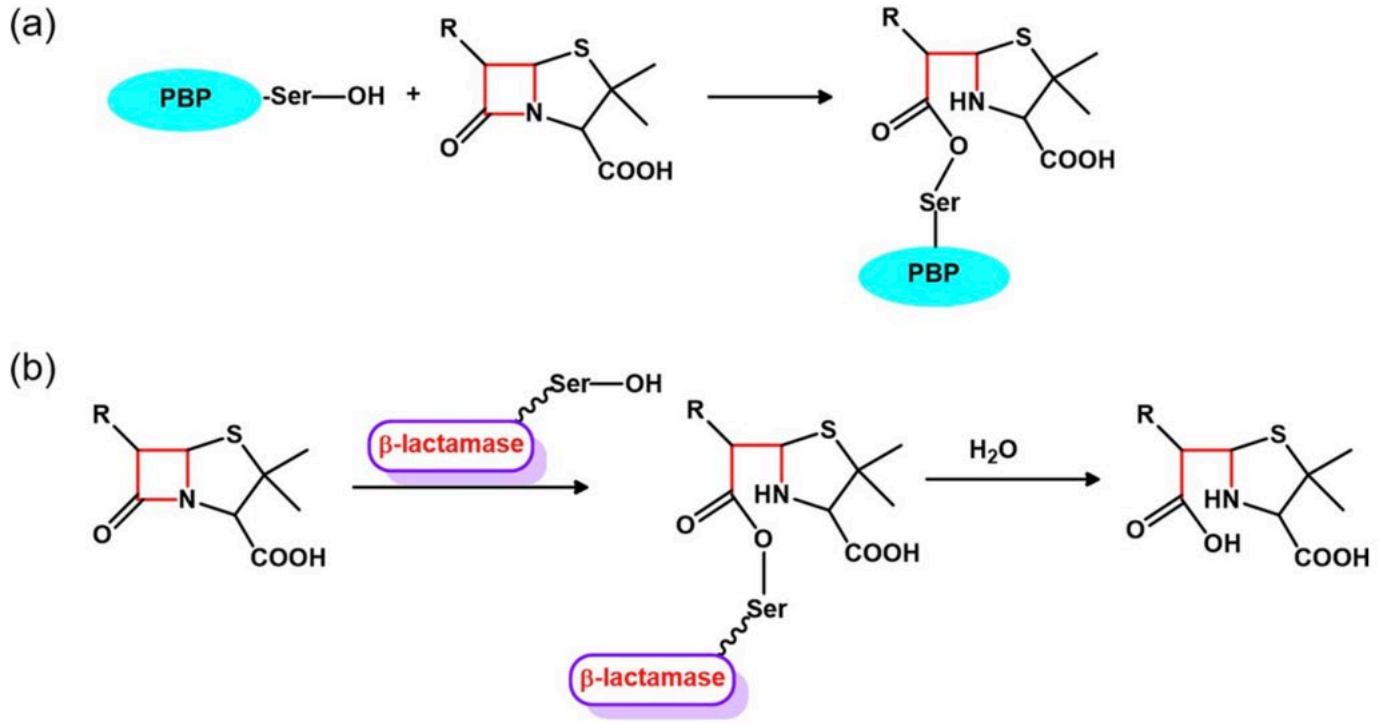
Antimicrobial Resistance Mechanisms



Reygaert WC. AIMS Microbiol. 2018;4(3):482-501

Enzymatic Resistance

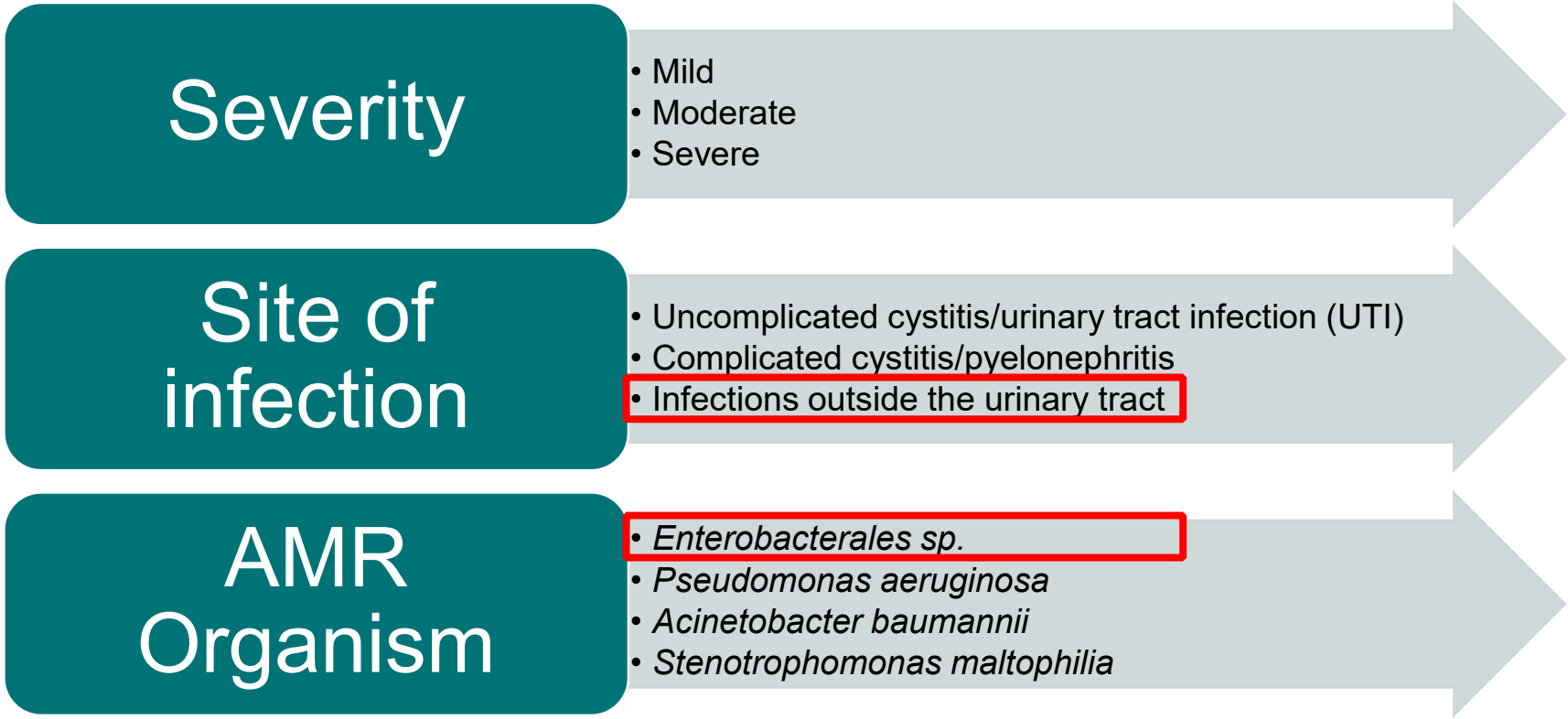
- Inactivates drugs by degradation
- β-lactamase
  - Ambler classification: A, B, C, D
    - Hydrolysis mechanism
    - Not increasing coverage
- Overcome resistance
  - Changing drug class
    - Penicillin -> Sulfonamide
  - Enzyme inhibitor
    - Piperacillin + Tazobactam



Reygaert WC. AIMS Microbiol. 2018;4(3):482-501

Infectious Diseases Society of America (IDSA) 2023 Guidance on the Treatment of AMR Infections

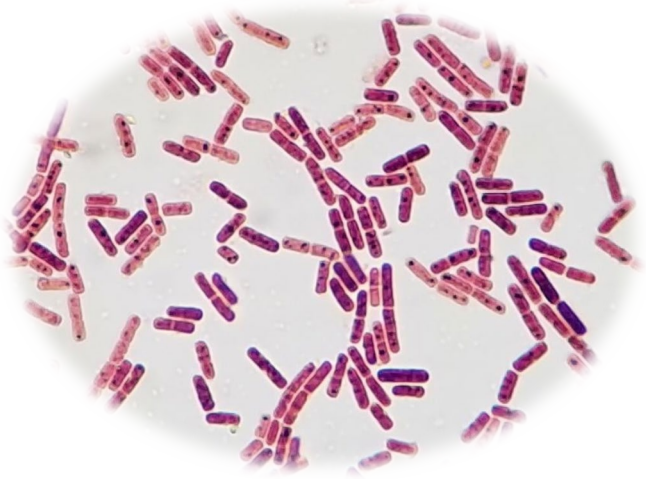
IDSA Treatment Considerations



Tamma PD, et al. Clin Infect Dis. 2023;ciad428

Enterobacterales sp.

- Previously called *Enterobacteriaceae*
  - Family of Gram-negative bacilli
- Natural habitat
  - "Entero" – pertaining to the intestines
  - Gut flora
- Typical susceptibility
  - Organism dependent
  - 1st-3rd generation cephalosporin
- Resistance categories
  - Extended-spectrum β-lactamase (ESBL)
  - Carbapenem-Resistant *Enterobacterales* (CRE)
  - **AmpC β-lactamase**



BioScience Diagnostics. Food Safety – Enterobacteriaceae. 2020
Tamma PD, et al. *Clin Infect Dis*. 2023;ciad428

AmpC β-lactamase

- Ambler class C β-lactamase
  - Assists with cell wall recycling
  - Targets and degrades β-lactam antibiotics
    - Basal levels: penicillin, **cephamycin**
    - Hyperexpression: 3rd generation cephalosporins
  - No effect on non-β-lactam antibiotics

- Increasing AmpC production
  - **Induction**
    - Exposure to initially susceptible β-lactam
    - May develop resistance during/after treatment
  - Stable gene de-repression
  - Plasmid-mediated resistance

Bacteria	Penicillins	1st Gen Ceph.	2nd Gen Ceph.	3rd Gen. Ceph.	4th Gen. Ceph.	Carbapenems	β-lactamase inhibitors *in vitro*	Aztreonam
Low level AmpC	R	V	S	S	S	S	R	S
High level AmpC	R	R	R	R	S	S	R	R

Tamma PD, et al. Clin Infect Dis. 2019;69(8):1446-1455

AmpC Producing Organisms

SPACE/SPICE

- *Serratia*
- *Providencia/Pseudomonas*
- *Acinetobacter*/Indole-positive *Proteus*
- *Citrobacter*
- *Enterobacter*

- Does not address range of inducibility
- Does not address differences of species

Garcia, B. HECK YES! IDstewardship. 2022

Treatment Considerations

β-lactams	Strong Inducer	Weak Inducer
Good Substrate	Aminopenicillins, 1st generation cephalosporins, Cefoxitin, Cefotetan	Ceftazidime, Ceftriaxone, Cefotaxime, Piperacillin, Ticarcillin, Aztreonam "**WIGS" = ???**
Poor Substrate	Imipenem	Cefepime, Meropenem "**WIPS" = Preferred**
Non-β-lactams	No effect on induction or substrate Fluroquinolones (FQ), Sulfamethoxazole/trimethoprim (SMX/TMP)	

Inducer – Increases AmpC production
Substrate – Susceptible to AmpC hydrolysis

Garcia, B. HECK YES! IDstewardship. 2022
Tamma PD, et al. Clin Infect Dis. 2023;ciad428

AmpC Induction Example

	Enterobacter cloacae complex MIC	
Amikacin	<=8	Susceptible *
Amoxicillin/Clavulanic Acid	>16/8	Resistant *
Ampicillin	>16	Resistant *
AMPICILLIN/SULBACTAM	>16/8	Resistant *
Aztreonam	<=4	Susceptible *
Cefazolin	>16	Resistant *
Cefepime	<=2	Susceptible
Cefotaxime	<=2	Susceptible *
Cefoxitin	>16	Resistant *
Ceftazidime	<=1	Susceptible *
Ceftriaxone	<=1	Susceptible *
Cefuroxime	>16	Resistant *

Exposure to cefazolin

(Strong inducer, Good substrate)

	Enterobacter cloacae complex MIC	
	<=8	Susceptible *
	>16/8	Resistant *
	>16	Resistant *
	>16/8	Resistant *
	16	Resistant
	>16	Resistant *
	>16	Resistant
	>32	Resistant *
	>16	Resistant *
	>16	Resistant *
	>32	Resistant *
	>16	Resistant *

Weak Inducers Good Substrates (WIGS)

Ceftriaxone (CRO)

- Induction potential uncertain
  - Most studies mix weak with high-risk AmpC producers
  - Possibly noninferior to cefepime in clinical outcomes
- **Not recommended** for moderate to high risk AmpC producers
- Reasonable for treating **uncomplicated cystitis**

Piperacillin/tazobactam (TZP)

- Tazobactam less effective from protecting against AmpC hydrolysis
- Possibly noninferior to meropenem in clinical outcomes
- Possible **increase in microbiologic failure**
- **Not recommended** for serious infections caused by AmpC *Enterobacterales*

Tamma PD, et al. Clin Infect Dis. 2023;ciad428

Previous Literature: Ceftriaxone

	Evaluating Third-Generation Cephalosporins for Bloodstream Infections Secondary to AmpC Organisms
Study design	Multicenter Retrospective Observational cohort
Population	Adult (≥ 18 years) Definitive bloodstream infection due to a AmpC producer (SPACE/SPICE)
Intervention	3rd generation cephalosporin (3GC) (n=65) Non-3rd generation cephalosporin (non-3GC) (n=316)
Result	Treatment failure • 3GC: 33.8% • Non-3GC: 29.7% • p = 0.513

Derrick C, et al. Antibiotics (Basel). 2020;9(5):254

Previous Literature: TZP

Study	Population	Intervention	Results
Harris PN, et al. Systematic Review with Meta-analysis	Adults Bacteremia from *Enterobacter, Serratia, Citrobacter, Providencia,* or *Morganella sp*.	TZP (n=179) Carbapenem (n=474)	Mortality on definitive therapy • 18% vs 14%; OR = 0.87 Mortality on empiric therapy • 10% vs 21%; OR = 0.48
Stewart AG, et al. (MERINO-2) International Open-label Parallel-group Randomized control trial	Adults Bacteremia from SPACE/SPICE	TZP (n = 38) MER (n = 34)	Treatment failure • 29% vs 21%; p = 0.41 Mortality • 0% vs 6%; p = 0.13 **Clinical failure** • **21% vs 12%**; p = 0.29 **Microbiologic failure** • **13% vs 0%; p = 0.03** Microbiologic relapse • 0% vs 9%; p = 0.06

Harris PN, et al. J Antimicrob Chemother. 2016;71(2):296-306
Stewart AG, et al. Open Forum Infect Dis. 2021;8(8):ofab387

Assessment #1

Which of the following organisms is a moderate to high risk AmpC producing organism?

A. *Serratia marcescens*

B. *Citrobacter freundii*

C. *Citrobacter koseri*

D. *Escherichia coli*

Comparing WIGS vs WIPS and non-β-lactams

Purpose

Evaluate the efficacy of WIGS compared to standard of care for the treatment of bacteremia caused by moderate to high risk AmpC producing organisms.

Study Design

- Institutional Review Board approved
- Multi-center, retrospective chart review
- 6 sites within Louisiana Children's Medical Center health system
- January 2017 to December 2023

Inclusion/Exclusion Criteria

Inclusion

- Age ≥ 18 years
- Inpatient status
- ≥ 1 blood culture detecting:
  - *Hafnia alvei*
  - *Enterobacter cloacae*
  - *Citrobacter freundii*
  - *Klebsiella aerogenes*
  - *Yersinia enterocolitica*

Exclusion

- Antibiotic initiated at an outside hospital
- Baseline resistance to study antibiotics
- Polymicrobial blood cultures
- Discharge against medical advice
- > 48 hours on study and control antibiotic for definitive therapy
- No definitive therapy

Study Groups

Study	Control

• WIGS
  • Ceftriaxone
  • Piperacillin/tazobactam
	• WIPS
	  • Cefepime
	  • Meropenem
	• Non-β-lactam antibiotic
	  • Fluoroquinolone
	  • SMX/TMP

Outcomes

Primary

- 30-day all-cause mortality

Secondary

- Microbiologic failure
- Microbiologic relapse
- Development of AmpC-mediated resistance
- Hospital length of stay

Statistical Analysis

Power

- 1531 patients for 80% power

Primary

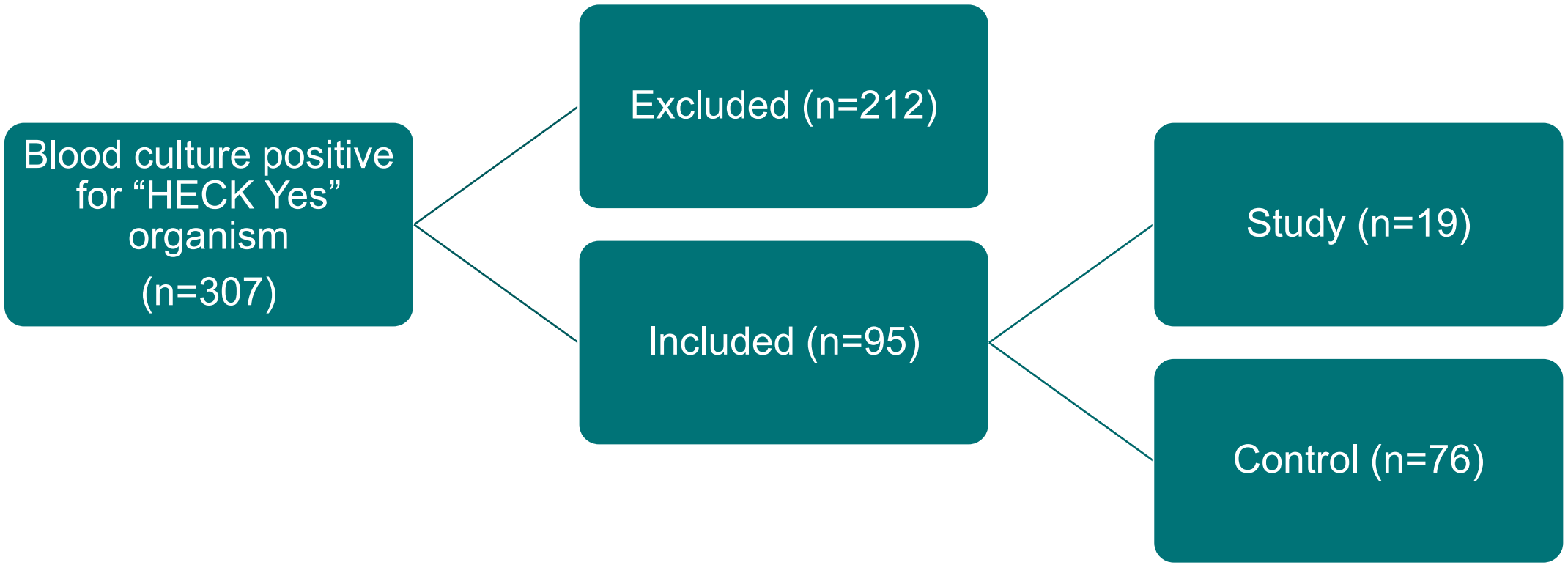
- Fischer's exact

Secondary

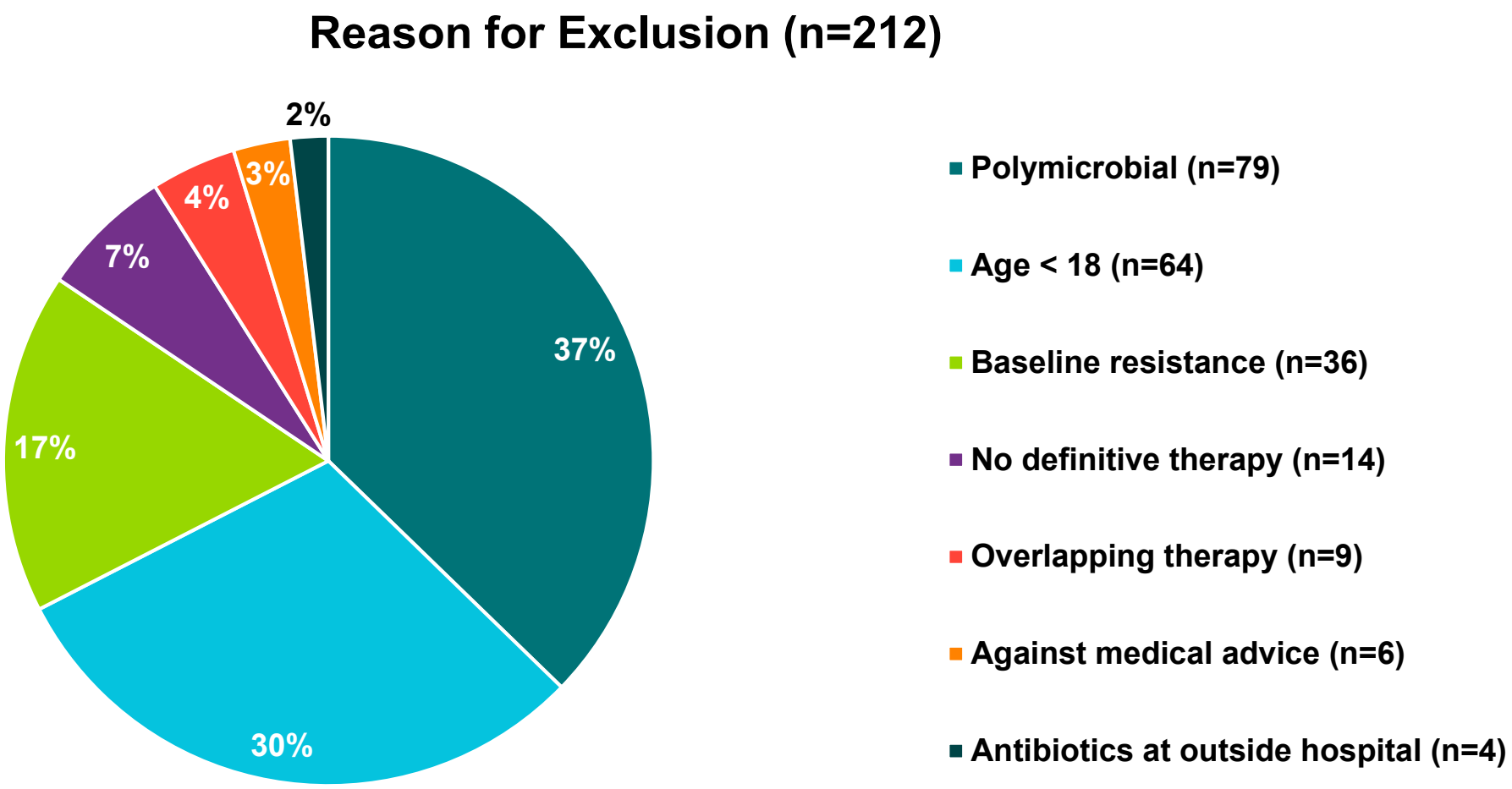
- Fischer's exact
- Mann-Whitney U test

Results

Study Population



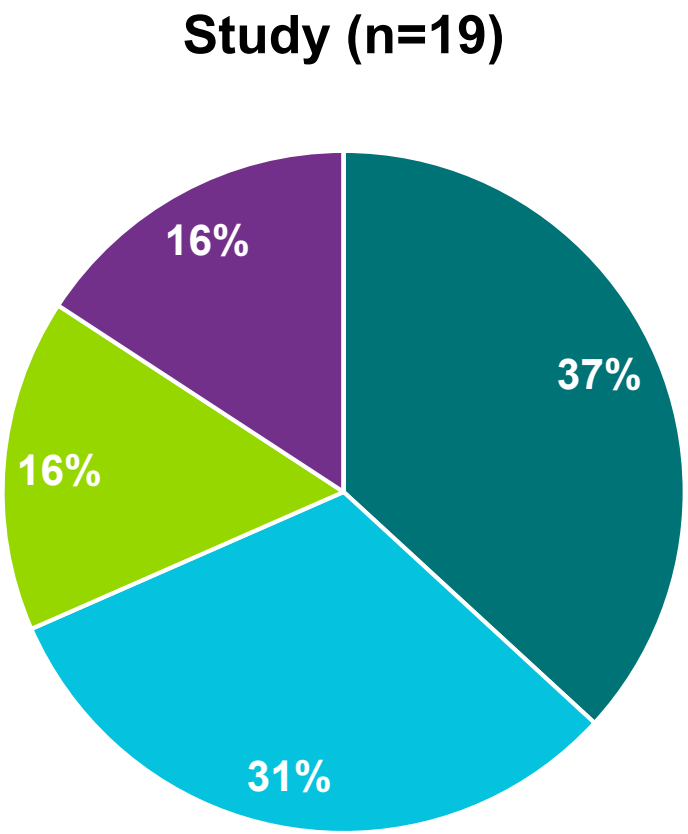
Exclusion Population

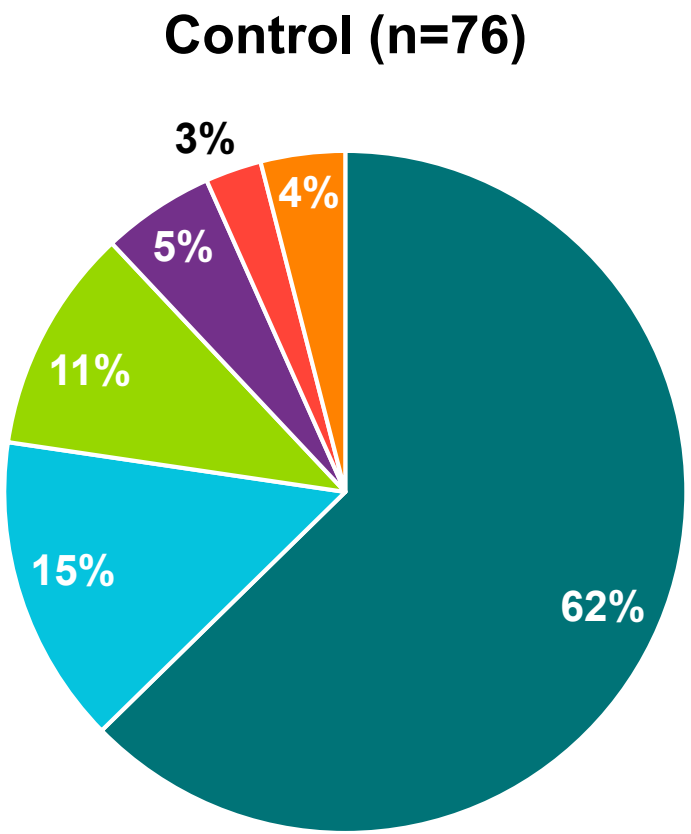


Baseline Characteristics

Baseline Demographics	Study (n=19)	Control (n=76)	P-value
Median age, years (IQR)	56 (44 – 74)	54 (38 – 64)	0.189
Male, n (%)	13 (68)	49 (64)	0.795
Race, n (%)			0.199
White Black/African American	12 (63) 6 (32)	27 (36) 38 (50)	- -
Infectious diseases consult, n (%)	6 (32)	37 (49)	0.198
Median Pitt bacteremia score (IQR)	3 (1 – 3)	2 (0 – 2)	0.239
Median duration of therapy, day (IQR)	10 (7 – 14)	14 (11 – 16)	**0.032**
Empiric duration Definitive duration	3 (2 – 4) 7 (4 – 10)	1 (1 – 3) 13 (9 – 14)	0.320 **0.002**
Repeat blood culture, n (%)	18 (95)	56 (74)	0.063

Therapy Location





Hospital 1 Hospital 2 Hospital 3
Hospital 4 Hospital 5 Hospital 6

Culture Data

Organism, n (%)	Study (n=19)	Control (n=76)	p-value
E. cloacae	11 (58)	55 (72)	0.268
C. freundii	1 (5)	3 (4)	0.896
H. alvei	1 (5)	1 (1)	0.362
K. aerogenes	6 (32)	17 (22)	0.388
Y. enterocolitica	0	0	-

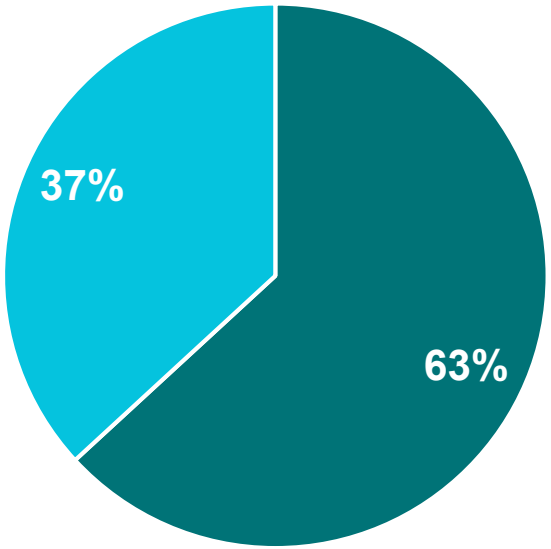
Source of infection, n (%)	Study (n=19)	Control (n=76)	p-value
Intra-abdominal	7 (37)	16 (22)	0.229
Genitourinary	5 (26)	22 (29)	0.892
Catheter-related	3 (16)	18 (24)	0.552
Other/Unknown	4 (21)	20 (25)	0.773

Empiric Therapy

Gram-negative antibiotic, n (%)	Study (n=19)	Control (n=76)	p-value
Piperacillin-tazobactam	9 (47)	31 (41)	0.614
Cefepime	6 (32)	19 (25)	0.569
Ceftriaxone	1 (5)	10 (13)	0.454
Fluroquinolone	0	3 (4)	0.656
Meropenem	0	4 (5)	0.580
Other	1 (5)	4 (5)	1
None	2 (11)	5 (7)	0.624

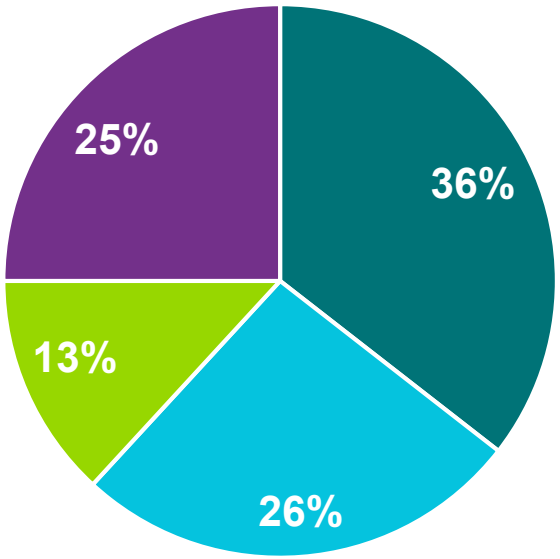
Definitive Therapy

Study (n=19)



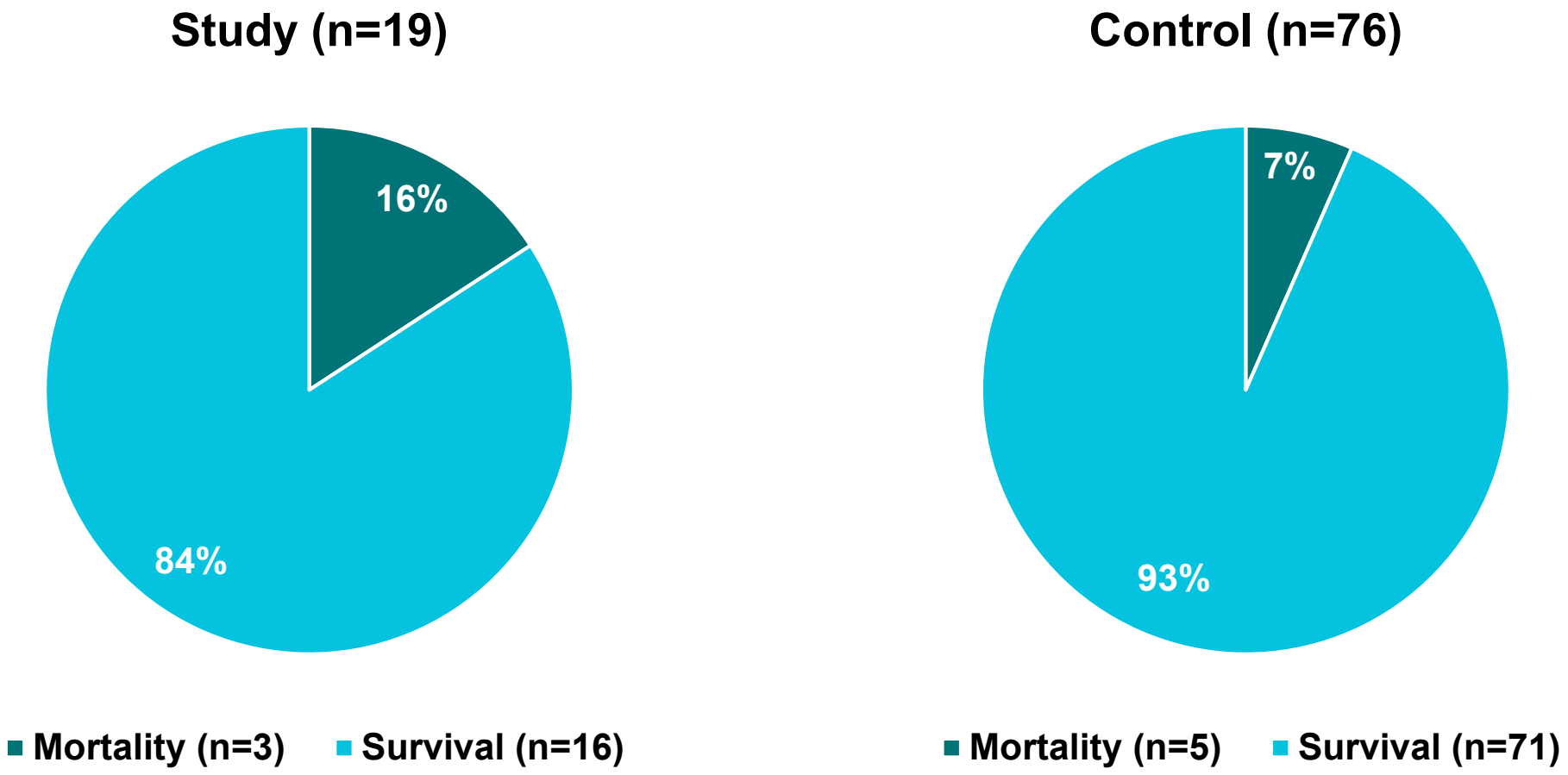
TZP (n=12) CRO (n=7)

Control (n=76)



FQ (n=27) FEP (n=20)
MER (n=10) Two control (n=19)

Primary Outcome: 30-Day Mortality



p-value = 0.196

Secondary Outcomes

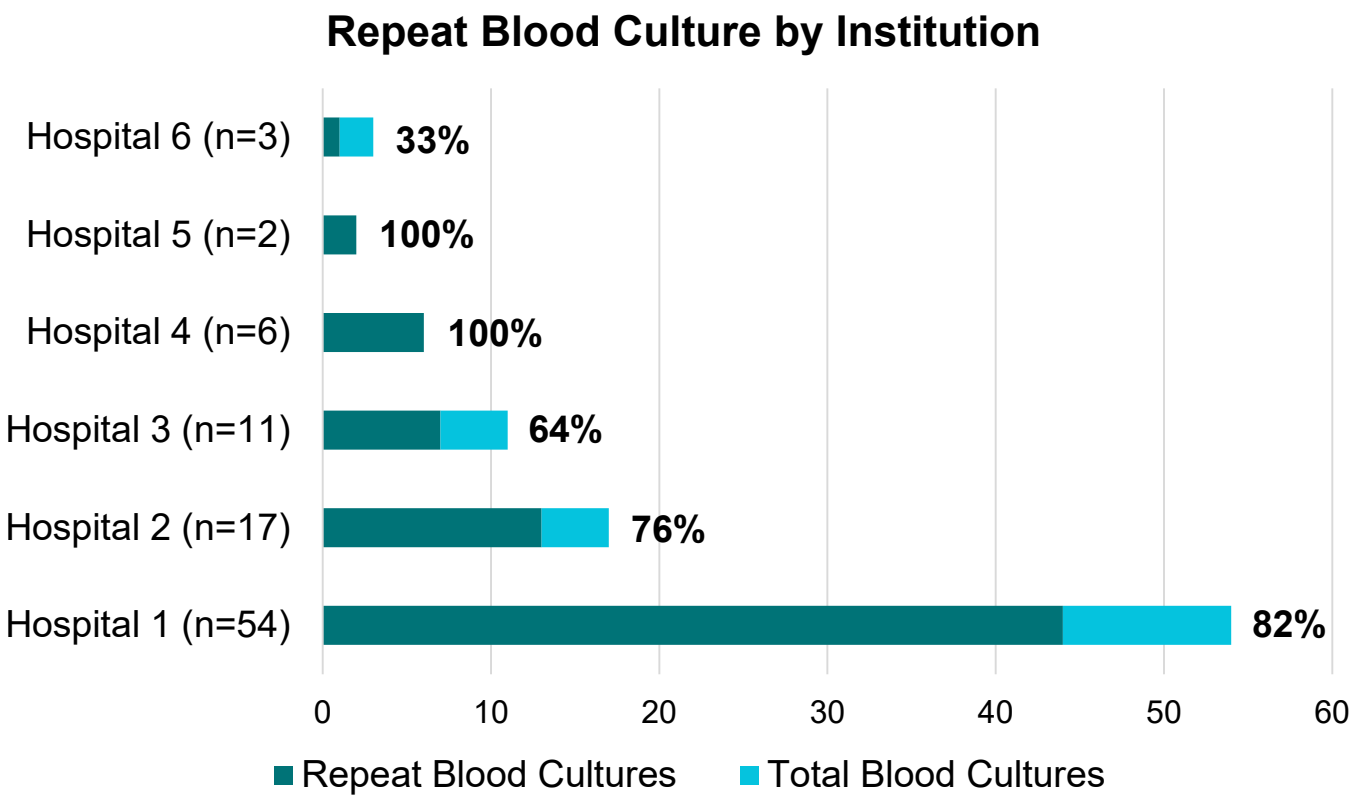
Secondary Outcomes	Study (n=19)	Control (n=76)	p-value
Microbiologic failure, n (%)	1 (5)	4 (5)	1
Microbiologic relapse, n (%)	-	-	-
Development of AmpC-mediated resistance, n (%)	-	-	-
Hospital-LOS, median (IQR)	10 (6.5 - 32.5)	12.5 (5 – 33.5)	0.798

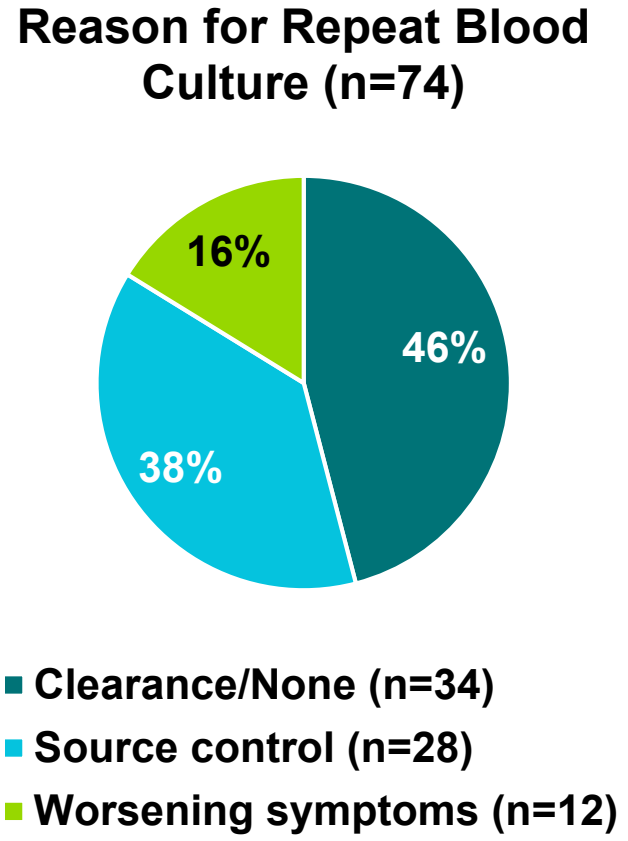
Discussion and Conclusion

Discussion

- The most common AmpC producing organism *E. cloacae*
- Majority of patients treated with guideline-directed therapy
- Longer duration of therapy in control group
- 30-day mortality was more than double in patients receiving WIGS compared to standard of care
- High proportion of Gram-negative repeat blood cultures

Repeat Blood Cultures





Strengths and Limitations

Strengths

- Evaluation of moderate-high risk AmpC organisms
- Clinically relevant

Limitations

- Small sample size
- Retrospective
- Expanding health-system

Conclusion

Conclusion

- WIGS should not be recommended to treat bacteremia caused by moderate-high AmpC producing organisms.
- The results from this study support current guideline recommendations from the IDSA on AmpC infections.

Future Direction

- Reduce use of WIGS for AmpC bacteremia
- Reduce repeat blood cultures for Gram-negative bacteremia for clearance
- Reduce duration of therapy to 7 days for Gram-negative bacteremia

Case Assessment #2

- Day 1
  - RC is a 55 year old female presents to the emergency department with dysuria and fever of 100.8^0F.
  - Blood and urine cultures are taken before she is started on empiric vancomycin and cefepime.
  - Urinalysis is positive for white blood cells, bacteria, and leukocyte esterase. Squamous epithelial cells 0-20. Reflex to urine culture

- Day 2
  - Blood cultures: Gram-negative rods (2/2)
  - Urine culture: Gram-negative rods >100 k
  - Vancomycin is discontinued

Case Assessment #2 (continued)

Later on day 2, culture results come back detecting *E. cloacae*. What would be the preferred treatment option?

A. Ceftriaxone

B. Cefazolin

C. Cefepime

D. Meropenem

	Enterobacter cloacae complex MIC	
Amikacin	<=8	Susceptible *
Amoxicillin/Clavulanic Acid	>16/8	Resistant *
Ampicillin	>16	Resistant *
AMPICILLIN/SULBACTAM	>16/8	Resistant *
Aztreonam	<=4	Susceptible *
Cefazolin	>16	Resistant *
Cefepime	<=2	Susceptible
Cefotaxime	<=2	Susceptible *
Cefoxitin	>16	Resistant *
Ceftazidime	<=1	Susceptible *
Ceftriaxone	<=1	Susceptible *
Cefuroxime	>16	Resistant *

Case Assessment #3

After initiating appropriate therapy, her symptoms have resolved and the team classifies her bacteremia as uncomplicated. What would be the shortest duration of therapy?

A. 7 days from initiation of therapy

B. 7 days from first negative blood culture

C. 14 days from initiation of therapy

D. 14 days from first negative blood culture

	Enterobacter cloacae complex MIC	
Amikacin	<=8	Susceptible *
Amoxicillin/Clavulanic Acid	>16/8	Resistant *
Ampicillin	>16	Resistant *
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Cefepime	<=2	Susceptible
Cefotaxime	<=2	Susceptible *
Cefoxitin	>16	Resistant *
Ceftazidime	<=1	Susceptible *
Ceftriaxone	<=1	Susceptible *
Cefuroxime	>16	Resistant *

Take-Away Points

- Antimicrobial resistance is a growing concern, especially with Gram-negative organisms.
- AmpC is an inducible resistance mechanism with the highest concern in HECK Yes.
- WIPS and non-β-lactams are preferred to treat infections caused by moderate-high AmpC producing organisms.

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