Amped up about AmpC Resistance? Use of Piperacillin-Tazobactam or Cefepime in the Treatment of Bacteremia caused by AmpC-β-Lactamase-Producing Bacteria

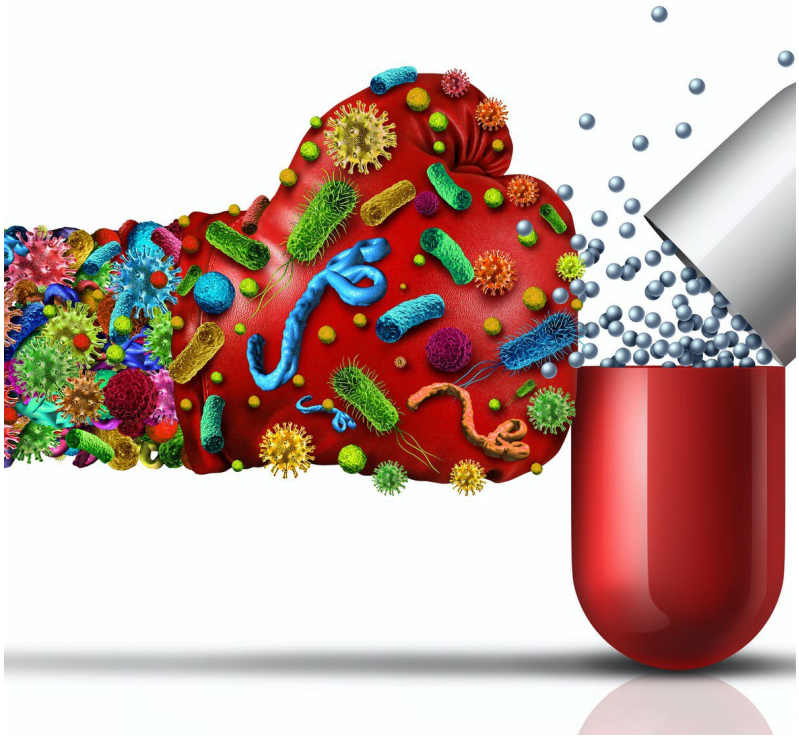

Illustration from https://theconversation.com/

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Learning Objectives

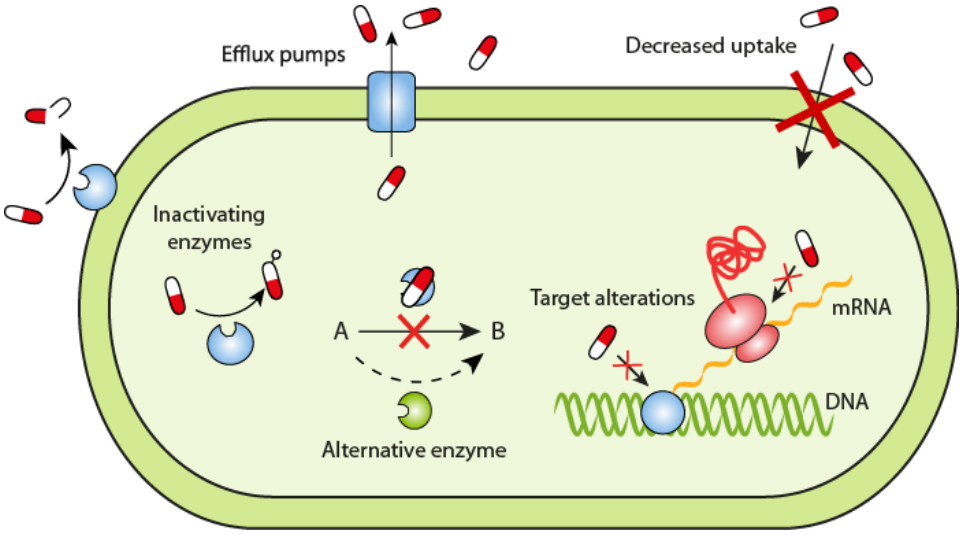
- Pharmacists:
    1. Identify gram-negative bacteria that are likely to have AmpC-β-lactamase resistance
    2. Summarize current literature comparing the use of piperacillin-tazobactam or cefepime to carbapenems for treatment of bacteremia caused by AmpC-β-lactamase producing bacteria
    3. Given a clinical case, determine an appropriate empirical regimen for treatment of bacteremia caused by AmpC-β-lactamase producing bacteria
- Pharmacy Technicians:
    1. List two common AmpC producing bacteria
    2. Recall the landmark trial that compared the use of piperacillin-tazobactam to meropenem for treatment of bacteremia caused by AmpC-β-lactamase producing bacteria
    3. Explain the risk associated with overuse of carbapenems in relation to antimicrobial resistance

Abbreviations

Abbreviation	Meaning		
AMG	Aminoglycosides	**FQ**	Fluoroquinolones
ampC	Refers to the allele or gene encoding the enzyme	**IAI**	Intra-abdominal infection
AmpC	AmpC-β-lactamase enzyme or AmpC-β-lactamase producing	**IDSA**	Infectious Diseases Society of America
BCID	Blood culture identification	**LRTI**	Lower respiratory tract infection
BLBI	β-lactam/β-lactamase inhibitor	**MEM**	Meropenem
BSI	Bloodstream infection	**NHSN**	National Healthcare Safety Network
CBM	Carbapenems	**OR**	Odds ratio
CI	Confidence interval	**OXA**	Oxacillinase
CLSI	Clinical and Laboratory Standards Institute	**PK**	Pharmacokinetic
CNS	Central nervous system	**PNA**	Pneumonia
CoNS	Coagulase-negative *Staphylococcus*	**SDD**	Susceptible dose dependent
ESBL	Extended-spectrum-β-lactamase	**spp.**	Species
EUCAST	European Committee on Antimicrobial Susceptibility Testing	**TZP**	Piperacillin-tazobactam
FEP	Cefepime	**UTI**	Urinary tract infection

Introduction to Bacterial Resistance

Figure 1. Mechanisms of Resistance[1-3]



- β-lactamase[1-3]
  - Hydrolyzes the amide bond on a β-lactam ring
  - Inactivates β-lactam antibiotics (e.g., penicillins, cephalosporins)

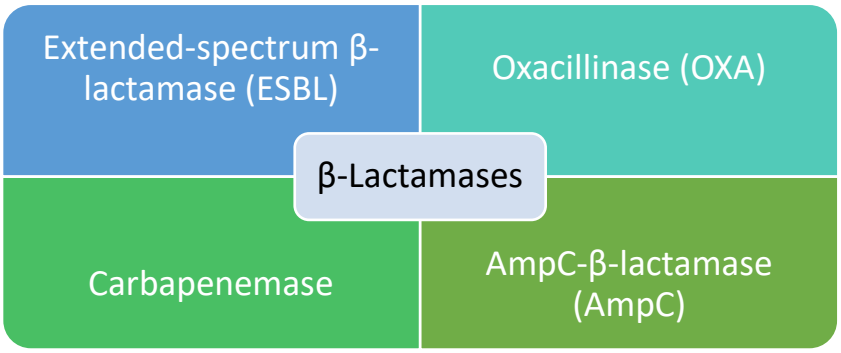
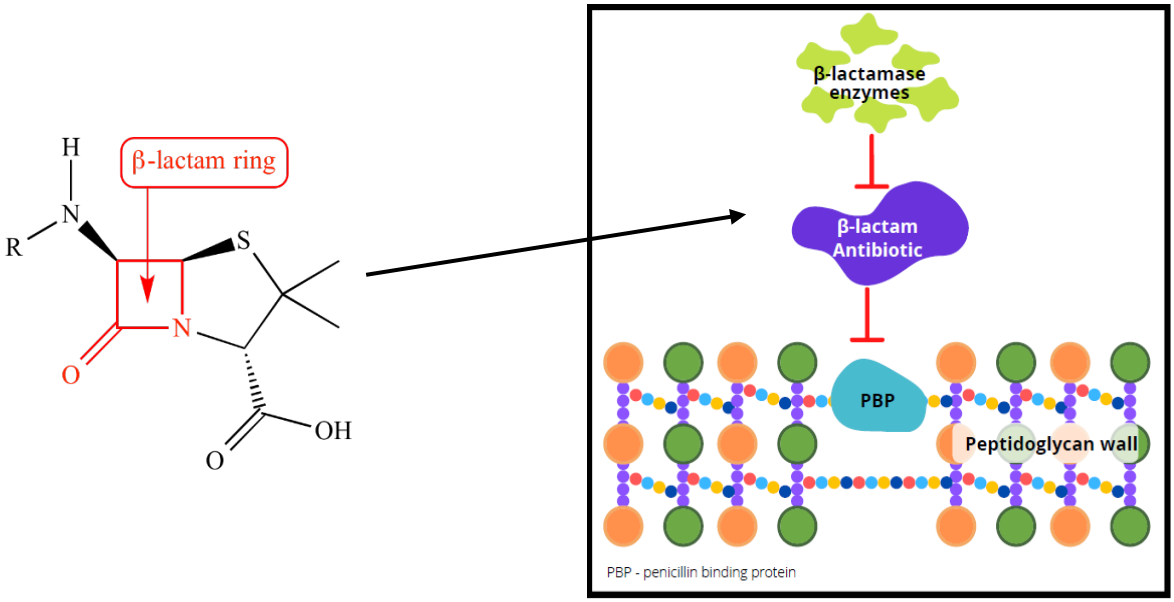


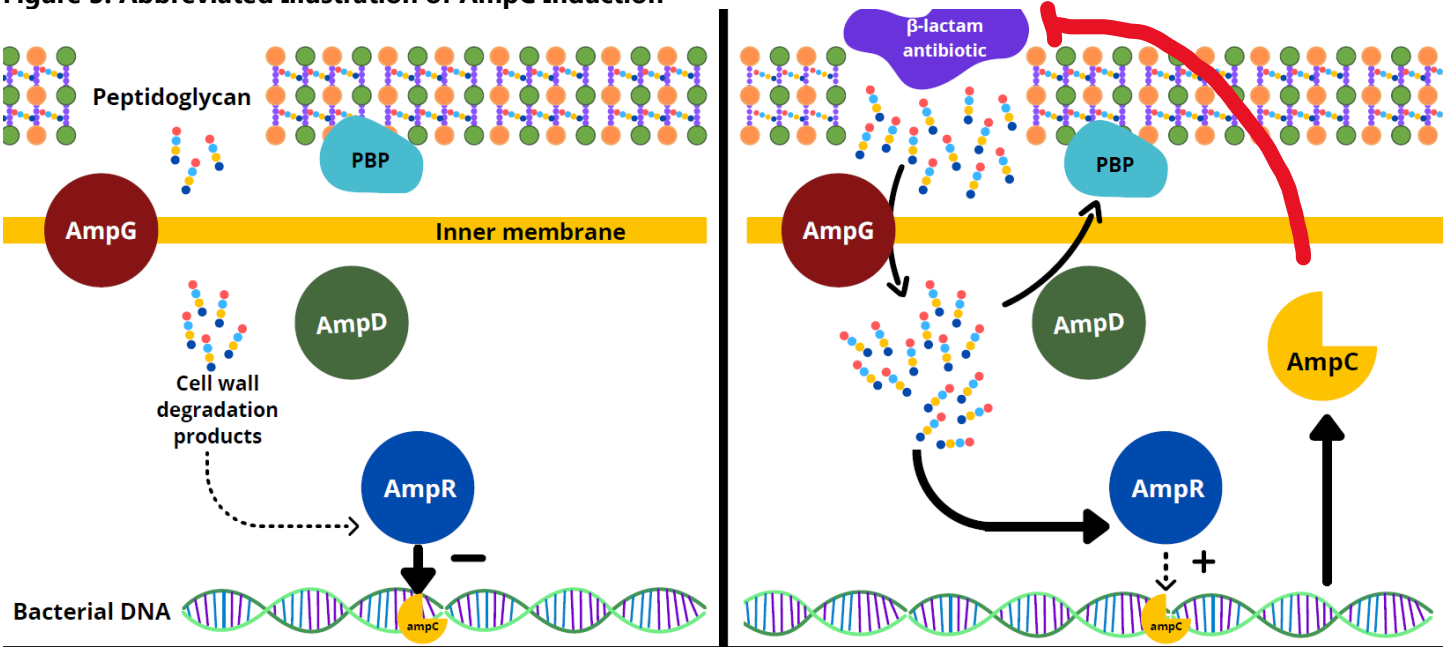
Figure 2. Mechanism of β-Lactamase Resistance[2, 4]



AmpC-β-Lactamase

- Mechanism of AmpC Resistance[2, 5, 6]
  - Constitutive – AmpC production occurs without a trigger (i.e., chromosomally encoded and expressed)
  - Inducible – Trigger (e.g., cell wall products) cause derepression of ampC gene, thus AmpC production
  - Resistance can be induced in as little as 1 day of antibiotic exposure

Figure 3. Abbreviated Illustration of AmpC Induction[2, 6]



- Moderate to high risk AmpC- β-lactamase producing bacteria[7]

Enterobacter spp.	*Klebsiella aerogenes*	*Citrobacter freundii*

- Detection of AmpC-β-lactamase production[2]
  - Sensitivity assays (e.g., cloxacillin, boronic acid)
  - Phenotypic assays cannot distinguish derepression of gene versus plasmid-associated genes
  - Molecular typing reserved for research use
  - Interpretation of blood culture identification (BCID) results

Figure 4. Example of BCID Results Before and After Initiating a Third-Generation Cephalosporin

Before

Antibiotic	MIC (mg/L)	Susceptibility *Enterobacter cloacae*
Ampicillin	>32	R
Cefoxitin	>8	**R**
Ceftriaxone	<1	**S**
Piperacillin-tazobactam	<8/4	**S**
Cefepime	<2	**S**
Gentamicin	<4	S
Ciprofloxacin	>4	R
Meropenem	<1	**S**

After

Antibiotic	MIC (mg/L)	Susceptibility *Enterobacter cloacae*
Ampicillin	>32	R
Cefoxitin	>8	**R**
Ceftriaxone	>2	**R**
Piperacillin-tazobactam	<32/4	**I**
Cefepime	<2	**S**
Gentamicin	<4	S
Ciprofloxacin	>4	**R**
Meropenem	<1	**S**

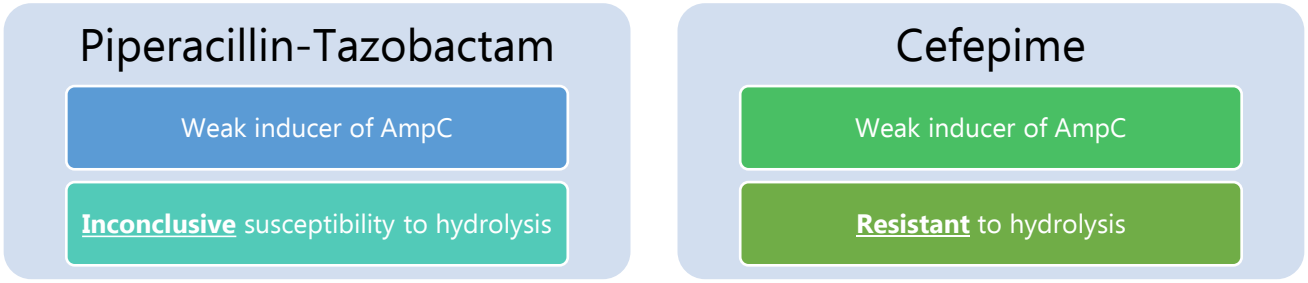
- Nomenclature of bacteria [7-9]
  - New taxonomy nomenclature as of 2020
    - Enterobacterales – order of gram-negative rod-shaped bacteria; preferred term
    - *Enterobacteriaceae* – family of bacteria within the "Enterobacterales" order
  - Outdated nomenclature incorrectly includes bacteria that are not likely to possess ampC genes
    - SPICE – *Serratia* spp., *Pseudomonas aeruginosa*, indole-positive *Proteus* spp. (e.g., *Proteus vulgaris*), *Citrobacter* spp., *Enterobacter* spp.
    - SPACE – *Serratia* spp., *Providencia* spp., *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp.
    - ESCPM – *Enterobacter* spp., *Serratia marcescens, Citrobacter freundii, Providencia* spp., *Morganella morganii*
    - Examples of limitations
      - Indole-positive *Proteus* and *Citrobacter koseri* do not possess ampC genes
      - *Serratia marcescens* and *Morganella morganii* are less likely to harbor AmpC

Antibiotics versus AmpC-β-Lactamase

Table 2. Pharmacodynamics of β-lactams Against Inducible AmpC β-lactamase Production[2]

Antibiotic	AmpC Induction	Hydrolysis
Aminopenicillins	Potent inducers	Susceptible
First-generation cephalosporins		
Second-generation cephalosporins		
Third-generation cephalosporins (ceftriaxone, ceftazidime)	Weak inducers	Susceptible
Carbapenems	Weak inducers	Resistant

- An early prospective, observational study conducted by Chow and colleagues in 1991 determined that third-generation cephalosporins should be avoided as treatment for nosocomial infections caused by *Enterobacter* spp.[10]



Use (and Overuse) of Carbapenems

- Burden of gram-negative resistance on healthcare systems[11-13]
  - Common cause of nosocomial infections (urinary tract infection, pneumonia, sepsis)
  - Recurrent or undertreated infection
  - Potential for carbapenem resistance development
- Carbapenems belong to the class of beta-lactam antibiotics[11,12]
  - Broadest spectrum of activity
  - High potency against variety of bacteria
  - Previously used as last-line therapy
- Centers for Disease Control and Prevention (CDC) reports on antibiotic resistance in the United States[7, 13, 14]
  - 2.8 million antibiotic-resistant infections detected per year
  - 35,000 deaths due to antibiotic resistance per year

Urgent	Serious	Concerning
• **Carbapenem-resistant *Acinetobacter***	• Drug-resistant *Campylobacter*	• Erythromycin-resistant Group A *Streptococcus*
• *Clostridioides difficile*	• **ESBL-producing Enterobacterales**	• Clindamycin-resistant Group B *Streptococcus*
• **Carbapenem-resistant Enterobacterales**	• Vancomycin-resistant *Enterococci*	
• Drug-resistant *Neisseria gonorrhoeae*	• Multi-drug resistant *Pseudomonas aeruginosa*	
	• Methicillin-resistant *Staphylococcus aureus*	
	• Drug-resistant *Streptococcus pneumoniae*	

Table 1. National Healthcare Safety Network (NHSN) Reported Resistance Patterns of Select Gram-Negative Bacteria in 2019[10]

Bacteria	Resistance to Carbapenems
***Acinetobacter* spp.**	33.9%
Pseudomonas aeruginosa	13.3%
Enterobacterales	2.4%
***Enterobacter* spp.**	4.6%
Escherichia coli	0.6%
***Klebsiella* spp.**	4.7%

Treatment Considerations

- Bacteremia[12, 16-19]
  - Definition
    - Viable bacteria in the bloodstream
    - Body's immune response fails or is overwhelmed (e.g., bacterial resistance)
  - Etiology
    - Usually secondary to another infection (urinary tract, respiratory tract, intra-abdominal)
    - Other sources come from invasive devices and medical procedures (intravascular catheter, dental procedure)
  - Risk Factors

Immunocompromised	Chronic Conditions	Other
•Stem cell transplant •Solid organ transplant •Human immunodeficiency virus (HIV)	•Diabetes •Chronic kidney disease (CKD) requiring dialysis •Chronic wound care	•Previous infection with resistant organism •Extended hospitalization (>5 days)

  - Clinical Presentation
    - Asymptomatic
    - Symptomatic (chills, abdominal pain, nausea, vomiting, diarrhea)
    - Can devolve into sepsis

- Guideline recommendations[9, 20, 21]

7/1/2009	9/8/2020	11/22/2021
•Management of Intravascular Catheter-Related Infection: 2009 Update (Archived)	•Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0	•Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

  - Prior guidelines did not offer recommendations on resistant organisms
  - Version 1.0 provides information regarding ESBL-producing bacterial resistance, carbapenemase resistance, and *Pseudomonas aeruginosa* resistance
  - Version 2.0 provides information regarding **AmpC-β-lactamase-producing bacterial resistance**, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*
    - Cefepime is recommended to treat bacteria with moderate to high risk of producing AmpC when MIC ≤ 2 mcg/mL
    - Piperacillin-tazobactam is not recommended to treat infections with moderate to high risk of producing AmpC

Question

- Can piperacillin-tazobactam or cefepime be used to spare carbapenem utilization in bacteremias caused by AmpC β-lactamase producing bacteria?

Literature Review

Table 3. Cheng L et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC-β-lactamase-Producing *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2017;61(6):e00276-17.[23]

Objective	To evaluate the outcome in patients receiving TZP compared to outcomes for patients receiving FEP or MEM for bloodstream infections due to AmpC *Enterobacteriaceae*	
Methods		
Study design	• Retrospective cohort study conducted in New York • Patients were hospitalized between January 2009 and December 2015 • Microbiology and molecular typing - *In vitro* susceptibility defined by Clinical and Laboratory Standards Institute (CLSI) breakpoints - Kirby-Bauer disc diffusion and Vitek 2 system for susceptibility - PCR for AmpC genes	
Population	**Inclusion Criteria** • Bloodstream infection with *Enterobacter* spp., *Serratia* spp. or *Citrobacter* spp. • ≥ 18 years old • Received antibiotic therapy for at least 72 hours within 5 days of first positive blood culture	**Exclusion Criteria** • Polymicrobial bacteremia (exception CoNS) • Received alternative antibiotic (e.g., FQ) for definitive therapy (exception AMG)
Intervention	TZP versus FEP or MEM	
Outcomes	**Primary** • 30-day mortality • Persistent bacteremia	**Secondary** • 7-day all-cause mortality • Treatment failure
Statistical Analysis	• Unmatched case-control analysis • Propensity scoring with 1:1 nearest-neighbor matching without replacement with covariates: - Duration of hospital stay prior to bacteremia - ICU length of stay - Immunosuppressive agents - Charlson Comorbidity Index (CCI), Pitt Bacteremia Score (PBS) - Source of infection, pathogen - Septic shock • Chi-square or Fisher's exact test used for categorical variables • Two-sample Wilcoxon rank-sum used for continuous variables • Conditional logistic regression in matched patients • 95% confidence interval for odds ratios, P - value < 0.05 statistically significant	
Results		

Baseline characteristics

Covariate	Overall Cohort (N = 165)			Propensity Matched Scoring (N = 82)		
	TZP (n = 88)	FEP/MEM (n = 77)	P - Value	TZP (n = 41)	FEP/MEM (n = 41)	P - Value
Age	65 (52-75)	65 (47-75)	0.41	68 (59-78)	57 (40-69)	**0.012**
Male Sex	50 (57)	48 (62)	0.58	25 (61)	26 (63)	0.84
Comorbidities						
Neutropenia	3 (3)	7 (9)	0.26	0	3 (7)	0.99
Immunosuppressed	18 (21)	25 (33)	0.12	7 (17)	9 (22)	0.34
Severity of Illness						
Charlson Comorbidity Index	3 (1-7)	3 (2-5)	0.65	3 (1-6)	3, (2-4)	0.47
ICU Stay	30 (34)	36 (60)	0.002	17 (41)	15 (37)	0.34

Septic Shock	14 (16)	26 (34)	0.07	7 (17)	7 (17)	1
Pitt Bacteremia Score	1 (0-3)	2 (0-6)	0.012	2 (0-4)	1 (0-3)	0.40
Source						
Urinary Tract	19 (22)	12 (21)	0.83	10 (24)	8 (20)	0.60
LRTI/VAP	12 (14)	16 (21)		6 (15)	8 (20)	
Catheter related	10 (11)	12 (16)		3 (7)	4 (10)	
Intra-abdominal	20 (23)	13 (17)		10 (24)	5 (12)	
Unknown	11 (13)	8 (10)		4 (10)	5 (12)	
Causative Pathogen						
Enterobacter spp.	51 (58)	52 (68)	0.12	23 (56)	23 (56)	0.54
Serratia spp.	24 (27)	21 (27)		12 (29)	15 (37)	
Citrobacter spp.	13 (15)	4 (5)		6 (15)	3 (7)	
Data represented as no. (%) or median (interquartile 1-3)						

Isolate Susceptibilities

- All AmpC negative *Enterobacter* isolates (n = 8) were resistant to cefoxitin

Outcomes

Primary Outcome

Outcome	Overall Cohort No. (%)			Propensity Score-Matched No. (%)		
	TZP (n = 88)	FEP/MEM (n = 77)	OR (95% CI) P - value	TZP (n = 41)	FEP/MEM (n = 41)	OR (95% CI) P - value
30-day mortality	9 (10)	9 (12)	1.16 (0.44, 3.09) P = 0.96	6 (15)	3 (7)	0.5 (0.13, 2.0) P = 0.50
Persistent bacteremia	14 (16)	10 (13)	P = 0.66	8 (20)	4 (10)	P = 0.26

Secondary Outcomes

Outcome No. (%)	TZP (n = 88)	FEP/MEM (n = 77)	95% CI	P - value
7-day mortality	1 (1)	3 (4)	---	0.34
Treatment escalation	12 (14)	8 (10)	---	0.63

- No mortality seen in cefoxitin-susceptible patients
- No instances of developed resistance

Conclusions and Evaluation

Author's Conclusions

TZP may be a valuable treatment option for BSIs caused by AmpC β-lactamase positive *Enterobacteriaceae* and may be used as an alternative to FEP or MEM.

Critique

Strengths

- Appropriate inclusion/exclusion criteria
- Molecular typing used
- Listed sources of infection
- Primary outcomes applicable to practice
- Propensity matched
- Included *Enterobacter* spp.

Limitations

- Single-center retrospective study in Germany
- Confounded with FEP and MEM arm
- Dosing schema of antibiotics not elucidated (was based on hospital protocol)
- ~10% unknown source of infection
- Included *Serratia* spp. and all *Citrobacter* spp. including *Citrobacter koseri*
- Differences in antibiotic selection based on location of patient (e.g., ICU)

Takeaway Summary

TZP is a reasonable alternative to either FEP or MEM in *Enterobacter* spp., *Serratia* spp., or *Citrobacter* spp. bacteremia. This is mostly applicable to patients with a UTI or IAI source of infection, and those infected with *Enterobacter* spp. Although FEP was placed in the same arm as MEM, if we were to assume that all the events occurred due to the former, there was still no statistically significant difference compared to TZP.

Table 4. Herrmann L et al. Early Treatment Outcomes for Bloodstream Infections Caused by Potential AmpC β-Lactamase-Producing *Enterobacterales* with Focus on Piperacillin-Tazobactam: A Retrospective Cohort Study. *Antibiotics (Basel)*. 2021;10(6):655.[24]

Objective	To evaluate treatment outcomes of the most common empiric antibiotics in hospitalized patients with potential AmpC *Enterobacterales* bacteremia, and to identify predictors of early treatment response.	
Methods		
Study design	• Single-center retrospective cohort study at the University Hospital of Jena, Germany • Patients hospitalized between January 2011 and February 2019 • Microbiology and (lack of) molecular typing - Vitek MS to identify isolates, Vitek 2 to test susceptibilities - Phenotypic antimicrobial susceptibility testing to identify ESBL-resistant isolates	
Population	**Inclusion Criteria** • At least one positive blood culture caused by any SPICE organism (*Serratia* spp., indole-positive *Proteus*, *Citrobacter* spp., or *Enterobacter* spp.) • Suspicion of infection • ≥ 18 years old	**Exclusion Criteria** • Antibiotic therapy < 72 hours or in vitro resistance to empiric antibiotic treatment • Death within first 48 hours of antibiotic initiation • Transfer to another hospital • Palliative care
Intervention	**Antibiotics** • TZP • CBM (MEM or imipenem-cilastatin) • FQ (ciprofloxacin, moxifloxacin) • Cephalosporins (cefuroxime, ceftriaxone, cefotaxime, ceftazidime) • Other (clotrimazole, gentamicin) • Combination	**Dosing** • TZP - Standard: 4.5 g bolus every 8 hours (normal ward) or 13.5 g continuous infusion after initial 4.5 g bolus (ICU) - High: 17-18 g continuous infusion after initial 4.5 g bolus (ICU) • MEM - Standard: 1 g every 8 hours - High: 1-2 g every 6-8 hours, 4-6 g continuous infusion after initial 1-2 g bolus, or 1 g every 6 hours up to 2 g every 8 hours
Outcomes	**Primary Outcome:** Early treatment response 72 hours after start of active treatment **Secondary Outcomes:** Clinical success 14 days after initial positive blood culture, 14-day mortality rate, and relapse or persistent bacteremia	
Statistical Analysis	• Fischer exact test used for nominal data, Kruskal-Wallis test used for ordinal and numeric data • Holm-Bonferroni method used to adjust for multiple testing • Baseline characteristics compared across treatment groups • Primary and secondary outcomes calculated for TZP and CBM only with covariates • Logistic regression analysis to find predictors of early clinical response • 2-tailed P - value < 0.05 statistically significant	
Results		

Baseline characteristics

Variable	TZP (N = 81)	CBM (N = 82)
Male	52 (64.2)	62 (75.6)
Age, years	68.0 (59-75)	66.5 (56.8-73.3)
BMI	26.1 (23.0-31.0)	26.0 (24.2-30.0)
Comorbidities		
Lung Disease	20 (24.7)	26 (31.7)
Kidney Disease	16 (19.8)	11 (13.4)
Liver Disease	13 (16.0)	14 (17.1)
Metastatic carcinoma/ leukemia	8 (9.9)	4 (4.9)
Severity of Illness		

	Pitt Bacteremia Score	1.0 (0-2.0)	1.0 (0-4.0)
	Baseline SOFA score	3.0 (1.0-7.5)	4.5 (1.0-11.0)
	Charlson Comorbidity Index	3.0 (2.0-4.0)	3.0 (2.0-5.0)
	Source		
	Unknown	20 (24.7)	16 (19.5)
	Respiratory tract	19 (23.5)	29 (35.4)
	Urinary tract	7 (8.6)	16 (19.5)
	Vascular catheter	11 (13.6)	10 (12.2)
	Data are represented as no. (%) or median (quartile 1-3)		

- Causative pathogen was mainly *Enterobacter* spp., followed by *Serratia* spp.

Outcomes

Early Treatment Response Outcomes

Variable	TZP (N = 81)	CBM (N = 82)	P - value
Treatment duration of initial regimen, days	5 (3-9)	8 (5.8-11)	**0.021**
Early Treatment Response Day 3	17 (21.0)	40 (48.8)	**0.006**
ICU	2/30 (6.7)	7/35 (20.0)	0.161
Normal Ward	15/51 (29.4)	33/47 (70.2)	**0.002**
Correlates of Early Treatment Failure			
Treatment escalation within 72 hours	19 (23.5)	1 (1.2)	**<0.001**
Early source control	31 (38.3)	31 (37.8)	1.000
In vitro resistance to initial regimen with relapsed bacteremia	3/48 (6.3)	0/54 (0)	0.101
Data are represented as no. (%) or median (quartile 1-3)			

- Initial therapy changed in 125/295 (42.4%) after median of 3 days (IQR, 3-5 days)
  - Escalation (n = 58) occurred most often with TZP (n = 30, 37.0%)
  - De-escalation (n = 42) occurred most often with CBM (n = 25, 65.8%)

Predictors of Early Treatment Response

Variable	Early Response		Odds Ratio (95% CI) P - value	Adjusted Odds Ratio (95% CI) P - value
	Yes (n = 119)	No (n = 176)		
Baseline SOFA	2.0 (0-4.0)	6.0 (2.0-11.0)	0.80 (0.75-0.86), P < 0.001	0.83 (0.77-0.91), **P < 0.001**
Chronic Liver Disease	11 (9.2)	35 (19.0)	0.41 (0.20-0.85), P = 0.016	0.32 (0.13-0.82), **P = 0.018**
UTI	32 (26.9)	21 (11.9)	2.72 (1.48-5.00), P = 0.001	1.64 (0.74-3.62), P = 0.225
Vascular Related	17 (14.3)	17 (9.7)	1.56 (0.76-3.19), P = 0.225	---
Cholangitis	23 (19.3)	14 (8.0)	2.77 (1.36-5.64), P = 0.005	3.49 (1.36-8.94), **P = 0.009**
Empiric TZP	17 (14.2)	64 (36.2)	0.29 (0.16-0.53), P < 0.001	0.25 (0.12-0.53), **P < 0.001**
Early Source Control	55 (46.2)	56 (31.8)	1.84 (1.14-2.98), P = 0.013	1.15 (0.61-2.19), P = 0.668
Data are represented as no. (%) or median (quartile 1-3)				

Conclusions and Evaluation

Author's Conclusions

TZP may be associated with early treatment failure in patients being treated for AmpC SPICE bacteremia.

Critique

Strengths	Limitations
- Dosing schema well-defined	- Retrospective single center study
- Evaluated treatment response	- No molecular typing for ampC
- Evaluated 3-day and 14-day outcomes	- ~20% unknown source of infection
- Testing identified ESBL	- Cephalosporins utilized did not include FEP

Takeaway Summary

In patients with likely AmpC bacteremia, it would be favorable to use CBM over TZP for empiric treatment. This especially applies to patients who have a higher acuity of illness or chronic liver disease at baseline. If TZP is initially used, it should be escalated to a CBM to reduce risk of treatment failure.

Table 5. Harris PNA et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter, Citrobacter* or *Serratia* species: a systematic review with meta-analysis. *J Antimicrob Chermother* 2016; 71: 296-306.[25]		
Objective	To identify studies comparing therapies used in the treatment of bloodstream infections due to AmpC-β-lactamase-producing *Enterobacteriaceae* (ESCPM), and to assess all-cause mortality for patients treated with CBM, BLBLI, FEP, and FQ.	
Methods		
Study design	Systematic review and meta-analysis of 11 observational studies	
Study Selection	• Registered with PROSPERO international prospective register of systematic reviews • Utilized EMBASE, PubMed, the Cochrane database, and Scopus • Additional search with Google Scholar, contacting authors, and unpublished data from the Australian Group for Antimicrobial Resistance (AGAR) • Timeframe: January 1980 to August 2015 • Studies were included with the following parameters: - **Population:** patients with bloodstream infections caused by ampC genetically encoded gram-negative bacteria - **Intervention:** antibiotic therapy - **Comparator:** CBM - **Outcome:** all-cause mortality - **Setting**: hospitalized • Studies were excluded if: - Case report - No report of mortality associated with each class of antibiotic - Authors unable to provide mortality data on request - Only included non-BSI infections • Search protocol: (Enterobacter OR Serratia OR Citrobacter OR Providencia OR Morganella) AND (bacteremia OR bacteraemia OR blood-stream infection) AND (piperacillin-tazobactam OR ticarcillin/clavulanate OR cefepime OR carbapenem OR β-lactam/β-lactamase inhibitor OR quinolone OR mortality)	
Data Extraction	• Three authors independently screened studies • Baseline characteristics collected: - Demographics - Comorbidity or physiological risk scores	• Other data collected: - Empiric or definitive therapy - All-cause mortality
Outcomes	• 30-day mortality	
Statistical Analysis	• Newcastle-Ottawa Quality Assessment Scale used for bias • Unadjusted odds ratios calculated with 95% CI for mortality • Pooled odds ratios calculated using random-effects model • Chi-square and I^2 assessed heterogeneity with $P < 0.01$ statistically significant • Mixed-effect logistic regression model used to estimate odds ratios • Sensitivity analysis assessed outliers in the pooled estimate	

Results

Study Characteristics (Retrospective or Prospective Cohorts)

Study	Population Characteristics	Outcome
Marcos 2008	N = 370: diabetes (14%), malignancy (15%), solid organ malignancy (27%)	30-day mortality
Qureshi 2011	N = 135: diabetes (32%), CRF (16%), liver disease (24%), malignancy (16%), transplant (27%)	28-day mortality
O'Neal 2012	N = 95: diabetes (25%), coronary artery disease (22%), transplant (28%), malignancy (32%)	In-hospital mortality
Hilty 2013	Adult, mean Charlson score 4.3	28-day mortality
Tamma 2013	N = 64: Immunocompromised (43%), liver disease (48%), renal disease (56%), cardiovascular disease (33%)	30-day mortality
Chaubey 2014	N = 458: malignancy (18%), heart failure (14%), diabetes (16%), renal disease (14%)	In-hospital mortality
Huh 2014	N = 192: malignancy (100%), diabetes (16%), liver disease (17%)	30-day mortality
AGAR 2014	Adults and children	30-day mortality
Siedner 2014	N = 368: solid organ malignancy (38%), diabetes (25%), cardiovascular disease (40%), chronic obstructive pulmonary disease (11%)	In-hospital mortality
Harris 2015	N = 229: diabetes (24%), renal failure (27%), solid tumor (14%)	28-day mortality
Lin 2015	N = 109: solid tumor (27%), diabetes (39%), cardiovascular disease (39%), renal disease (30%)	14-day mortality

- Antibiotics: CBM, BLBLI, FQ, FEP

Outcomes

Pooled Unadjusted ORs for Mortality by Antibiotic Therapy Versus Carbapenems

Antibiotic	Comparator	# Studies, definitive/ empirical	Definitive Therapy OR (95% CI) I^2	Empirical Therapy OR (95% CI) I^2
BLBLI	**CBM**	8/8	0.87 (0.32–2.36) I^2 = 65.5%	0.48 (0.14–1.60) I^2 = 33%
FQ		7/8	**0.39 (0.19-0.78) I^2 = 35.1%**	0.66 (0.25-1.75) I^2 = 21.3%
FEP		6/7	0.61 (0.27-1.38) I^2 = 31.6%	0.60 (0.17-2.20) I^2 = 50.5%

Logistic Regression Analysis from Three Studies Investigating Definitive Therapy

Patient deaths/number treated (%)			Adjusted for age and sex	Adjusted for age, sex, and illness severity
Intervention		Comparator (CBM)	OR (95% CI)	OR (95% CI)
BLBLI	3/27 (11.1%)	10/69 (14.5%)	0.72 (0.18-2.93)	0.94 (0.22-4.12)
FQ	7/104 (6.7%)	10/69 (14.5%)	0.39 (0.13-1.17)	0.64 (0.21-2.00)
FEP	3/34 (8.8%)	10/69 (14.5%)	0.46 (0.11-1.94)	0.59 (0.14-2.52)

- Increased mortality with: higher markers of severity, diabetes, unknown source of infection, and ESBL

Conclusions and Evaluation

Author's Conclusions

Noncarbapenem therapies such as BLBLI, FEP, and FQ may be used as either empiric or definitive therapy in bloodstream infections caused by AmpC-β-lactamase producing bacteria. Limitations due to the heterogenous pool of studies and lack of randomized controlled trials warrants additional research.

Critique

Strengths

- Maintained focus on bacteremia
- Sensitivity analysis conducted to determine mortality risk factors
- Reasonable inclusion and exclusion criteria

Limitations

- No RCTs at the time of analysis
- Mostly single center trials
- No more than 40% AmpC phenotypes detected
- Heterogenous assortment of bacteria and treatment preferences
- Poor differentiation of ESBL versus AmpC resistance

Takeaway Summary

In bacteremias with organisms that are likely to have AmpC resistance, the use of non-CBM therapies such as FEP and TZP may be used in place of CBM. However, randomized controlled trials should be conducted to determine treatment failure and mortality outcomes.

Table 6. Stewart AG et al. 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). *Open Forum Infect Dis*. 2021;8(8):ofab387.[26]

Objective	Assess the efficacy of TZP versus MEM in the treatment of bloodstream infections caused by AmpC-β-lactamase-producing *Enterobacteriaceae*	
Methods		
Study design	• International, multicenter, open-label, parallel-group, pilot randomized controlled trial • 7 hospitals located in Australia, Singapore, and Turkey • Microbiology and molecular typing - Kirby-Bauer disc diffusion and Vitek 2 system for susceptibilities - PCR used to detect ampC genes	
Population	**Inclusion Criteria** • ≥ 18 years old • ≥ 21 years old in Singapore • At least one positive blood culture with likely AmpC producers • Positive blood culture showed susceptibility to third generation cephalosporins, TZP, and MEM	**Exclusion Criteria** • Allergy to penicillins or carbapenems • Survival expected to be 4 days or less • Polymicrobial infection (unless skin contaminant) • Treatment without curative intent • Pregnancy or breast feeding • Combination with other antibiotic during first 4 days after randomization • Central nervous system (CNS) source of infection
Intervention	TZP 4.5 g every 6 hours versus MEM 1 g every 8 hours Treatment for at least 3 days up to 14 days	
Outcomes	• **Primary**: composite of all-cause mortality at 30-days, ongoing fever or leukocytosis on day 5 of post randomization, microbiological failure on days 3-5 of post randomization, and microbiological relapse on days 5-30 of post randomization • **Subgroup analysis** - Infecting species - Urinary tract vs non-urinary tract source - Healthcare vs non-healthcare associated - Appropriate vs inappropriate empirical antibiotic therapy - Immunocompromised vs non-immunocompromised - qSOFA score ≥ 2 vs < 2 - Total duration of study drug (≥ 5 vs < 5 days) • **Secondary**: - Time to clinical resolution of infection (resolution of fever) - Clinical and microbiological success at day 5 (resolution of fever and leukocytosis) - Requirement of ICU admission - Length of hospital or ICU stay - Infection with organism resistant to interventions, or *Clostridium difficile* - Microbiologic failure with third-generation cephalosporin in subsequent sterile site - Colonization with multidrug resistant organisms - Requirement of escalation of antibiotic therapy	
Statistical Analysis	• No formal sample size calculated due to nature of pilot study (anticipated 100 subjects total) • Per-protocol populations defined • Subgroup analysis performed	

Results

Baseline characteristics

Baseline Characteristics	TZP (n = 38)	MEM (n = 34)
Age, mean ± SD	63 ± 15	67 ± 16
Female, no. (%)	11 (29)	11 (32)
Species, no. (%)		
Klebsiella aerogenes	3 (8)	2 (6)
Enterobacter cloacae	15 (39)	12 (35)
Citrobacter freundii	1 (3)	1 (3)
Morganella morganii	5 (13)	6 (18)
Serratia marcescens	11 (29)	12 (35)
Source, no. (%)		
Urinary Tract Infection	8 (21)	6 (18)
Line-related infection	9 (24)	8 (24)
Severity of illness, no. (%)		
Charlson Comorbidity Score, median (IQR)	2 (1-3)	3 (2-5)
Pitt Score, median (IQR)	0 (0-1)	0 (0-2)
Empirical antibiotic, no. (%)		
β-lactam/β-lactamase inhibitor	12 (32)	8 (24)
Carbapenem	8 (21)	4 (12)
Third-generation cephalosporin	6 (16)	3 (9)
Hours to first effective antibiotic, median (IQR)	**7.0 (1.0-18.0)**	**1.5 (1.0-12.0)**
Duration of study drug, days, mean ± SD	6.15 ± 6.65	5.79 ± 3.54

Outcomes

Primary Analysis	Primary Outcome no./total no. (%)		Risk Difference, % (2-sided 95% CI)	P - Value
	TZP	MEM		
Primary Analysis	11/38 (29)	7/34 (21)	8.4 (-11 to 28)	0.41
Per Protocol Analysis	8/32 (25)	6/32 (19)	6.2 (-14 to 26)	0.55
Subcomponents of Primary Outcome				
Death	0/38 (0)	2/34 (6)	5.9 (-13 to 2)	0.13
Clinical failure	8/38 (21)	4/34 (12)	9.3 (-8 to 26)	0.29
Microbiological failure	5/38 (13)	0/34 (0)	12.3 (2 to 24)	**0.03**
Microbiological relapse	0/38 (0)	3/34 (9)	8.8 (-18 to 1)	0.06

- No statistically significant differences in the subgroup analysis nor secondary analysis
- Escalation in 4/38 patients (11%) using TZP and 1/34 (3%) using MEM (risk difference 8%, CI -4% to 19%)

Conclusions and Evaluation

Author's Conclusions

TZP results in more microbiological failures but fewer microbiological relapses than MEM.

Critique

Strengths

- Randomized controlled trial
- Subgroup analysis
- Excluded isolates with ESBL or OXA lactamases
- Listed specific genes identified in the patients with microbiological failure or microbiological relapse
- Included *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*

Limitations

- Pilot study
- Did not utilize pharmacokinetic-enhancing dosing regimens
- Difference in time to source control
- Only 79% of index blood culture isolates were sent to the coordinating lab
- Included *Serratia marcescens* and *Morganella morganii*
- Some patients had microbiologic cure at enrollment
- Trial clinicians did not control initial empiric therapy

Takeaway Summary	This pilot study provided further framework on how to structure future randomized controlled trials to assess the safety and efficacy of TZP in bacteremias with AmpC. As there was no difference in mortality or clinical failure, TZP may be reasonable to use empirically depending on the clinical status of the patient and organism isolated.

Table 7. Other Observational Studies[27-30]

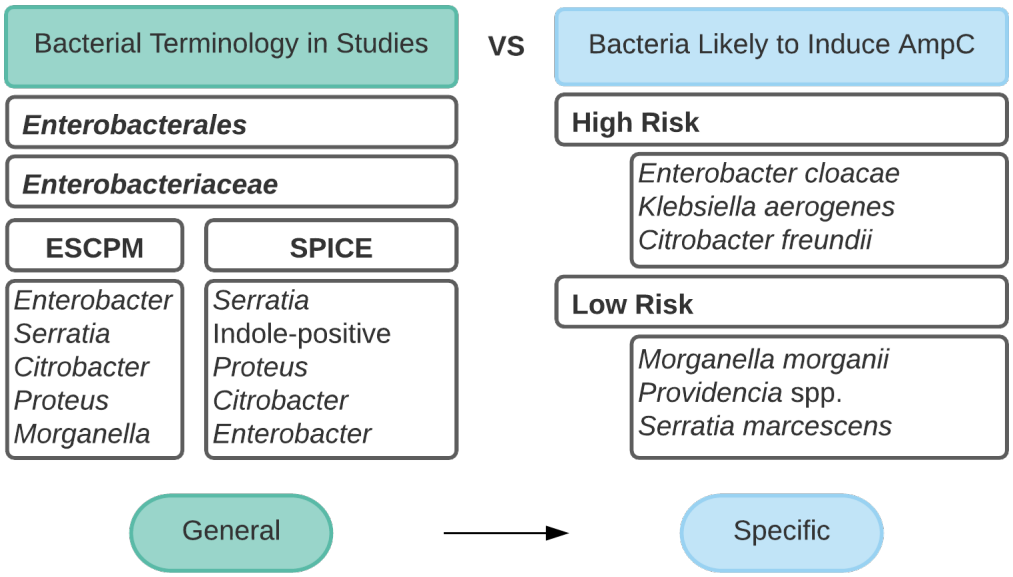
Study	Design	Population	Intervention	Results
Lee et al. (2015)	Retrospective cohort study	Patients with monomicrobial *Enterobacter cloacae* bacteremia	FEP vs CBM	- FEP susceptible dose dependent (SDD) should not be used in place of CBM for *E. cloacae* bacteremia - Higher likelihood of 30-day mortality in FEP arm associated with o Critical illness o Rapidly fatal underlying disease o ESBL production o FEP SDD MIC 4-8 mg/L
McKamey et al. (2018)	Retrospective cohort study	Patients hospitalized with bacteremia caused by *Enterobacter*, *Citrobacter*, or *Serratia* spp.	FEP or TZP	- *Enterobacter* spp. was the most common pathogen (78%) - 87.1% clinical cure rate overall - 98% of isolates were susceptible to FEP when MIC was ≤ 2 mg/L with 92.6% microbiological eradication - 79% of isolates were susceptible to TZP with 95.8% microbiological eradication - Only 20% of isolates had baseline resistance to third-generation cephalosporins (constitutive resistance)
Cheng MP et al. (2019)	Updated systematic review and meta-analysis	Patients with bacteremia caused by *Serratia, Providencia, Citrobacter, Enterobacter,* and *Morganella* spp.	BLBLI vs CBM	- 13 studies included in the analysis (five new studies, eight from previous meta-analysis) - Non-statistically significant difference in 30-day mortality (OR 1.13, 95% CI 0.58-2.20) - No studies favored BLBLIs over CBM; two studies favored the use of CBM over BLBLIs
Tan et al. (2020)	Retrospective cohort study	Patients with ESCPM bacteremia	CBM vs TZP or FEP monotherapy (empiric and definitive)	- Common infectious sources included urinary (22.8%) and vascular lines (22.0%) - Risk factors for 30-day mortality: higher Pitt bacteremia score and higher age - Neither empiric TZP nor definitive FEP therapy were associated with greater 30-day mortality compared to CBM
Overall Takeaway	FEP can be a definitive therapy option for AmpC bacteremias if the MIC ≤ 2 and source control is achieved. TZP may be used definitively in specific situations such as response to treatment and reduction of signs of infection but should have a lower threshold to escalate to a CBM. Overall, neither TZP nor FEP are associated with an increase in 30-day mortality compared to CBM.			

Summary and Conclusions

- Guideline recommendations

Cefepime	Carbapenem	Piperacillin-Tazobactam
•Suggested for treatment of organisms with moderate to high risk of significant AmpC production when MIC ≤ 2 mcg/mL	•Recommended when cefepime MIC ≥ 4 mcg/mL	•Not suggested for treatment of organisms with moderate to high risk of significant AmpC production

- My Recommendations
  - The use of empiric TZP or empiric FEP should be guided by likelihood of the causative organism producing AmpC and disease severity
  - FEP is a reasonable option for high risk AmpC bacteria if MIC ≤ 2 mcg/mL
  - TZP should have a low threshold to escalate to a CBM
    - TZP may be continued as definitive treatment for bacteremia if clinical signs are improving over 72 hours
    - TZP should be escalated to CBM if a) clinical signs are not improving or remain tenuous or b) cultures come back with bacteria that have high risk to induce AmpC
  - Mortality is not substantially increased with the use of empiric treatment with TZP or FEP
- Overall limitations of current studies
  - No consistency in study design
  - Lack of consensus on classification of AmpC producing bacteria
  - Results diluted by infection sources, geographical resistance patterns, and therapeutic regimens utilized



- Recommendation for future studies
  - Head-to-head trial of FEP versus MEM
  - Restrict included isolates to those that are a) high risk AmpC, or b) confirmed AmpC with molecular typing
  - Document and use pharmacokinetic-enhancing dosing regimens (i.e., extended interval infusions)
  - Continue the use of propensity-score matching to compare subjects with similar severity of illness

Treatment Algorithm

*Based on clinical presentation, assessment tools, and clinical judgement
**Pending sensitivities
***Blood Culture Identification

Appendices

Pharmacokinetics and dosing of select antibiotics[31-33]

Kinetics	Antibiotic	Traditional Dosing	Extended Interval Infusion Dosing	Renal Dose Adjustments?
Time above MIC	**Piperacillin-Tazobactam**	3.375–4.5 g over 30 minutes every 6 hours	3.375–4.5 g over 4 hours every 8 hours	Yes
	Cefepime	1–2 g over 30 minutes every 8 – 12 hours	1–2 g over 3–4 hours every 8 hours	
	Meropenem	1-2 g over 30 minutes every 6 hours	1-2 g over 3 hours every 8 hours	
Clinical Pearl	Pharmacokinetics of beta-lactams is optimized through extended interval infusion, which prolongs the time above MIC			

Pitt Bacteremia Score[34]

Points	Variable
2 **1** **0**	Fever (oral temperature) - ≤35 °C or ≥40° C - 35.1-36 °C or 39.0-39.9 °C - 36.1-38.9 °C
2	Hypotension - Acute hypotensive even with systolic drop of >30 mmHg or diastolic drop of >20 mmHg, or - Vasopressors required, or - Systolic blood pressure < 90 mmHg
2	Mechanical ventilation
4	Cardiac arrest
0 **1** **2** **4**	Mental status - Alert - Disoriented - Stuporous - Comatose

Charlson Comorbidity Index[35]

Points	Variable	Points	Variable
0 **1** **2** **3** **4**	Age <50 50-59 60-69 70-79 ≥80	**2**	Diabetes with End-Organ Damage
1	Myocardial Infarction or Congestive Heart Failure		Hemiplegia
	Peripheral Vascular Disease		Moderate to Severe CKD
	CVA or TIA or Dementia		Localized Solid Tumor
	COPD		Leukemia
	Connective Tissue Disease		Lymphoma
	Peptic Ulcer Disease	**3**	Moderate to Severe Liver Disease
	Mild Liver Disease	**6**	Metastatic Solid Tumor
	Uncomplicated Diabetes		AIDS

References

1. Resistance mechanisms – antibiotic resistance. ReAct. https://www.reactgroup.org/toolbox/understand/antibiotic-resistance/resistance-mechanisms-in-bacteria/. Published December 9, 2021.
2. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol*. 2015;13(1):42-51. doi:10.1038/nrmicro3380
3. Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. *Microbiol Spectr.* 2016;4(2):10.1128/microbiolspec.VMBF-0016-2015. doi:10.1128/microbiolspec.VMBF-0016-2015
4. Beta-Lactam. Illustrated glossary of organic chemistry - beta-lactam. https://www.chem.ucla.edu/~harding/IGOC/B/beta_lactam.html. Accessed December 23, 2021.
5. Holmes CL, Anderson MT, Mobley HLT, Bachman MA. Pathogenesis of Gram-Negative Bacteremia. *Clin Microbiol Rev.* 2021;34(2):e00234-20. Published 2021 Mar 10. doi:10.1128/CMR.00234-20
6. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ; Antibacterial Resistance Leadership Group. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. *Clin Infect Dis*. 2019;69(8):1446-1455. doi:10.1093/cid/ciz173
7. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Infectious Diseases Society of America 2021; Version 2.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance-2.0/.
8. Adeolu M, Alnajar S, Naushad S, S Gupta R. Genome-based phylogeny and taxonomy of the 'Enterobacteriales': proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov. *Int J Syst Evol Microbiol*. 2016;66(12):5575-5599. doi:10.1099/ijsem.0.001485
9. Carbapenem-resistant Enterobacterales (CRE). Healthcare-Associated Infections (HAIs). https://www.cdc.gov/hai/organisms/cre/index.html. Published November 5, 2019.
10. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med.* 1991;115(8):585-590. doi:10.7326/0003-4819-115-8-585
11. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. *Antimicrob Agents Chemother*. 2011;55(11):4943-4960. doi:10.1128/AAC.00296-11
12. Jacoby GA. AmpC beta-lactamases. *Clin Microbiol Rev*. 2009;22(1):161-182. doi:10.1128/CMR.00036-08
13. 2019 antibiotic resistance threats report. Centers for Disease Control and Prevention. https://www.cdc.gov/drugresistance/biggest-threats.html. Published November 23, 2021. Accessed December 23, 2021.
14. Ahmed YA, Banerjee S, Balkhy HHA, Balachandran A. Global Antimicrobial Resistance and Use Serveillance System (GLASS) Report: Early Implementation 2020. World Health Organization. https
15. Antibiotic resistance. Centers for Disease Control and Prevention. https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance. Accessed January 6, 2022.
16. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol*. 2013;34(1):1-14. doi:10.1086/668770
17. Smith DA, Nehring SM. Bacteremia. [Updated 2021 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441979/
18. Christaki E, Giamarellos-Bourboulis EJ. The complex pathogenesis of bacteremia: from antimicrobial clearance mechanisms to the genetic background of the host. *Virulence*. 2014;5(1):57-65. doi:10.4161/viru.26514
19. Tan C, Shojaei E, Wiener J, Shah M, Koivu S, Silverman M. Risk of New Bloodstream Infections and Mortality Among People Who Inject Drugs With Infective Endocarditis. *JAMA Netw Open*. 2020;3(8):e2012974. doi:10.1001/jamanetworkopen.2020.12974
20. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. *Infectious Diseases Society of America 2020*; Version 1.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/.

21. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America [published correction appears in Clin Infect Dis. 2010 Apr 1;50(7):1079. Dosage error in article text] [published correction appears in Clin Infect Dis. 2010 Feb 1;50(3):457]. *Clin Infect Dis*. 2009;49(1):1-45. doi:10.1086/599376
22. Comstedt P, Storgaard M, Lassen AT. The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study. *Scand J Trauma Resusc Emerg Med*. 2009;17:67. Published 2009 Dec 27. doi:10.1186/1757-7241-17-67
23. Cheng L, Nelson BC, Mehta M, et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC β-Lactamase-Producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2017;61(6):e00276-17. Published 2017 May 24. doi:10.1128/AAC.00276-17
24. Herrmann L, Kimmig A, Rödel J, et al. Early Treatment Outcomes for Bloodstream Infections Caused by Potential AmpC β-Lactamase-Producing Enterobacterales with Focus on Piperacillin/Tazobactam: A Retrospective Cohort Study. *Antibiotics (Basel)*. 2021;10(6):665. Published 2021 Jun 2. doi:10.3390/antibiotics1006066
25. Harris PNA, Wei JY, Shen AW, et al. Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by Enterobacter, Citrobacter or Serratia species: a systematic review with meta-analysis. *J Antimicrob Chemother*. 2016;71(2):296-306. doi:10.1093/jac/dkv346
26. Stewart AG, Paterson DL, Young B, et al. 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). *Open Forum Infect Dis*. 2021;8(8):ofab387. Published 2021 Aug 2. doi:10.1093/ofid/ofab387
27. Tan SH, Ng TM, Chew KL, et al. Outcomes of treating AmpC-producing Enterobacterales bacteraemia with carbapenems vs. non-carbapenems. *Int J Antimicrob Agents*. 2020;55(2):105860. doi:10.1016/j.ijantimicag.2019.105860
28. McKamey L, Venugopalan V, Cherabuddi K, et al. Assessing antimicrobial stewardship initiatives: Clinical evaluation of cefepime or piperacillin/tazobactam in patients with bloodstream infections secondary to AmpC-producing organisms. *Int J Antimicrob Agents*. 2018;52(5):719-723. doi:10.1016/j.ijantimicag.2018.08.007
29. Cheng MP, Lee RS, Cheng AP, et al. β-Lactam/ β-Lactamase Inhibitor Therapy for Potential AmpC-Producing Organisms: A Systematic Review and Meta-Analysis. *Open Forum Infect Dis*. 2019;6(7):ofz248. doi:10.1093/ofid/ofz248
30. Lee NY, Lee CC, Li CW, et al. Cefepime Therapy for Monomicrobial Enterobacter cloacae Bacteremia: Unfavorable Outcomes in Patients Infected by Cefepime-Susceptible Dose-Dependent Isolates. *Antimicrob Agents Chemother*. 2015;59(12):7558-7563. doi:10.1128/AAC.01477-15
31. Cefepime (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc. Updated 1/20/22. https://online-lexi-com.uiwtx.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/6553?cesid=6XAUnqI2XcI&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dcefepime%26t%3Dname%26va%3Dcefepime
32. Piperacillin and Tazobactam (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc. Updated 1/20/22. https://online-lexi-com.uiwtx.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7499?cesid=9SxudtiJ9RL&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dpiperacillin%252520tazobactam%26t%3Dname%26va%3Dpiperacillin%252520tazobactam
33. Meropenem (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc. Updated 1/21/22. https://online-lexi-com.uiwtx.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7253?cesid=7MDRTnX2W3a&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmeropenem%26t%3Dname%26va%3Dmeropenem
34. Paterson DL. International prospective study of Klebsiella pneumoniae bacteremia: Implications of extended-spectrum β-lactamase production in nosocomial infections. *Annals of Internal Medicine*. 2004;140(1):26. doi:10.7326/0003-4819-140-1-200401060-00008
35. Charlson M. Charlson Comorbidity index (CCI). MDCalc. https://www.mdcalc.com/charlson-comorbidity-index-cci.