Clinical Outcomes Associated with Oral β-lactams versus Fluoroquinolones/TMP-SMX Therapy for Gram-Negative Bacteremia

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BACKGROUND

- Agents commonly used as oral step-down therapy in *Enterobacterales* bacteremia include fluoroquinolones and TMP-SMX
- The use of these oral step-down agents have been associated with safety concerns and increased resistance rates
- Oral β-lactams are usually not recommended to treat *Enterobacterales* bacteremia because of concerns for sub therapeutic serum concentrations
- Given the limited data on clinical effectiveness and increased limitations with fluoroquinolones or TMP-SMX, oral β-lactams may be a valuable alternative option

OBJECTIVE

To evaluate the clinical effectiveness in patients transitioned to oral beta-lactams versus oral fluoroquinolone or TMP-SMX for the step-down treatment of uncomplicated gram-negative bacteremia

METHODS

A multi-center retrospective observational cohort study was conducted from July 1, 2017 to December 31, 2020 at 11 Memorial Hermann Health System Hospitals

Inclusion Criteria	Exclusion Criteria

• Adult patients ≥ 18 years of age
• Positive blood cultures for one of the following organisms:
  • *Escherichia coli*
  • *Klebsiella spp.*
  • *Proteus spp.*
  • *Citrobacter spp.*
  • *Serratia marcescens*
  • *Enterobacter spp.*
• Received in vitro active parenteral empirical antibiotics for ≥ 1 day
• Therapy was transitioned to an active single oral agent:
  • Beta-lactam
  • FQN
  • TMP-SMX
	• Polymicrobial bacteremia
	• Complicated infection defined as the following:
	  • Infectious endocarditis
	  • Prosthetic joint involvement
	  • CNS involvement
	  • Osteomyelitis
	  • No source control requiring >6 weeks of therapy
	• Diagnosis of a urological abscess or chronic prostatitis in the 90 days before blood culture collection
	• Gram-negative bacteremia in the past 365 days before blood collection
	• MDR organisms (ESBL and CRE)
	• Patients who did not survive for at least 72 hours after first positive blood culture
	• Enrolled in hospice care at admission

Primary Outcome

Incidence of clinical failure within 30 days of starting oral antibiotic therapy defined as at least 1 of the following:
- Recurrent BSI due to the original organism
- Transition to IV antibiotics after initiating PO therapy
- New-onset sepsis after initiation of PO therapy
- 30-day hospital readmission due to infectious process
- 30-day all cause mortality

Secondary Outcomes

- 30-day hospital readmission due to infectious process
- 30-day all cause mortality
- Length of hospital stay
- Length of ICU stay
- PO antibiotic duration
- *C. difficile* infection within 30 days of discharge date

RESULTS

Figure 1. Patient Population

790 patients assessed for eligibility

Patients were excluded for the following reasons
- Polymicrobial bacteremia
- Previous bacteremia in previous 365 days
- Not transitioned to PO antibiotics
- ESBL bacteremia
- Admitted for observation ≤1 day
- Source control not achieved
- Enrolled in hospice at admission

690 patients included in the Propensity Score Matching 1:1
- β-lactams, n=199
- FQN & TMP-SMX, n=199

Figure 2. PO Step-Down Therapy

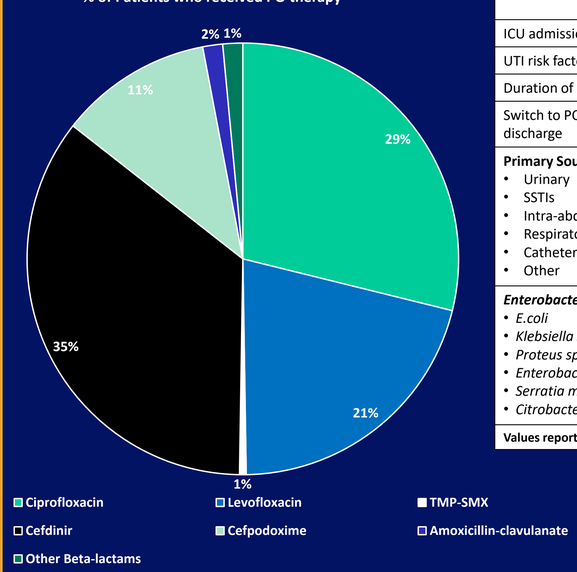
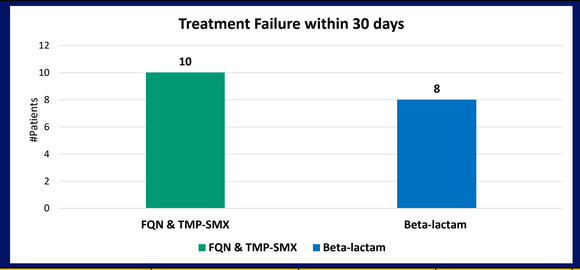


Table 1. Baseline Characteristics

	PO β-lactam (n=199)	PO FQN & TMP-SMX (n=199)	*P*-value
Age, median [IQR]	71 [58-79]	70 [60-78]	0.616
Gender, female,	122 (61)	122 (61)	1.00
BMI≥30 kg/m²	101 (51)	109 (55)	0.422
Race			
• White	97 (49)	77 (39)	--
• African American	26 (13)	33 (17)	--
• Unknown or other	106 (53)	86 (43)	--
Beta-lactam allergy, n (%)	36 (18)	30 (15)	0.419
Comorbidities			
• DM	80 (40)	82 (41)	0.838
• HTN	137 (69)	140 (70)	0.744
• CKD stage I-IV	25 (13)	25 (13)	1.00
• ESRD on HD	4 (2)	2 (1)	0.411
• CHF (EF<45%)	12 (6)	13 (7)	0.836
• Structural lung disease	5 (3)	5 (3)	1.00
• End-stage liver disease	6 (3)	5 (3)	0.760
Immunosuppression			
• AIDs (CD4 count<200)	2 (1)	2 (1)	1.00
• History of SOT	4 (2)	1 (0.5)	0.177
• Chemotherapy (<6 months)	10 (5)	12 (6)	0.661
• ANC<500	4 (2)	6 (3)	0.522
• Immunomodulatory/ steroids	18 (9)	17 (9)	0.860
Charlson comorbidity index, median [IQR]	4 [2-4]	4 [2-4]	0.925
PITT bacteremia score, median [IQR]	3 [1-3]	3 [1-3]	0.605
ICU admission on day 1	45 (23)	42 (21)	0.716
UTI risk factors	45 (23)	42 (21)	1.00
Duration of IV antibiotics	5 [4-6]	4 [4-6]	0.367
Switch to PO therapy prior to discharge	68 (34)	66 (33)	0.978
Primary Source			
• Urinary	149 (75)	141 (71)	
• SSTIs	1 (0.5)	4 (2)	
• Intra-abdominal	36 (18)	40 (20)	
• Respiratory	6 (3)	7 (4)	
• Catheter-related	1 (0.5)	2 (1)	
• Other	6 (3)	5 (3)	
Enterobacterales			
• *E.coli*	167 (84)	167 (84)	
• *Klebsiella spp.*	24 (13)	21 (11)	
• *Proteus spp.*	6 (3)	3 (2)	
• *Enterobacter spp.*	0	3 (0.5)	
• *Serratia marcescens*	0	4 (1.5)	
• *Citrobacter spp.*	1 (0.5)	1 (0.5)	

Values reported as N (%)

RESULTS



Outcome	PO FQN & TMP-SMX (n=199)	PO β-Lactams (n=199)	OR (95% CI)	*P*-value
Composite Primary Outcome				
Treatment failure within 30 days of starting PO antibiotics defined as at least one of following:	10 (5)	8 (4)	0.79 (0.306 – 2.04)	0.629
Recurrent BSI due to the original organism	1 (0.5)	2 (1)	2.01 (0.181-22.348)	1.00
Transition to IV antibiotics	0 (0)	0 (0)	--	--
New-onset sepsis	0 (0)	1 (0.3)	1.01 (0.995-1.01)	1.00
30-day hospital readmission due to infectious process	8 (4)	5 (3)	0.615 (0.198-1.915)	0.398
30-day all-cause mortality	2 (1)	0 (0)	0.99 (0.976-1.01)	0.249

Secondary Outcomes	PO FQN & TMP-SMX (n=199)	PO β-Lactams (n=199)	*P*-value
Length of hospital stay, median, days [IQR]	5 [4-6]	5 [4-7]	0.911
Total PO antibiotic duration, median, days [IQR]	10 [9-14]	11 [9-14]	0.377
C. *difficile* infection within 30 days of discharge date	0 (0)	0 (0)	--
Length of ICU stay, median, days [IQR]	3 [2-4]	3 [1-3]	0.064

CONCLUSIONS

- Based on the results of this study, no significant difference in treatment failure was seen in patients who were transitioned to β-lactams vs fluoroquinolones or TMP-SMX as PO step-down therapy for uncomplicated *Enterobacterales* bacteremia
- Oral β-lactams appear to be a safe and effective PO step-down option in uncomplicated *Enterobacterales* bacteremia infections compared to oral fluoroquinolones & TMP-SMX

REFERENCES

1. Tamma PD, Conley AT, Cosgrove SE, et al; Antibacterial Resistance Leadership Group. Association of 30-day mortality with oral step-down vs continued intravenous therapy in patients hospitalized with Enterobacteriaceae bacteremia. *JAMA Intern Med*. 2019;179(3):316-323.
2. Sutton JD, Stevens VW, Chang NN, Khader K, Timbrook TT, Spivak ES. Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source. *JAMA Netw Open*. 2020;3(10):e2020166. Published 2020 Oct 1.
3. Nisly SA, McClain DL, Fillius AG, Davis KA. Oral antibiotics for the treatment of Gram-negative bloodstream infections: A retrospective comparison of three antibiotic classes. *J Glob Antimicrob Resist*. 2020;20:74-77.

DISCLOSURES

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.