Re-purposing Beta-lactam Antibiotics as Fluoroquinolone Sparing Stepdown Therapy for Enterobacteriales Bloodsteam Infections

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Background

- Oral antimicrobial therapy as stepdown therapy (SDT) for Enterobacteriales bloodstream infection (EB-BSI) is advantageous to reduce the risk of central line complications, cost of care and length of stay.[1]
- Given their high bioavailability, fluoroquinolones (FQ) are commonly used in the treatment of EB-BSI. However, due to increasing warnings around FQ use including *Clostridiodes difficile* infection (CDI) and increasing resistance alternative oral options are warranted.[2,3,4]
- There is limited evidence suggesting that de-escalating to oral beta-lactams (OBLM) may be an option for EB-BSI treatment.[5]
- At our large academic medical center, to avoid the overuse and the risks of FQs OBLM as SDT for EB-BSI is a common practice.

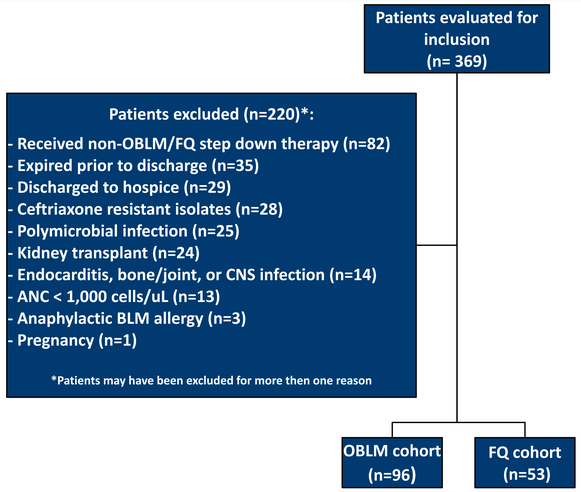
Objectives

- The purpose of this study is to evaluate the efficacy and safety of SDT with OBLM for EB-BSI.

Methods

- Retrospective chart review conducted at Yale New Haven Hospital (YNHH).
- **Inclusion criteria**: All patients over the age of 18 admitted to the hospital and prescribed antibiotic therapy for EB-BSI from November 2016 to August 2019.
- Enterobacteriales organisms included: *E. coli, Klebsiella pneumoniae, Klebsiella oxytoca or Proteus mirabilis.*
- **Exclusion criteria**: Age<18, pregnancy, ANC<1000 cells/uL, ceftriaxone resistant isolates, non OBLM/FQ SDT, complicated infection (i.e., endocarditis, bone/joint/device, source control unobtainable, CNS), discharge to hospice, expired before discharge or completion of therapy, kidney transplant patients, anaphylactic beta-lactam allergy, polymicrobial bacteremia.
- **Primary outcome**: clinical cure defined as completion of therapy without signs of persistent infection (increase in WBC > 2000 cells/mL if WBC was ≥ 12,000 cells/mL, fever (>38°C), or change in antibiotic due to failure).
- **Secondary outcomes**: 30-day readmission rates, reinfection rate defined as positive blood culture within 30 days of completion of therapy, antibiotic associated adverse events defined as side effects leading to discontinuation, and CDI within 90 days from start of treatment.
- All end points were statistically analyzed for significance by utilizing a student pair t-test assuming unequal variances with an alpha value of 0.05 considered to be significant.
- Categorical data was analyzed using the chi-squared test.

Results



Baseline Demographics	OBLM (n=96)	FQ (n=53)	P-value
Age, median (IQR)	78 (70-84)	72 (65-80)	0.008
Female Sex, n (%)	47 (49)	19 (36)	0.121
BMI ≥30-40 Kg/m², n (%)	30 (31)	13 (25)	0.5
BMI ≥40 Kg/m², n (%)	10 (10)	6 (11)	0.715
Chronic kidney disease (Stage III or greater), n (%)	15 (16)	12 (23)	0.359
Dialysis, n (%)	1 (1)	2 (4)	0.339
Heart failure, n (%)	17 (18)	7 (13)	0.463
Cirrhosis, n (%)	3 (3)	2 (4)	0.839
Diabetes, n (%)	42 (44)	18 (34)	0.762
Neurogenic bladder, n (%)	7 (7)	4 (8)	0.955
History of malignancy, n (%)	30 (31)	21 (40)	0.207
Immunosuppression*, n (%)	9 (9)	13 (25)	0.045
Chronic indwelling Foley catheter, n (%)	14 (15)	4 (8)	0.099
Charlson comorbidity index, median (IQR)	3 (2-4)	3 (2-4)	0.11
PITT bacteremia score, median (IQR)	2 (1-3)	1 (1-2)	0.037

*Cancer treatment within 1 year, the use of an immunosuppressive drug (TNF-alpha agents, prednisone ≥ 20 mg or equivalent, mycophenolate, sirolimus, rituximab, vedolizumab, abatacept, eculizumab), bone marrow transplant recipient, human immunodeficiency virus, acquired immunodeficiency syndrome, leukemia, lymphoma, solid organ transplant recipient, lupus erythematosus & vasculitis

Clinical Characteristics	OBLM (n=96)	FQ (n=53)	P-value
Source of infection			
• Urinary Tract	69 (72)	37 (70)	0.793
• Biliary	17 (18)	9 (17)	0.911
• Gastrointestinal	5 (5)	1 (2)	0.263
• Pneumonia	2 (2)	2 (4)	0.577
• Other	2 (2)	1 (2)	0.935
• Central line associated bloodstream infection (CLABSI)	1 (1)	3 (6)	0.175
Empiric Antimicrobial Therapy≠, n (%)			
• Piperacillin/tazobactam or ceftazidime	73 (76)	46 (87)	0.1
• Ceftriaxone	23 (24)	13 (25)	0.95
• Fluoroquinolone	8 (8)	1 (2)	0.1
Step Down Therapy, n (%)			
• Cefuroxime	60 (63)	0	N/A
• Amoxicillin/clavulanic acid	18 (19)	0	
• Cephalexin/cefadroxil	11 (11)	0	
• Amoxicillin	6 (6)	0	
• Cefpodoxime	1 (1)	0	
• Ciprofloxacin	0	52 (98)	
• Levofloxacin	0	1 (2)	
Days from empiric to oral therapy, median (IQR)	3 (2-5.25)	3 (2-5)	0.469
Total days of antibiotic therapy, median (IQR)	13 (9-15)	14 (12-15)	0.034

≠ Empiric therapy may have included multiple agents

Results	OBLM (n=96)	FQ (n=53)	P-value
Clinical cure, n (%)	95 (99)	52 (98)	0.7
30-day readmission, n (%)	17 (18)	12 (23)	0.483
30-day readmission due to infection, n (%)	5 (5)	5 (9)	0.366
Antibiotic associated adverse events, n (%)	0 (0)	2 (4)	0.16
• Diarrhea	0 (0)	1	
• Nausea/vomiting	0 (0)	1	
• Cardiotoxicity	0 (0)	0	
• Nephrotoxicity	0 (0)	0	
• Hepatotoxicity	0 (0)	0	
CDI within 90 days from start of treatment	1 (1)	2 (4)	0.34

Discussion

- There was no statistically significant difference in clinical cure, the primary endpoint, in patients who used OBLM SDT compared to those that used FQ SDT.
- OBLM patients had a higher median age, higher median PITT bacteremia score, were less likely to be immunosuppressed, and had shorter median duration of therapy.
- There was also no statistically significant differences noted in any secondary endpoints however the number of adverse events and CDI were higher in the FQ group.
- Limitations for the study include retrospective review and small sample size.

Conclusions

- Results of this study suggest that OBLM may be non-inferior to FQs in SDT of EB-BSI.
- The use of OBLM may enhance stewardship efforts as a FQ sparing option for the treatment of EB-BSI.
- Prospective studies in this area are warranted.

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