Oral ß-Lactams vs. Oral Fluoroquinolones as Step-Down for Uncomplicated Enterobacterales Blood-Stream Infections

Nichol Ngo, PharmD Candidate[1]*; Lionel Sielatchom-Noubissie, PharmD Candidate[1]*; Kyle C. Molina, PharmD[1,2]; Tanner Johnson, PharmD[1,2]; Tyree Kiser, PharmD[1]; Leila Hojat, MD[3]; Misha Huang, MD, MS[3]; Matthew Miller, PharmD[1.2]

1 University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA. 2. UCHealth University of Colorado Hospital, Aurora, CO, USA
3.University of Colorado Anschutz Medical Campus – Division of Infectious Diseases, Aurora, CO, USA.
*Authors contributed equally to the submitted work.

Background

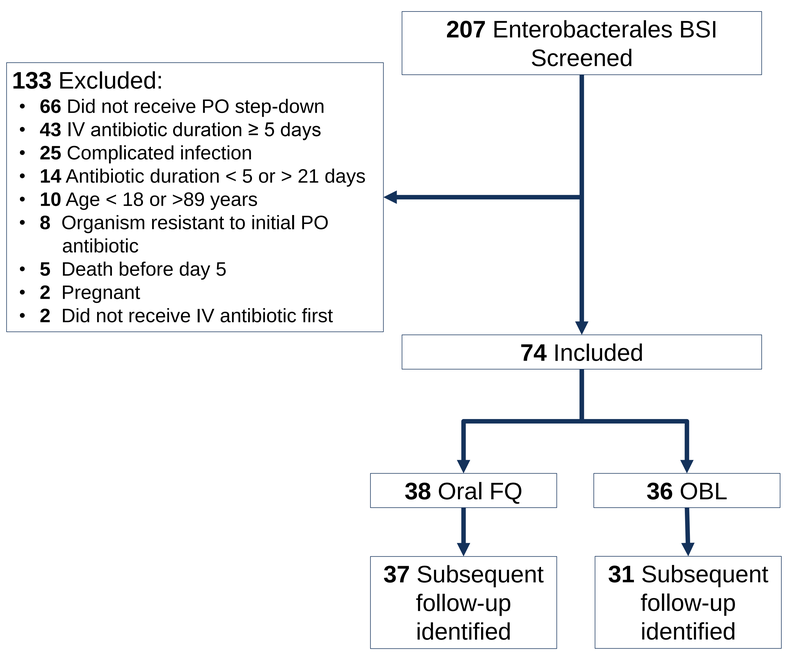
- Bloodstream infections (BSI) are a frequent complication of commonly encountered infections (e.g. pyelonephritis) among hospitalized adults
- Enterobacterales (formerly Enterobacteriaceae) group account for most BSI causes
- Recent studies have demonstrated similar outcomes among patients transitioned to oral antibiotics compared to those managed solely with parenteral routes[1,2]
- Most evidence supports PO step-down with highly bioavailable agents such as fluoroquinolones (FQ); however, limited comparative evidence exists utilizing oral β-lactams (OBL) in this setting.
- Due to mounting concerns over FQ safety and resistance, we sought to compare outcomes of FQ vs. OBL for Enterobacterales BSI step-down.

Methods

- Single-center, retrospective cohort of adults seen at University of Colorado Hospital from 2015-2017 with uncomplicated Enterobacterales BSI
- Inclusion criteria: age 18-89 years old, step-down to oral FQ or OBL for completion of therapy, received at least one IV antibiotic dose
- Exclusion criteria:
  - Pregnant or incarcerated
  - Causative organism identified as *Salmonella spp., Enterobacter spp., Citrobacter freundii, Serratia spp.* and/or *Klebsiella aerogenes*
  - IV antibiotic duration ≥ 5 days, or Total antibiotic duration < 5 days or > 21 days.
  - Death before day 5
  - Complicated infections: deep-seated (e.g. endocarditis, osteomyelitis), lack of source control, intravascular or metastatic foci, polymicrobial BSI not including contaminants, persistent bacteremia, infection associated with implanted prosthesis
- Primary outcome: clinical failure defined as the composite of any of the following occurring within 30-days of antibiotic completion: death, recurrence or relapse of infection
- Secondary outcomes: all-cause hospital re-admission or ED visit within 30-days, adverse drug events, and *C. difficile* infection within 30-days after discharge

Results

Figure 1. Patient Disposition



Results

Table 1. Baseline Characteristics

Characteristic	FQ, n=38	OBL, n=36	P-value
Age, mean years (SD)	56 (17)	59 (19)	0.40
Sex, male n (%)	11 (29)	17 (47)	0.15
Obesity (BMI ≥ 30 kg/m^2), n (%)	16 (42)	14 (39)	0.82
BMI ≥ 40 kg/m^2	2 (5)	3 (8)	0.67
Penicillin Allergy History, n (%)	14 (37)	5 (14)	0.03
Comorbidities, n (%)			
Diabetes	13 (34)	14 (39)	0.81
Severe CKD (GFR < 30 mL/min)	4 (11)	6 (17)	0.51
Malignancy	7 (18)	11 (31)	0.28
Hematologic	1 (3)	3 (8)	0.35
Solid-tumor	6 (16)	9 (25)	0.39
Heart Failure	2 (5)	4 (22)	0.42
HIV positive	0 (0)	0 (0)	0.99
Cirrhosis	3 (8)	1 (3)	0.62
Transplant History, n (%)	8 (21)	4 (11)	0.35
Solid Organ Transplantation	8 (21)	3 (8)	0.19
Hematopoietic Cell Transplant	0 (0)	1 (3)	0.49
Immunosuppressive Medication, n (%)	4 (11)	8 (22)	0.22

Table 2. Infection Characteristics

Characteristic	FQ, n=38	OBL, n=36	P-value
Pitt Bacteremia Score, median (IQR)	3 (1,3)	2 (1,3)	0.25
Initial Treatment Location, n (%)			
Emergency Department	20 (53)	21 (58)	0.65
Inpatient	18 (47)	15 (42)	0.65
ICU Admission, n (%)	9 (24)	4 (11)	0.22
ICU Length of Stay, median (IQR)	2 (1,2)	1 (1,3)	0.45
Hospital Length of Stay (IQR)	3 (3,5)	3 (2,5)	0.52
***Enterobacterales* spp. Identified, n (%)**			
Escherichia coli	23 (61)	25 (69)	0.47
Klebsiella pneumoniae	12 (32)	7 (19)	0.29
Klebsiella oxytoca	0 (0)	1 (3)	0.49
Proteus mirabilis	1 (3)	2 (6)	0.61
Proteus vulgaris	1 (3)	1 (3)	0.99
Raoultella ornithinolytica	2 (5)	1 (3)	0.61
Repeat Blood Cultures Performed, n (%)	33 (87)	25 (70)	0.09
Repeat Cultures Negative	32 (97)	24 (96)	0.99
Ceftriaxone Resistant, n (%)	3 (8)	0 (0)	0.24
Site of Infection, n (%)			
Urinary Tract	30 (79)	22 (61)	0.13
Complicated UTI	27 (90)	18 (82)	0.44
Catheter/Stent/Nephrostomy Present	9 (33)	6 (33)	0.99
Device Removed or Exchanged	6 (67)	5 (83)	0.60
Intra-Abdominal	4 (11)	8 (22)	0.22
Cholangitis	3 (75)	8 (100)	0.33
Source control performed	3 (75)	8 (100)	0.33
Line-Related	1 (3)	2 (6)	0.61
Line removed or exchanged	1 (100)	2 (100)	0.99
Pneumonia	1 (3)	0 (0)	0.99
Unclear	2 (5)	4 (11)	0.42

Table 3. Treatment Characteristics

Characteristic	FQ, n=38	OBL, n=36	P-value
Empiric IV Antibiotic, n (%)			
Ceftriaxone	22 (58)	17 (47)	0.49
Cefepime	8 (21)	5 (14)	0.54
Piperacillin-tazobactam	2 (5)	5 (14)	0.26
Ertapenem	0 (0)	4 (11)	0.051
Levofloxacin or Ciprofloxacin	3 (8)	1 (3)	0.62
Other ß-Lactam	3 (8)	4 (11)	0.71
Initial antibiotic coverage adequate, n (%)	36 (95)	35 (97)	0.99
Definitive Oral Antibiotic, n (%)			
Levofloxacin	25 (66)	0 (0)	-
Ciprofloxacin	13 (34)	0 (0)	-
Amoxicillin-Clavulanate	0 (0)	11 (31)	-
Cefpodoxime	0 (0)	10 (28)	-
Cefuroxime	0 (0)	6 (17)	-
Cephalexin	0 (0)	4 (11)	-
Cefdinir	0 (0)	3 (8)	-
Amoxicillin	0 (0)	2 (6)	-
High-Dose Used, n (%)	23 (61)	20 (56)	0.81
Total Antibiotic Duration, median (IQR)	12 (10,15)	14 (10,15)	0.55
PO Antibiotic Duration, median (IQR)	10 (6,11)	10 (7,11)	0.89

Table 4. Treatment Outcomes

Characteristic	FQ, n=38	OBL, n=36	P-value
Clinical Failure within 30-days, n (%)	9 (24)	10 (28)	0.79
30-day All-Cause Mortality	0 (0)	0 (0)	0.99
Relapse of Signs or Symptoms After Oral Switch	4 (44)	2 (20)	0.35
Recurrent Infection with Same Organism	4 (44)	3 (30)	0.65
Recurrent Infection with Different Organism at Same Site	1 (12)	5 (50Sa)	0.14
Hospital Readmission or ED Visit within 30-days, n (%)	9 (24)	9 (25)	0.99
Safety, n (%)			
Adverse Drug Effect	3 (8)	2 (6)	0.99
C. difficile Infection	1 (3)	1 (3)	0.99

- In multivariable logistic regression analysis, presence of nephrostomy tubes was the only predictor of clinical failure at 30-days (OR 8.1; 95% CI, 1.1-61.2).

Conclusions and Limitations

- Overall, the groups were well matched. Clinical and safety outcomes did not differ between FQ vs. OBL as step-down from initial IV antibiotics
- Use of OBL as step-down following initial IV antibiotics was safe and effective in our cohort of uncomplicated *Enterobacterales* BSIs, and could be considered particularly considering resistance and safety implications with FQ use
- Median duration of antibiotics was 12-14 days, thus it is unclear if step-down to OBL when applying shorter durations of therapy provides similar outcomes to FQ's

References

1. Mercuro NJ, et al. *Int J Antimicrob Agents.* 2017; 51(5): 687-92.
2. Kutob LF, et al. *Int J Antimicrob Agents*. 2016; 48 (55): 498-503.

Conflict of Interest Disclosures: None