Treatment failure rates in patients receiving low versus high oral bioavailability antibiotics for gram-negative bacteremia

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Background

- Gram-negative bacteremia (GNB) has a high rate of morbidity and mortality[1]
- Many cases of GNB are caused by *Klebsiella sp., Proteus mirabilis,* or *Escherichia coli,* which are generally considered susceptible to a broad range of intravenous (IV) and oral antibiotics[2]
- Oral beta-lactams have low bioavailability (LBA) but may be an alternative to high bioavailability (HBA) agents[3]

Purpose

- Determine treatment failure rates in adults with GNB caused by *Klebsiella sp., P. mirabilis,* or *E. coli* who were treated with step-down oral antibiotics with either low or high bioavailability

Methods

- Retrospective, single-center, non-inferiority, cohort study

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Received <7 total days of antibiotic therapy
GNB, defined as ≥1 positive blood culture, caused by *Klebsiella sp., P. mirabilis,* or *E. coli*	Concurrent oral antibiotic therapy while on the study antibiotic (excluding azithromycin)
Adequate doses of a study antibiotic for ≥2 days	Polymicrobial infections
	Pregnancy or lactation
	Discharge to hospice
	Inadequate GNB source control

Study Groups	
LBA Antibiotics	**HBA Antibiotics**
• Amoxicillin-clavulanate • Cephalexin • Cefuroxime • Cefdinir • Cefpodoxime	• Ciprofloxacin • Levofloxacin • Sulfamethoxazole-trimethoprim (SMX-TMP)

Primary Outcome

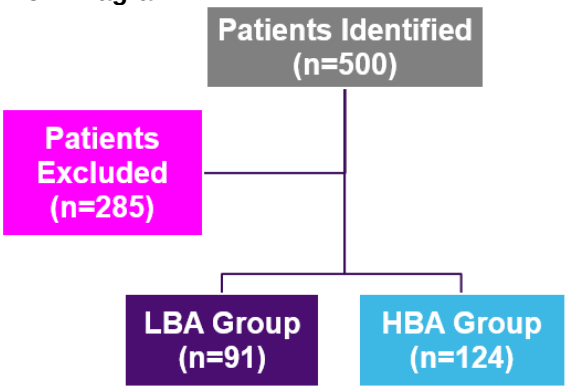
- Treatment failure, defined as hospital readmission due to the same infection source or bacteria or a change in antibiotic treatment within 30 days despite adequate dosing of a study antibiotic.

Secondary Outcomes

- 30-day all-cause mortality
- Length of therapy
- Length of hospital stay
- Treatment failure rates stratified by subject weight (obese versus non-obese) and infection source

Results

Flow Diagram

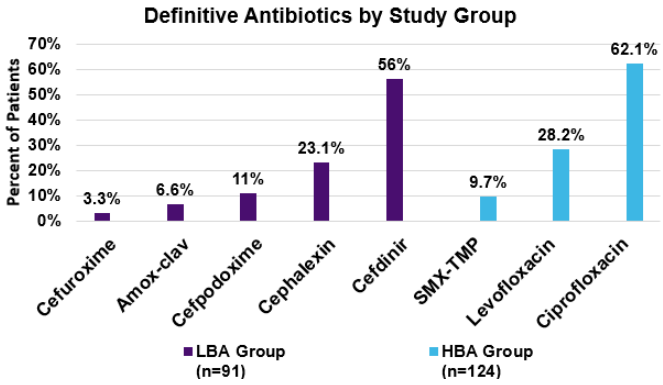


Baseline Characteristics

Characteristic	All Patients (n=215)	LBA Group (n=91)	HBA Group (n=124)	P Value
Age (years), mean ± SD	65.8 ± 16.7	67.2 ± 15.8	64.8 ± 17.3	0.377
Female, n (%)	142 (66.9)	63 (69.2)	79 (63.7)	0.515
Obesity, n (%)	77 (36.5)	34 (37.4)	43 (34.7)	0.68
Serum Creatinine (mg/dL), mean ± SD	1.2 ± 1.1	1.4 ± 1.3	1 ± 0.8	**0.011**
Creatinine Clearance (mL/min), mean ± SD	70.7 ± 35.7	65 ± 38.2	75.1 ± 33.8	**0.049**
PITT Bacteremia Score, mean ± SD	0.9 ± 1.3	0.9 ± 1.5	0.9 ± 1.2	0.749

Characteristic	All Patients (n=215)	LBA Group (n=91)	HBA Group (n=124)	P Value
Infection Source, n (%)				
Urinary tract	175 (81.4)	70 (76.9)	105 (84.7)	0.108
Intra-abdominal	20 (9.3)	8 (8.8)	12 (9.7)	
Other	20 (9.3)	13 (14.3)	7 (5.6)	
Bacteremia Pathogen, n (%)				
E. coli	207 (96.3)	86 (94.5)	122 (98.4)	0.06
P. mirabilis	8 (3.7)	5 (5.5)	2 (1.6)	
Klebsiella sp.	0 (0)	0 (0)	0 (0)	

Characteristic	All Patients (n=213)	LBA Group (n=91)	HBA Group (n=122)	P Value
Empiric Antibiotics, mean ± SD	2.5 ± 1.6	2.5 ± 1.7	2.5 ± 1.5	0.924
Empiric Antibiotic Distribution, n (%)				
Ceftriaxone	103 (48.4)			
Ciprofloxacin	34 (16)			
Piperacillin-tazobactam	25 (11.7)			
Cefepime	24 (11.3)			
Levofloxacin	12 (5.6)			
Other	15 (7)			



Outcomes

Result, n (%)	All Patients (n=215)	LBA Group (n=91)	HBA Group (n=124)	P Value (95% CI)
Total Treatment Failures	17 (8)	7 (7.7)	10 (8.1)	**<0.007** (-0.06 to 0.08)
Readmission for Infection Recurrence <30 days	3 (1.4)	3 (3.3)	0 (0)	**<0.016** (-0.08 to 0.02)
Change in Antibiotic Treatment <30 days	17 (7.9)	7 (7.7)	10 (8.1)	**<0.007** (-0.06 to 0.08)

Result	All Patients (n=215)	LBA Group (n=91)	HBA Group (n=124)	P Value
30-Day All-Cause Mortality, n (%)	3 (1.4)	1 (1.1)	2 (1.1)	0.734
Total Antibiotic Therapy Duration (days), mean ± SD	13.4 ± 6.4	13 ± 4.1	12.7 ± 7.7	0.404
Definitive Antibiotic Therapy Duration (days), mean ± SD	9.7 ± 5.7	9 ± 3.7	10.2 ± 6.7	0.1
Hospital Length of Stay (days), mean ± SD	5 ± 6	5.7 ± 8.1	4.7 ± 3.5	0.201
ICU Length of Stay (days), mean ± SD	2.5 ± 2.9	2.2 ± 1.8	2.8 ± 3.6	0.353

Discussion

- Treatment failure rates were lower than a previous comparative study[4] with similar oral antibiotics
- Similar rates of 30-day all-cause mortality, length of therapy, and hospital length of stay (LOS) between groups
- Outcomes similar between obese and non-obese patients
- Significant differences in total antibiotic therapy duration, definitive antibiotic therapy duration, and hospital LOS with GNB from *other* infection sources
- Increased lengths of hospital and intensive care unit stays with PITT bacteremia scores ≥4

Limitations

- Retrospective design; small sample size
- Definitions of concurrent antimicrobials and treatment failure led to non-clinically relevant exclusions
- Comorbidities not recorded

Conclusion

LBA oral antibiotics were non-inferior to HBA oral antibiotics in regards to treatment failure rates from GNB

References

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3. Sepsis Campaign: 2008. *Crit Care Med.* 2008;36(1):296-327.
4. Mercuro NJ, et al. *Int J Antimicrob Agents.* 2017.