Treatment Failure Rates in Patients Receiving Low versus High Oral Bioavailability Antibiotics for Gram-Negative Bacteremia

Ryan Gumbleton, PharmD
PGY1 Pharmacy Resident
Billings Clinic
Billings, Montana
April 21, 2018

Disclosure Statement

- IRB Status: Approved
- Co-Investigators:
  - Jennifer Ott, PharmD, BCPS
  - Camilla Reese, MD, FACP
  - Melanie Townsend, PharmD, BCPS
- Conflicts of Interest: None
- Project Sponsorship: None

2

Learning Objectives

- State treatment failure rates for patients receiving antibiotics with low versus high bioavailability for gram-negative bacteremia
- Compare 30-day all-cause mortality rates for individuals with gram-negative bacteremia treated with step-down oral antibiotics with low versus high oral bioavailability

3

Background

- Gram-negative bacteremia (GNB) has a high rate of morbidity and mortality
- Many cases of gram-negative bacteremia are caused by *Klebsiella sp., Proteus mirabilis,* or *Escherichia coli*
- These bacteria are generally considered susceptible to a broad range of intravenous (IV) and oral antibiotics

1. Gram-negative bacillary bacteremia in adults. In: UpToDate, Post TW (Ed).
2. Lee CC, et al. *Int J Antimicrob Agents.* 2017;50(3):371-6.

4

Background

- Oral beta-lactams have low bioavailability (LBA) but may be an alternative to high bioavailability (HBA) agents
  - –Fluoroquinolones
  - –Sulfamethoxazole-trimethoprim
- Due to increasing resistance to many HBA antibiotics, it is important to explore options for treating infections

3. Dellinger RP, et al. Surviving Sepsis Campaign. *Crit Care Med.* 2008;36(1):296-327.
4. Tadesse DA, et al. Centers for Disease Control and Prevention Web site.

5

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

GNB: gram-negative bacteremia

6

Methods: Study Design

- Retrospective, single-center, cohort study
- Billings Clinic Hospital and Emergency Department
  - –1 infectious diseases pharmacist
  - –3 infectious diseases physicians

7

Methods: Study Groups

- LBA antibiotics
  - –Oral Beta-Lactams
    - Amoxicillin-clavulanate
    - Cephalexin
    - Cefuroxime
    - Cefdinir
    - Cefpodoxime
- HBA antibiotics
  - –Fluoroquinolones
    - Ciprofloxacin
    - Levofloxacin
  - –Sulfamethoxazole-trimethoprim

HBA: high bioavailability; LBA: low bioavailability

8

Methods: Inclusion Criteria

- Age ≥18 years
- Gram-negative bacteremia, defined as ≥1 positive blood culture, caused by *Klebsiella sp., P. mirabilis,* or *E. coli*
- Treatment with adequate doses of a study antibiotic for ≥2 days

9

Methods: Exclusion Criteria

- <7 total days of antibiotic therapy
- Concurrent oral antibiotic therapy while on the study antibiotic (excluding azithromycin)
- Polymicrobial infections
- Pregnancy or lactation
- Discharged to hospice
- Inadequate GNB source control

GNB: gram-negative bacteremia

10

Methods: Primary Outcome

- Treatment failure despite adequate dosing of a study antibiotic
  - –Hospital readmission due to the same infection source or bacteria
  - –Change in antibiotic treatment within 30 days

11

Methods: 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)
  - –Infection source

12

Methods: PITT Bacteremia Scoring Tool

Item	Points
Fever (oral temperature)	**0 to 2**
36.1 – 38.9 °C	0
35.1 – 36 °C or 39 – 39.9 °C	1
≤35 °C or ≥40 °C	2
Hypotension	**0 or 2**
Absent	0
Present (e.g., SBP <90 mmHg)	2
Mechanical Ventilation	**0 or 2**
Absent	0
Present	2

SBP: systolic blood pressure

13

Methods: PITT Bacteremia Scoring Tool

Item	Points
Cardiac Arrest	**0 or 4**
Absent	0
Present	4
Mental Status	**0 to 4**
Alert	0
Disoriented	1
Stuporous	2
Comatose	4
Total	**0 to 14**

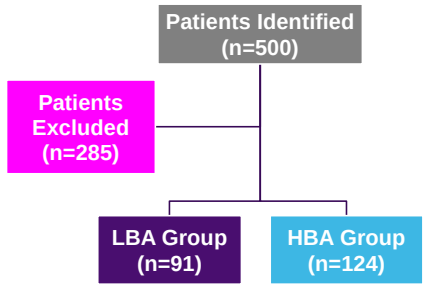
14

Methods: Statistics

- Sample size
  - One-sided alpha 0.025
  - 80% power
  - Non-inferiority margin -10%
  - 402 patients in a 1:1 allocation ratio
    - 201 HBA group
    - 201 LBA group
- Statistical tests
  - Descriptive statistics
  - Chi-square test
  - T-test

15

Results: Study Patients



16

Results: 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

17

Results: Infection Information

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)	
Intra-abdominal	20 (9.3)	8 (8.8)	12 (9.7)	0.108
Other	20 (9.3)	13 (14.3)	7 (5.6)	
Bacteremia Pathogen, n (%)				
E. coli	207 (96.3)	86 (94.5)	122 (98.4)	
P. mirabilis	8 (3.7)	5 (5.5)	2 (1.6)	0.06
Klebsiella sp.	0 (0)	0 (0)	0 (0)	

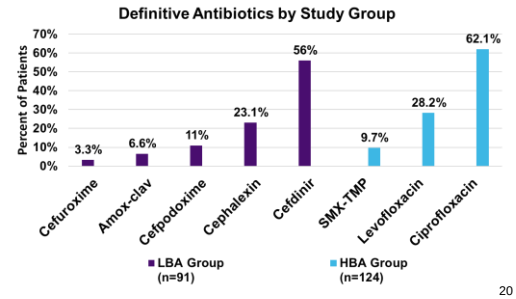
18

Results: Empiric Antibiotics

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)			

19

Results: Definitive Antibiotics



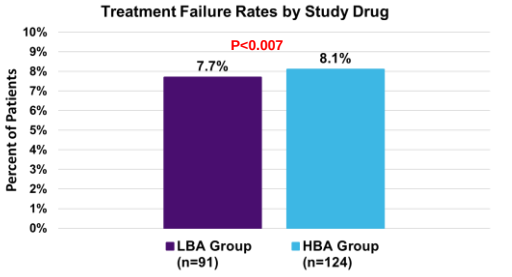
20

Results: Treatment Failure

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)

21

Results: Treatment Failure



22

Results: Secondary Outcomes

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

23

Results: Obese vs. Non-Obese Patients

Result, n (%)	All Patients (n=211)	Non-Obese Patients (n=134)	Obese Patients (n=77)	P Value
Total Treatment Failures	17 (8.1)	11 (8.2)	6 (7.8)	0.89
Readmission for Infection Recurrence <30 days	3 (1.4)	2 (1.5)	1 (1.3)	0.9
Change in Antibiotic Treatment <30 days	17 (8.1)	11 (8.2)	6 (7.8)	0.89
30-Day All-Cause Mortality	3 (1.4)	3 (2.2)	0 (0)	0.184

24

Results: Obese vs. Non-Obese Patients

Result (days), mean ± SD	All Patients (n=211)	Non-Obese Patients (n=134)	Obese Patients (n=77)	P Value
Total Antibiotic Therapy Duration	13.4 ± 6.4	13.1 ± 7.5	13.8 ± .1	0.427
Definitive Antibiotic Therapy Duration	9.7 ± 5.7	9.7 ± 6.7	9.7 ± 3.6	0.996
Hospital Length of Stay	5 ± 6	4.6 ± 3.8	5.7 ± 8.6	0.188
ICU Length of Stay	2.5 ± 2.9	2.6 ± 3.6	2.3 ± 2.1	0.729

25

Results: Infection Source

Result, n (%)	Urinary (n=175)	Intra-abdominal (n=20)	Other (n=20)	P Value
Total Treatment Failures	17 (9.7)	0 (0)	0 (0)	0.135
Readmission for Infection Recurrence <30 days	3 (1.7)	0 (0)	0 (0)	0.713
Change in Antibiotic Treatment <30 days	17 (9.7)	0 (0)	0 (0)	0.135
30-Day All-Cause Mortality	3 (1.7)	0 (0)	0 (0)	0.713

26

Results: Infection Source

Result (days), mean ± SD	Urinary (n=175)	Intra-abdominal (n=20)	Other (n=20)	P Value
Total Antibiotic Therapy Duration	12.8 ± 3.8	12.5 ± 2.8	19 ± 16.9	<0.001
Definitive Antibiotic Therapy Duration	9.4 ± 3.7	8.2 ± 2.7	13.7 ± 14.8	0.003
Hospital Length of Stay	4.3 ± 2.7	5.3 ± 2.3	11 ± 16.9	<0.001
ICU Length of Stay	2.1 ± 1.4	1.7 ± 1.3	4.5 ± 6.3	0.079

27

Results: PITT Stratification

Result, n (%)	Score 0 – 1 (n=174)	Score 2 – 3 (n=32)	Score ≥4 (n=9)	P Value
Total Treatment Failures	16 (9.2)	1 (3.1)	0 (0)	0.3
Readmission for Infection Recurrence <30 days	3 (1.7)	0 (0)	0 (0)	0.699
Change in Antibiotic Treatment <30 days	16 (9.3)	1 (3.1)	0 (0)	0.334
30-Day All-Cause Mortality	3 (1.7)	0 (0)	0 (0)	0.697

28

Results: PITT Stratification

Result (days), mean ± SD	Score 0 – 1 (n=174)	Score 2 – 3 (n=32)	Score ≥4 (n=9)	P Value
Total Antibiotic Therapy Duration	13 ± 5.6	13.9 ± 5.9	18.3 ± 16.3	0.051
Definitive Antibiotic Therapy Duration	9.6 ± 5.4	9.3 ± 5.1	11.6 ± 11.8	0.558
Hospital Length of Stay	4.2 ± 2.8	8.2 ± 12.8	10.1 ± 8	<0.001
ICU Length of Stay	1.5 ± 0.6	2.5 ± 1.9	5 ± 6.3	0.018

29

Discussion

- LBA antibiotics were non-inferior to HBA antibiotics for rates of treatment failure from gram-negative bacteremia
  - –Majority of GNBs were from a urinary source and caused *by E. coli*
- Treatment failure rates were lower than a previous comparative study with similar oral antibiotics
  - –LBA group 7.7% vs. HBA group 8.1%
  - –Beta-lactams 13.1% vs. fluoroquinolones 12.9%

5. Mercuro NJ, et al. *Int J Antimicrob Agents*. 2017.

30

Discussion

- Similar rates of secondary outcomes between LBA and HBA groups
- No differences in outcomes between obese and non-obese patients
- Significant differences in outcomes with GNB from "other" infection sources
  - Total antibiotic therapy duration
  - Definitive antibiotic therapy duration
  - Hospital length of stay

31

Limitations

- Retrospective design
- Small sample size
- Concurrent antimicrobial definition led to non-clinically relevant exclusions
- Definition of treatment failure yielded non-clinically relevant "failures"
- Comorbidities not recorded

32

Conclusion

- Low bioavailability oral antibiotics were non-inferior to high bioavailability oral antibiotics in regards to treatment failure rates from gram-negative bacteremia
  - Majority of infections were from a urinary source and caused *by E. coli*
- No differences in 30-day all-cause mortality, length of antibiotic therapy, or duration of hospital stay

33

Future Directions

- Present study results to Billings Clinic providers
- Consider development of a gram-negative treatment pathway that includes LBA agents as step-down therapy

34

Acknowledgements

- Co-investigators
  - Jennifer Ott, PharmD, BCPS
  - Camilla Reese, MD, FACP
  - Melanie Townsend, PharmD, BCPS
- Statistical Analysis
  - Ya Huei Li, PhD
- Pharmacy Informatics
  - Jacob Thiesse, PharmD, BCPS
  - Valerie Hatton, CPhT

35

Questions?

rgumbleton@billingsclinic.org

36

References

1. Moehring R, Anderson DJ. Gram-negative bacillary bacteremia in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on July 28, 2017.)
2. Lee CC, Wang JL, Lee CH, et al. Clinical benefits of antimicrobial de-escalation in adults with community-onset monomicrobial Escherichia coli, Klebsiella species, and Proteus mirabilis bacteremia. *Int J Antimicrob Agents.* 2017;50(3):371-6.
3. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for the management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.
4. Tadesse DA, Zhao S, Tong E , et al. Antimicrobial drug resistance in Escherichia coli from humans and food animals, United States, 1950-2002 (2012). Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov. Accessed October 23, 2017.
5. Mercuro NJ, Stogsdill P, Wungwattana M. Efficacy of oral quinolones and beta-lactams as stepdown therapy for Enterobacteriaceae bloodstream infections. *Int J Antimicrob Agents.* 2017.

Bioavailability

Antibiotic	Dose	Oral Bioavailability
Low Bioavailability		
Amoxicillin-clavulanate	≥500 mg-125 mg q8hrs	Cmax: 7.2 mcg/mL*
Cephalexin	≥500 mg QID	Cmax: 32 mcg/mL*
Cefpodoxime	≥400 mg q12hrs	50%
Cefuroxime	≥500 mg BID	37%
Cefdinir	≥300 mg BID	21%
High Bioavailability		
Ciprofloxacin	500 mg q12hrs or 750 mg q12hrs	60-80%
Levofloxacin	750 mg q24hrs	99%
Sulfamethoxazole-trimethoprim	800 mg-160 mg q12hrs	90-100%
• Denotes unreported bioavailability data • BID: twice daily; QID: four times daily		

Study Patients: Exclusions

Exclusion Reason	n (%)
Study antibiotic duration <2 days	180 (63.2)
Inadequate source control	35 (12.3)
Concurrent antibiotics at discharge	31 (10.9)
Hospice	15 (5.3)
Polymicrobial infection	14 (4.9)
Total antibiotic duration <7 days	11 (3.9)
Pregnant or breastfeeding	5 (1.8)
Total	**285**

Study Patients: "Other" Infection Source

Infection	n (%)
Unknown	13 (65)
Port/catheter	2 (10)
Pneumonia/upper respiratory tract infection	2 (10)
Cutaneous abscess	1 (5)
Osteomyelitis	1 (5)
Skin and soft tissue infection	1 (5)
Total	**20**

Methods: Study Design

- Non-inferiority design
- Hypotheses:
  - –Null: LBA antibiotics will result in higher rates of treatment failure in subjects with GNB than HBA antibiotics
  - –Alternate: LBA antibiotics will result in the same rates of treatment failure in subjects with GNB than HBA antibiotics

GNB: gram-negative bacteremia; LBA: low bioavailability; HBA: high bioavailability