# Oral Antibiotic for Definitive Therapy for Gram-negative Bacteremia

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# Objectives

- Review recent data regarding oral antibiotics for uncomplicated Gram-negative bacteremia (GNB).

- Discuss possible impacts of an Antimicrobial Stewardship bundle for GNB.

# Uncomplicated Gram-negative bacteremia

- No current or expected neutropenia
- No history of stem cell transplant or GVHD in last 12 months
- No history of solid organ transplantation on current immunosuppression
- Source control obtained
- No bone and joint, cerebral or endovascular complications
- Clinically improving
- *Common sources: UTI, intraabdominal infection, catheter-related bloodstream infection

# Background

- Current Treatment Strategies
  - Current guidelines recommend antibiotic treatment duration between “7 and 14 days”
  - “Intravenous antimicrobial therapy with transition to oral antibiotics if clinically appropriate”
  - Historically duration was 14 days frequently with PICCs
    - Associated harm has motivated evolving data

- More recent data suggest that durations of therapy shorter (7 days) lead to similar outcomes as prolonged durations, and with less harm

- Evolving Questions
  - Oral antibiotics
  - Role of repeat blood cultures
  - Shortest effective duration
  - Special populations/organisms

Goto M et al. Clin Microbiol Infect. 2013;19(6):501-509.
Uslan DZ et al. Arch Intern Med. 2007;167:834–9.
Mermel LA et al. Clin Infect Dis. 2009;49:1–45.
Sutton JD, Sayood S, Spivak ES. Open Forum Infect Dis. 2018 Apr 21;5(5):ofy087.

# IDSA Infection-Specific Guidelines & Bacteremia

| Guideline | Duration Recommendation |
|---|---|
| 2004 Bacterial meningitis | Not addressed |
| 2007 Community-acquired pneumonia | Not specifically addressed |
| 2009 Intravascular catheter-related infections | Organism specific |
| 2009 Catheter-associated urinary tract infections | Not addressed |
| 2010 Intra-abdominal infection | Not addressed |
| 2010 Uncomplicated urinary tract infections | Not addressed |
| 2012 Diabetic foot infections | Not addressed |
| 2014 Skin and soft tissue infections | Not addressed |
| 2016 Hospital- & ventilator-associated pneumonia | Not addressed |
| 2017 Nosocomial ventriculitis / meningitis | Not addressed |

www.idsociety.org/guidelines

# Background

- Potential treatment options (& limitations) for definitive therapy of Enterobacteriaceae bacteremia

| Parenteral antibiotics | Fluoroquinolones TMP-SMX* | Oral β-lactams |
|---|---|---|
| • Cost<br>• Line-associated adverse effects<br>• ↓ patient satisfaction | • Resistance<br>• Adverse effects | • Low - bioavailability<br>• Lack of clinical outcomes data |

*TMP-SMX: trimethoprim – sulfamethoxazole

Hale AJ, et al. J Hosp Med 2018;13(5):328
Hospenthal DR, et al. Open Forum Infect Dis 2019 [ahead of print]

JAMA Internal Medicine | Original Investigation | LESS IS MORE

# Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

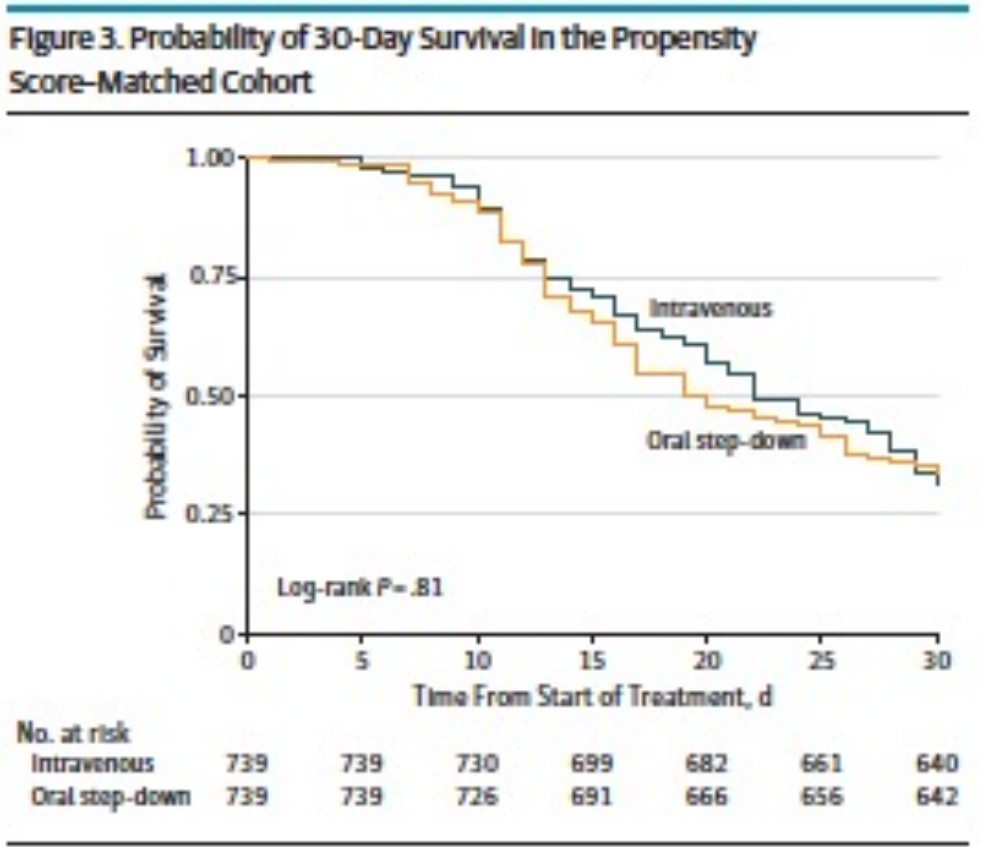
- Oral step-down (in 1st 5 days) vs. continued iv therapy for Gram-negative bacteremia

| Step-down therapy | N (%) N= 739 |
|---|---|
| Oral β-lactam | 122 (17) |
| Fluoroquinolone | 518 (70) |
| TMP/SMX | 99 (13) |

**30-day Recurrent bacteremia**

- 6 episodes (0.8%) in oral step-down group

- 4 (0.5%) in the IV group (HR, 0.82; 95% CI 0.33-2.01)

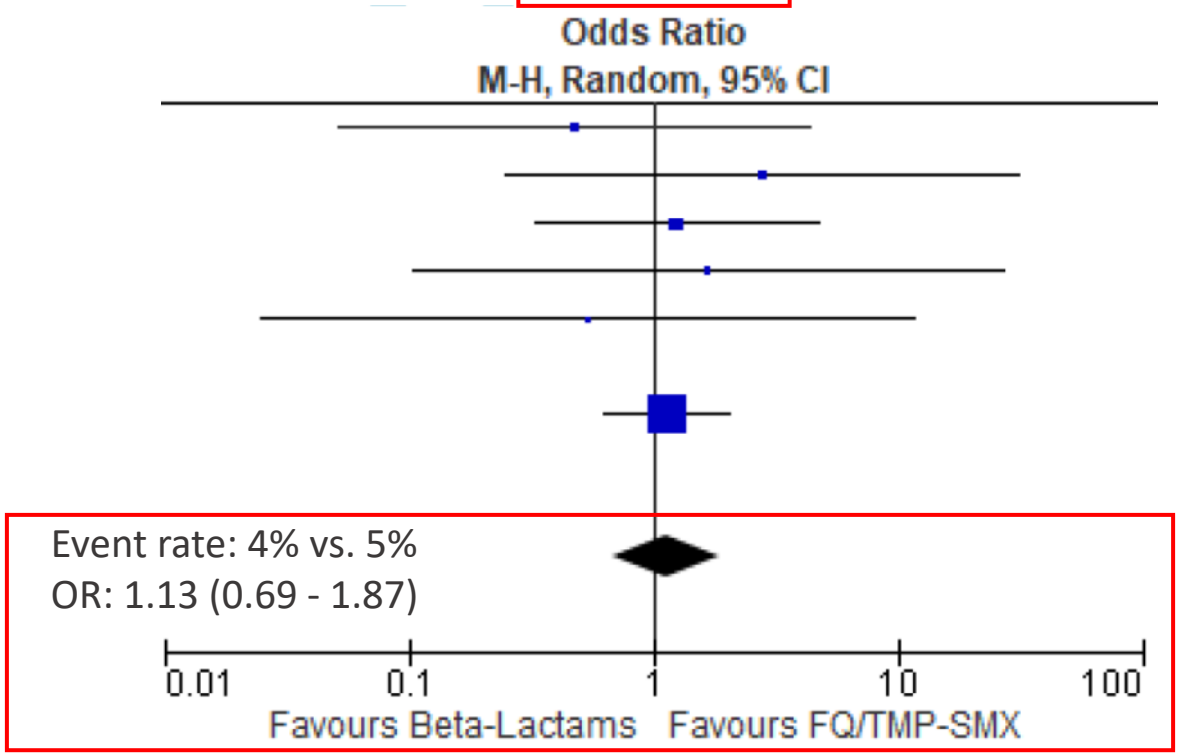



Tamma PD, et al. JAMA Intern Med. 2019 Mar 1;179(3):316-323.

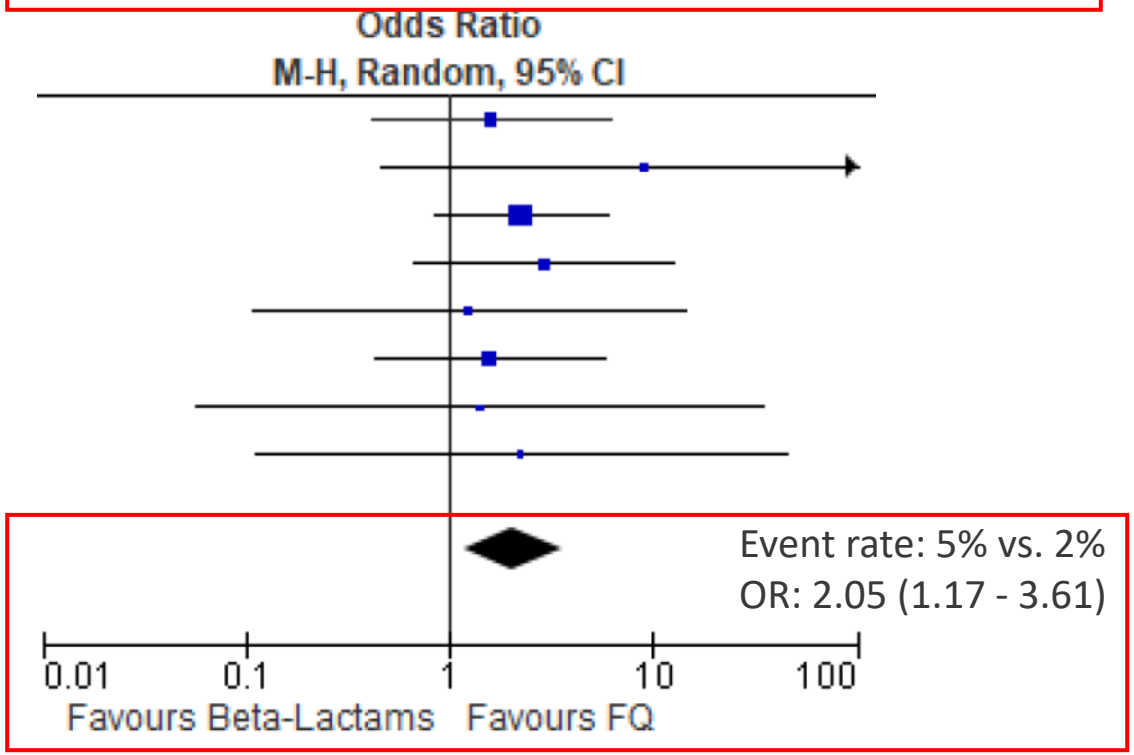
# Background

- 2019 meta-analysis (8 retrospective studies)
- Gram-negative bacteremia & definitive treatment = fluoroquinolones / TMP-SMX (n=1,666) vs. oral β-lactams (n=623)

**Mortality**




**Recurrent bacteremia or primary site infection**




Punjabi C, et al. Open Forum Infect Dis 2019 2019 Aug 14;6(10):ofz364.

# Thus far…

- Observational studies, subsets of RCTs and PK/PD principles support use of high bioavailability oral agents for Gram-negative bacteremia
  - Use of oral β-lactams more controversial

JAMA Network | Open

Original Investigation | Infectious Diseases

# Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source

Jesse D. Sutton, PharmD, MS; Vanessa W. Stevens, PhD; Nai-Chung N. Chang, PhD; Karim Khader, PhD; Tristan T. Timbrook, PharmD, MBA; Emily S. Spivak, MD, MHS

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- Retrospective cohort study
- Urine source
- Veterans Affairs hospitals (n = 114)
- January 1, 2006 – September 30, 2015

| High-bioavailability |
| --- |
| Fluoroquinolones |
| Trimethoprim-sulfamethoxazole (TMP-SMX) |

| Low-bioavailability |
| --- |
| Aminopenicillins |
| β-lactam/β-lactamase inhibitors |
| Cephalosporins |

Sutton JD, et al. JAMA Netw Open. 2020 Oct 1;3(10):e2020166.

# Inclusion Criteria

- Blood culture: *Escherichia coli, Klebsiella* species*, *Proteus* spp.
- Urine culture organism** = blood culture organism
- Hospitalization for ≥ 1 day**
- *In vitro* active, empiric, parenteral antibiotics for ≥ 1 day
- Conversion to oral antibiotics alone on day 2 – 6

*Not including *K. aerogenes* **Within ± 24 hours of blood culture collection **Within ± 48 hours of blood culture collection

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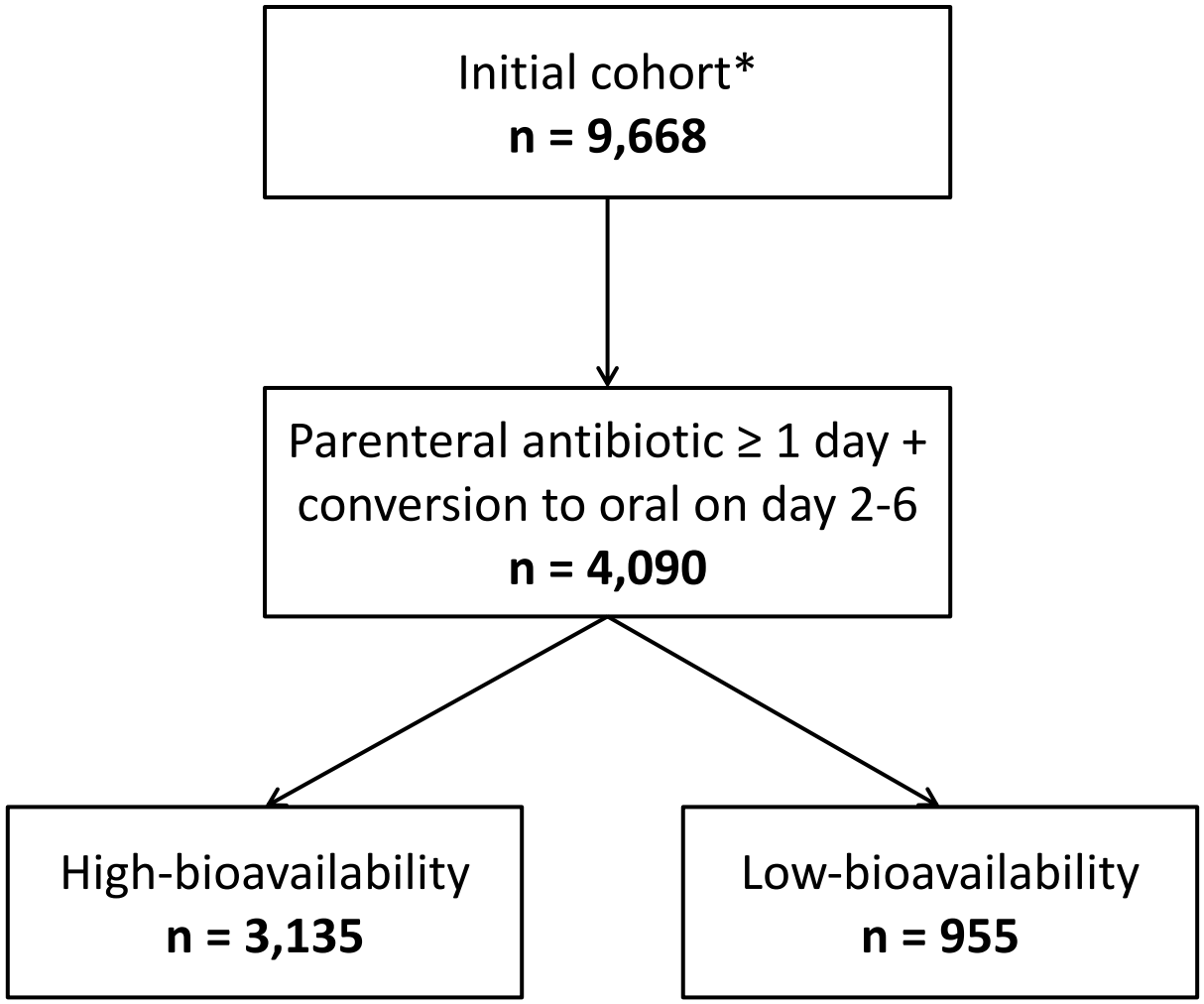
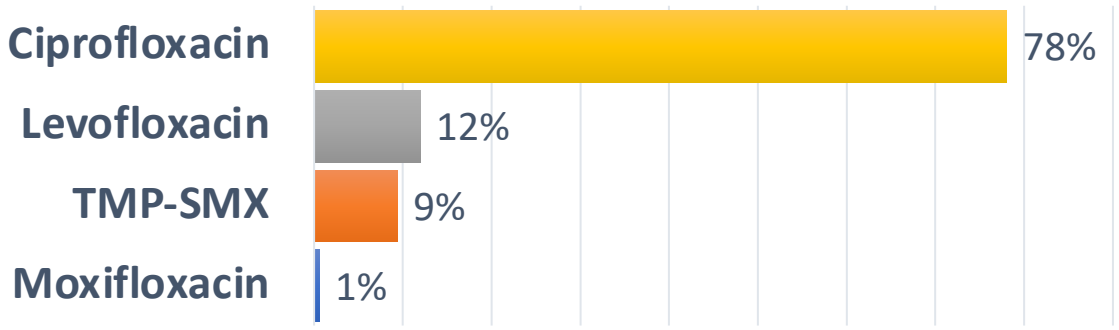
# Outcomes

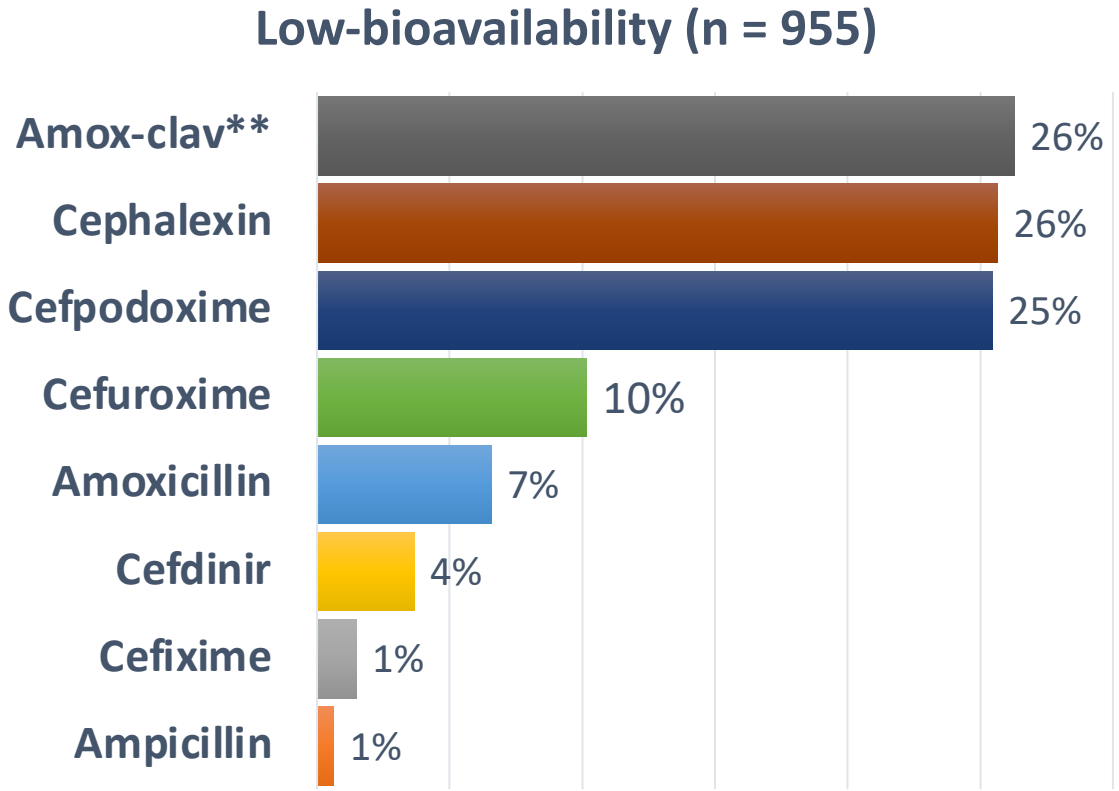
- Primary
  - 30-day mortality & recurrent Enterobacterales bacteremia*
- Secondary
  - 90-day mortality & recurrent Enterobacterales bacteremia*
- Propensity-based overlap weights
- Log binomial regression models → relative risk & risk differences

*Recurrent bacteremia: same organism species as initial culture. Outcome window begins on the first day of oral antibiotics.

Sutton JD, et al. JAMA Netw Open. 2020 Oct 1;3(10):e2020166.




*All inclusion/exclusion previously listed unless otherwise specified

**Amoxicillin-clavulanate

Sutton JD, et al. JAMA Netw Open. 2020 Oct 1;3(10):e2020166.

# Baseline Characteristics & Comorbidities

| Characteristic | High (n=3,315) | Low (n=955) |
|---|---|---|
| Age (years) – median (IQR) | 69 (62, 80) | 73 (64, 83) |
| Male sex | 2,848 (91%) | 884 (93%) |
| Comorbidity score – median (IQR)* | 1 (0, 2) | 1 (0, 3) |
| Comorbidity score > 2* | 782 (25%) | 296 (31%) |
| Chronic kidney disease | 565 (18%) | 227 (24%) |
| Diabetes w/ complication | 402 (13%) | 130 (14%) |
| Immunocompromised** | 182 (6%) | 61 (6%) |
| Cirrhosis | 88 (3%) | 20 (2%) |

*Combined Elixhauser – Charlson Comorbidity Index score (Gange J, et al. J Clin Epidemiol 2011;64:749)

**Organ transplant, WBC ≤ 1,000 / $mm^3$, high dose steroids, transplant antirejection medication, other medications

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# Outcomes

| Outcome | High (n=3,315) | Low (n=955) | Adjusted relative risk (95% CI) |
|---|---|---|---|
| 30-day mortality & bacteremia | 94 (3.0%) | 42 (4.4%) | 1.3 (0.9 – 1.9) |
| Mortality | 82 (2.6%) | 29 (3.0%) | 1.0 (0.7 – 1.5) |
| Recurrent bacteremia | 12 (0.4%) | 14 (1.5%) | 3.2 (0.5 – 21.9) |
| 90-day mortality & bacteremia | 238 (7.6%) | 96 (10.1%) | 1.3 (0.9 – 1.9) |
| Mortality | 208 (6.6%) | 75 (7.9%) | 1.1 (0.8 – 1.4) |
| Recurrent bacteremia | 34 (1.1%) | 25 (2.6%) | 2.1 (0.9 – 4.9) |

Relative risk reported based on receipt of a low-bioavailability antibiotic

Sutton JD, et al. JAMA Netw Open. 2020 Oct 1;3(10):e2020166.

# Conclusions

- No significant differences in mortality + recurrent bacteremia
  - Possible increased risk of recurrent bacteremia with oral β-lactams
  - Absolute risk and risk difference are small (~1%)

- Oral β-lactams are a reasonable definitive treatment in certain patients
  - Further understanding of risks of recurrence and optimal patient selection

- Considerations for interpretation
  - Shortest effective duration = unknown $\rightarrow$ null effect of oral antibiotics?
  - Residual confounding?

# Stewardship Bundle for Uncomplicated Gram-negative Bacteremia

*(Minimize repeat blood cultures, IV to PO ABX switch, 7 day duration of therapy)*

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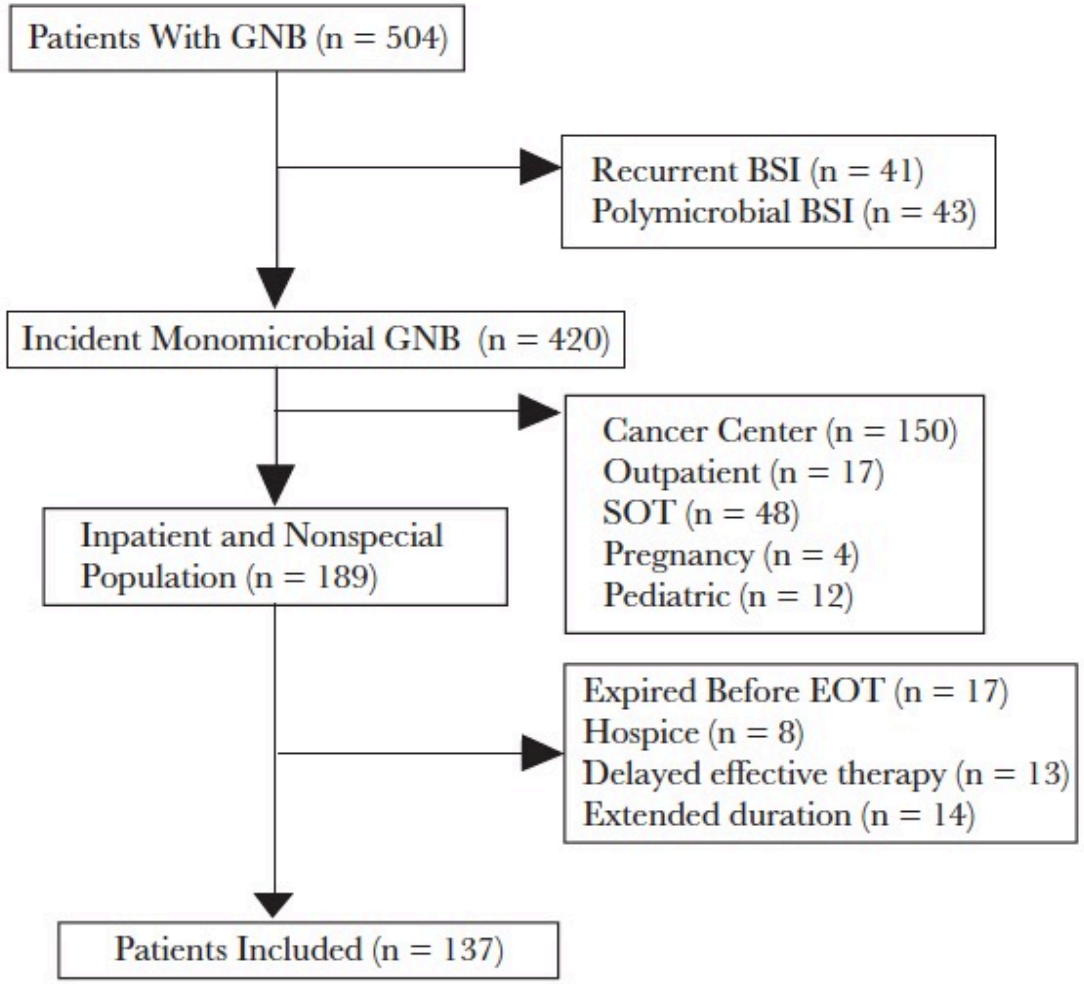
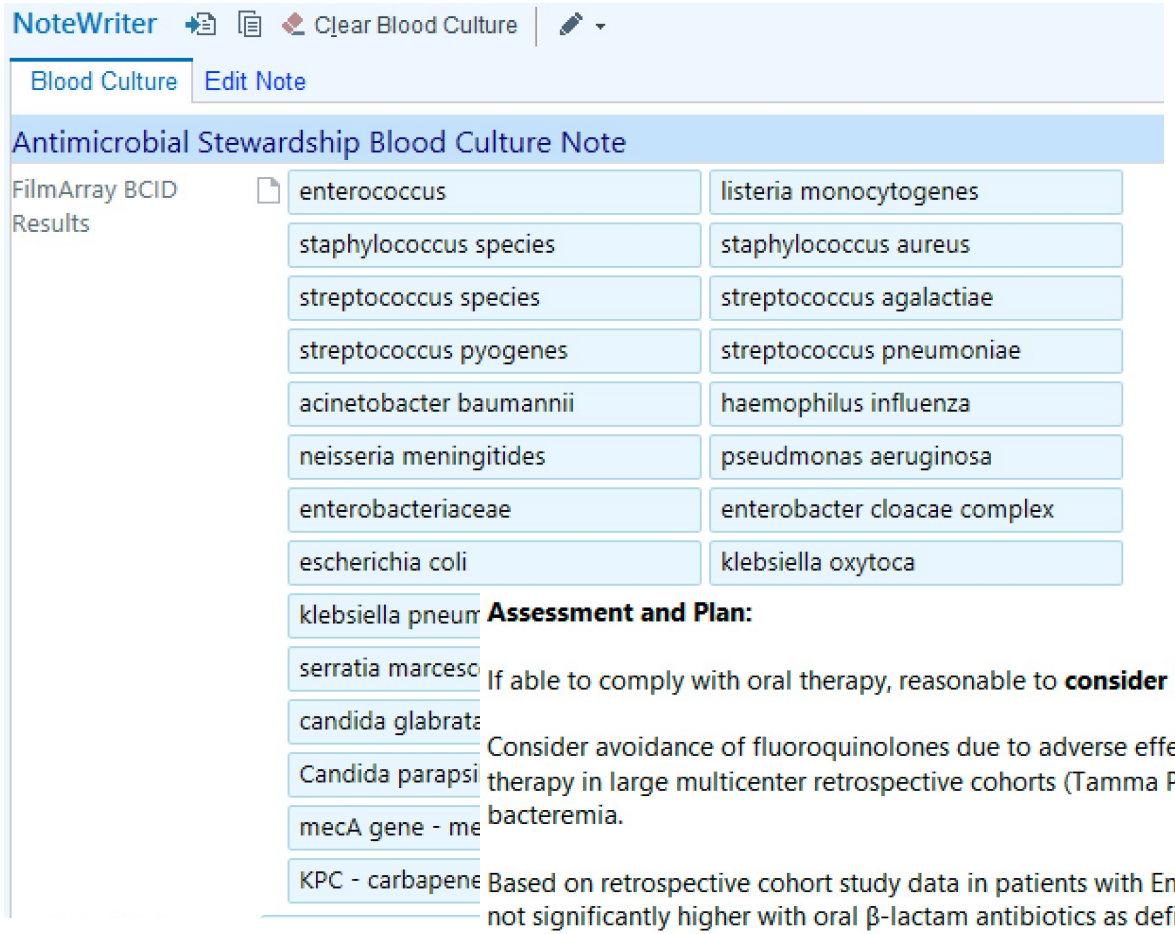
- Retrospective cohort study
- Inclusion
  - Adult patients admitted to the University of Utah Hospital
  - 11/2014-10/2015 and 10/2017-9/2018
  - At least one positive BCx for a Gram-negative organism
- Pre-ASP: prior to a formal ASP, after BCID implementation
- Post-ASP: Bundle




Erickson RM, et al. *Open Forum Infectious Diseases*. November 2019:ofz490.




**Assessment and Plan:**

If able to comply with oral therapy, reasonable to **consider [insert antibiotic agent].**

Consider avoidance of fluoroquinolones due to adverse effects when alternative agents are available (FDA Warning 2016). SMX/TMP has been effective as oral step down therapy in large multicenter retrospective cohorts (Tamma PD, JAMA Intern Med 2019) and randomized controlled trial (Yahav, Clin Infect Dis 2018) of Enterobacteriaceae bacteremia.

Based on retrospective cohort study data in patients with Enterobacterales bacteremia from a suspected urine source, the relative risk of recurrent bacteremia at 30 days was not significantly higher with oral β-lactam antibiotics as definitive therapy than with fluoroquinolones or trimethoprim-sulfamethoxazole, and the absolute risk difference was small. No significant difference in mortality was observed. (Sutton JD, JAMA Network Open 2020)

**Recommend treating Enterobacteriaceae bacteremia for 7 days total** rather than longer durations as shown to be effective in retrospective multicenter data (majority of urinary tract and gastrointestinal source) and possibly decrease risk of multi-drug resistance development (Chotiprasitsakul, Clin Infect Dis 2017; Mercuro, IJAA 2017; Rieger, Pharmacotherapy 2017). A multicenter randomized controlled trial (n=604) of Enterobacteriaceae bacteremia patients data, majority of pyelonephritis source, supports a 7-day duration (Yahav D, Clin Infect Dis 2018) as long as the patient had defervescence for 48 h and without an uncontrolled source of infection or neutropenia. Furthermore, shorter durations have been associated with decreased risk of C. Difficile infections (Stevens, Clin Infect Dis 2011). Finally, **consider avoidance of follow up blood cultures** based on clinical response and overall reported lack of clinical utility and unintended consequences (longer LOS, healthcare costs, inappropriate use of antibiotics; Canzoneri Clin, Infect Dis 2017; Wiggers, BMC Infect Dis 2016).

Submitted by: Emily R Sydnor Spivak, MD

*For additional questions please page the on call Infectious Disease - Antimicrobial Stewardship Program team member or Dr. Emily Spivak via SmartWeb.*

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## Workflow

- BioFire FilmArray BCID
- ASP review blood culture report in Epic (M – F)
- Most recs initially given in-person and documented in progress note

# Stewardship Bundle for Uncomplicated Gram-negative Bacteremia

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| | Pre-ASP Intervention (n=50) | Post-ASP Intervention (n=61) | P-value |
|---|---|---|---|
| **Duration of Therapy** | 14 (10-16) | 9 (7-14) | < 0.01 |
| **IV to PO Switch Day** | 5 (4-6) | 3.5 (3-5) | 0.02 |
| **PICC Placement** | 8 (16) | 5 (8.2) | 0.23 |
| **Definitive Therapy** | | | |
| **Beta-lactam/SMX-TMP** | 10 (20) | 29 (47.5) | < 0.01 |
| **Fluoroquinolone** | 23 (46) | 23 (37.7) | 0.38 |
| **Bacteremia Recurrence** | 0 (0) | 1 (1.6) | 0.36 |
| **Readmission Rates** | 20 (40) | 14 (23) | 0.05 |
| **30-day Mortality** | 0 (0) | 1 (1.6) | 0.36 |

**Total hospital cost per case decreased by 27%

Erickson RM, et al. Open Forum Infectious Diseases. November 2019:ofz490.

# Predictors of Long Treatment Duration

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**Table 3. Predictors of Long Treatment Duration**

| | Univariate OR (95% CI) | *P* | Multivariate OR (95% CI) |
|---|---|---|---|
| Age ≥65 y | 1.09 (0.59–1.50) | .80 | |
| Pre-ASP intervention period | 3.06 (1.50–6.43) | <.01 | 3.67 (1.60–8.44) |
| Charlson Comorbidity Index ≥2 | 1.19 (0.55–2.61) | .66 | |
| Immunosuppression | 0.49 (0.07–2.61) | .42 | |
| *E. coli* | 0.27 (0.12–0.59) | <.01 | 0.27 (0.11–0.68) |
| Pitt Bacteremia Score >3 | 1.51 (0.75–3.07) | .26 | |
| Repeat blood cultures | 3.46 (1.73–7.09) | <.01 | 3.54 (1.57–7.98) |
| Urinary source | 0.79 (0.40–1.58) | .51 | |
| Genito-urinary tract obstruction | 3.84 (1.28–14.25) | .03 | 8.03 (2.06–31.28) |

Abbreviations: ASP, antimicrobial stewardship program; CI, confidence interval; OR, odds ratio.

Erickson RM, et al. Open Forum Infectious Diseases. November 2019:ofz490.

# Conclusions

- Data is evolving, but doesn’t seem to be higher risk of recurrent bacteremia or mortality with oral beta-lacatams vs. FQ or TMP/SMX for uncomplicated GNB

- Bundle for GNB a great Stewardship opportunity!

- Areas for further research
  - Optimal dosing for oral step-down options
  - Role of oral antibiotics in severely immunocompromised populations
  - Duration and oral antibiotics in genitourinary obstruction (partial source control)

# Questions

# Urologic Comorbidities

| Characteristic | High (n=3,315) | Low (n=955) |
|---|---|---|
| History of UTI (1 year) | 887 (28%) | 401 (42%) |
| Previous UTI antibiotics (30 days) | 398 (13%) | 222 (23%) |
| Prostate hypertrophy | 877 (28%) | 324 (34%) |
| Urinary retention, obstruction, other structural abnormality | 723 (23%) | 288 (30%) |
| Urologic procedure (90 days) | 562 (18%) | 212 (22%) |
| Prostate cancer | 408 (13%) | 143 (15%) |
| Spinal cord injury / multiple sclerosis | 129 (4%) | 52 (5%) |
| Urinary calculi (30 days) | 138 (4%) | 35 (4%) |