Updates in (uncomplicated) Gram-Negative Rod Bacteremia

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Disclosures

- **Investigational/Off Label Use of Drugs Disclosure:** Antimicrobials (There are no antimicrobials with specific FDA labeling for Gram-negative bacteremia; therefore, all discussion of treatment for this condition necessarily involves discussion of off-label therapy.)

Key takeaways from the next 25min:

1. **Most patients with GNR bacteremia should be treated for 7 days**
   - Reserve longer courses for patients with:
     - Delayed clinical response (e.g., ongoing fever >3 days into therapy, persistent BSI)
     - An uncontrollable source of infection (e.g., undrainable abscess)
     - Concomitant infection needing longer tx (e.g., osteoarticular, CNS, or device infections)

2. Switch patients who are clinically improving from IV→PO abx

- FQ and TMP/SMX are great for this; oral beta-lactams are an option but may benefit from higher doses and/or longer total or initial-IV durations

3. Follow-up blood cultures are not routinely needed in GNR bacteremia; consider in pts with ineffective empiric treatment, deep-seated sources of infection, or delayed clinical response to therapy

Disclosures: no relevant COI

Duration of therapy: **most patients with GNR bacteremia should be treated for 7 days**

Seven vs 14 days of abx for GNR BSI: clinical trial data

Study	Population:	Inclusion & Exclusion criteria:	1° Clinical Outcome:	Results:
Yahav CID 2019	• 604 adults from 3 centers • ~25% with malignancy • ~25% with other underlying immunosuppression • ~67% with urinary source	Similar between studies: • Fever or unstable hemodynamics (at day 5 for Yahav; at day 3-5 for von Dach; Molina did not allow abx to stop until pt was afebrile for 72hr) • Persistent bacteremia and/or uncontrolled source of infection • Concurrent infection needing >7d treatment • Intense immune suppresion (e.g. recent HSCT, advanced HIV, neutropenia within 48h of enrollment)	28d composite of: • Mortality • Clinical failure • Readmission • Hospitalization >14d	**Primary outcome: equal** (45.8% vs 48.3% with 7d vs 14d; p>.05) **Mortality: equal** (4.9% vs 4.4%; p>.05)
von Dach JAMA 2020	• 504 adults from 3 centers • ~67% with urinary source • Median SOFA score of 1 (IQR 0-2) at enrollment		30d composite of: • Mortality • Relapsed BSI • New metastatic infxn • Resumption of abx for clinical worsening	**Primary outcome: equal** (6.6% vs 5.5% with 7d vs 14d; p>.05) **Mortality: equal** (3.6% vs 1.2%; p>.05)
Molia CMI 2022	• 248 adults from 5 centers • ~25% with malignancy • ~50% with urinary source		Clinical failure (any ongoing signs/symptoms of infection 28d after end of therapy)	**Primary outcome: equal** (7.3% vs 9.8% with 7d vs 14d; p>.05) **Mortality: equal** (2.5% vs 7%; p>.05)

Shorter durations for GNR BSI: observational data

Study:	Design:	Key finding:
Fabre CID 2019	Propensity score-weighted multicenter cohort of 249 adults with Pseudomonas bacteremia	Shorter versus longer antibiotic durations (median 9 days vs median 16 days) produced similar rates of 30d mortality (7% vs 4%) and recurrent infection (7% vs 11%)
Soto CID 2024	Propensity score-weighted multicenter cohort of 183 adults with CRE bacteremia	Shorter versus longer antibiotic durations (median 9 days vs median 14 days) produced similar rates of mortality (3.4% vs 4.6%) and recurrent BSI (6.1% vs 5.7%)
McAteer CID 2023	Propensity score-weighted multicenter cohort of 1099 adults with cUTI and associated bacteremia	Shorter antibiotic durations (median 7 days versus 14 days) produced similar rates of 30d recurrent infection **only if highly bioavailable oral antibiotics were used** (aOR 0.76; 95% 0.38-1.52)
Anderson Ann Pharm 2024	Propensity score-matched cohort of 225 critically ill adults with GNR bacteremia	Shorter versus longer antibiotic durations (mean 7.8 vs 15.1 days) resulted in similar 30-day mortality (3.8% vs 5.5%) and higher rates of cure without adverse drug events (53.4% vs 41.3%)
Ranganath Transplant ID 2023	Retrospective cohort of 206 adults with neutropenia due to hematologic malignancy or HSCT and GNR bacteremia	No differences in 90d all-cause mortality or relapsed infection noted between short (<10 days), intermediate (11-14 days), and prolonged (>14 days) durations of therapy
Herrera Microorg 2023	Retrospective cohort 74 adults with active malignancy or HSCT within 2yr transplant and GNR bacteremia	Shorter antibiotic durations (median 7 days versus 14 days) produced similar rates of 30d mortality (2.8% vs 7.9%) and recurrent bacteremia (2.8% vs 0%)

Route of therapy: **most patients with GNR bacteremia can be switched to oral agents once clinically improving**

- Multicenter RCT of 174 adults with Enterobacterales BSI who had received ≥3 days of IV abx with improvement (afebrile, stable hemodynamics)
- Excluded pts with endocarditis, CNS infection, uncontrolled source of infection, neutropenia or recent HSCT
- Randomized subjects 1:1 to complete IV therapy or switch to an oral quinolone, TMP/SMX, or beta-lactam
- Primary outcome was a 90-day composite of death, relapsed infection, infection-related readmission, or need for further abx treatment
- Power calculation called for n=438 to power for a 10% NI margin; however study was closed early due to poor enrollement

Key patient characteristics

	IV group (n=85)	Oral group (n=89)
Mean age (SD)	55.5 (±17.9)	57.6 (±15.5)
Site of care at enrollment		
ICU	6%	7%
Hospital ward	47%	44%
ED or outpatient	47%	49%
Diabetes	54%	60%
Active malignancy	9%	9%

- 60% had a urinary source of BSI
- 16% had ESBL-producing GNRs
- Median duration of therapy was 12 days (IQR 10-15)
- 65% of patients in the PO group switched to an oral beta-lactam

Results (mITT population)

Outcome	IV group	PO group	Difference (95% CI)
90d treatment failure (composite)	**25.6%**	**21.7%**	**–3.7% (–16.6% to 9.2%)**
90d all-cause mortality	3.7%	3.6%	–0.04% (–5.8% to 5.7%)
90d Microbiological relapse	12.2%	7.2%	–4.8% (–14.0% to 4.3%)
90d Infection-related readmission	11%	18.1%	7.5% (–3.1% to 18.1%)
90d need for additional antimicrobial therapy	12.2%	4.8%	–7.1% (–15.5% to 1.3%)

- Median hospital LOS was shorter in the PO switch group (6 days; IQR 5-8) versus the all-IV group (9 days; IQR 6-14)
- AE, serious AEs, and AEs leading to treatment discontinuation were similar between arms (p>.05 for all)

This trial exists in the context of prior RCT data also suggesting PO switch is effective in GNR BSI:

Yahav 2019: 73% of patients switched to PO agents, predominantly quinolones

von Dach 2020: PO switch was allowed at any time and was not associated with clinical failure (OR 0.59 with 95% CI 0.25-1.36)

Older RCTs with BSI subgroups:	Population:	Finding:
Amodio-Groton 1996	51 adults with Gram-negative bacteremia	Treatment success with oral ciprofloxacin (20/24) was as good as with IV agents (20/27)
Mombelli Arch Intern Med 1999	53 adults with bacteremia cUTI/pyelo	Clinical outcomes with PO vs IV ciprofloxacin were similar with no need to change abx due to early clinical failure in either group
Monmaturapoj 2012	17 adults with bacteremic pyelo	Switch from ceftriaxone to oral cefditoren was as effective as all-IV therapy (treatment success in 6/6 versus 10/11)
Park 2014	59 adults with bacteremic cholangitis	Treatment success was equally high with early switch to oral ciprofloxacin versus all-IV therapy (27/29 versus 28/30)

“But my patients are sicker!” - what about PO switch for the highly immunocompromised?

Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study

Nussbaum et al., 2024 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

January 2016 — December 2021

Patient Population

All solid organ transplant recipients at Massachusetts General Hospital and Brigham and Women's Hospital (n=162) with uncomplicated gram-negative bacteremia.

Methods

Compared outcomes of those transitioned to oral antibiotics vs those who continued IV therapy using propensity score weighted models.

	PRIMARY OUTCOME: Bacteremia Recurrence	SECONDARY OUTCOME: *C. difficile* Infection	SECONDARY OUTCOME: Other Adverse Events
COHORT 1: Patients Transitioned to Oral Therapy	2%	2%	3%
Significance	p =0.27	p = 0.015	p =0.002
COHORT 2: Patients Continued on IV Therapy	5%	12% OR = 8.4	10% OR = 6.4

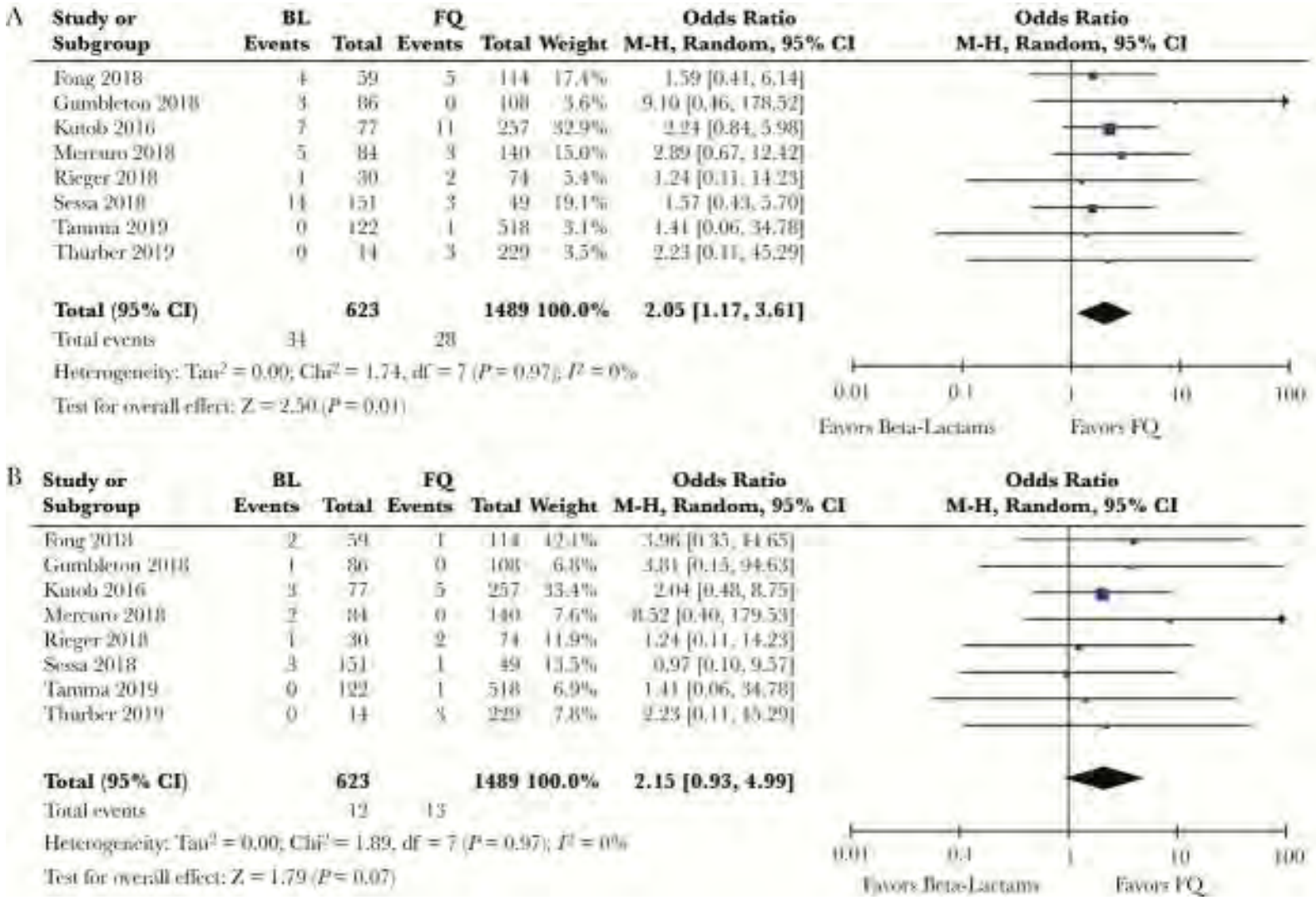
Zero patients died in either group within 30 days of treatment completion. Length of stay was on average 1.97 days shorter in the oral group.

Oral step-down therapy was effective and associated with fewer treatment-related adverse events and shorter length of hospital stay compared with continued IV therapy.

Not all oral antibiotics created equal: "High-bioavailablity" mostly means "not PO beta-lactams"

Oral antibiotics whose standard PO dosing achieves serum and tissue drug levels similar to its IV counterpart	**Quinolones** **Macrolides** **Tetracyclines** **Trimethoprim-Sulfamethoxazole** **Linezolid** **Clindamycin** **Rifampin** **Metronidazole**
Oral antibiotics whose standard PO dosing achieves substantially lower serum and tissue drug levels vs its IV counterpart	**Oral beta-lactams** (**especially** 2nd and 3rd-gen oral cephalosporins) **Fosfomycin**
Oral antibiotics that stay in the gut	**Vancomycin**

Punjabi OFID 2019: more recurrent infections (A) and possibly more recurrent bacteremia (B) with switch to oral beta-lactams vs quinolones in GNR BSI

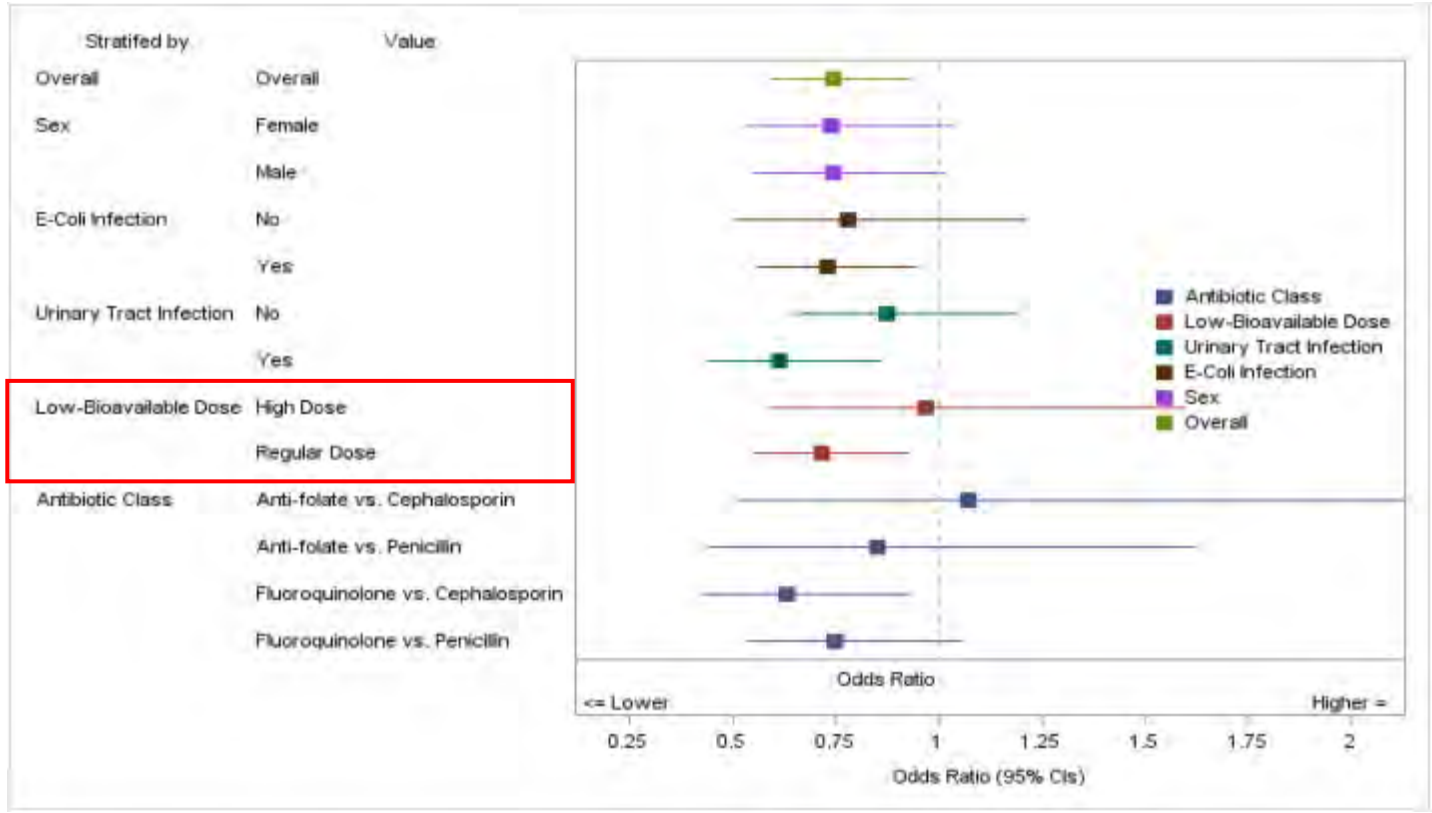


Note: Subsequent studies demonstrating similar outcomes with oral beta-lactams and FQs or TMP/SMX have largely used longer (10-14 day) total durations of therapy and/or higher than standard doses of oral beta-lactams[1-4]

[1]Geyer ASHE 2023
[2]Alzaidi OFID 2024
[3]McAlister 2023
[4]Saad BMC ID 2020

Mponponsuo OFID 2023: switch to standard dose, but not high-dose, oral beta-lactams is inferior to switch to quinolones or TMP/SMX in GNR BSI

In a propensity-score matched cohort of 2012 patients, the 1° outcome, (composite of mortality, recurrent BSI, and re-admission at 90d) was **more frequent** with switch to oral beta-lactams vs FQs or TMP/SMX (21.5% vs 17%; p=0.01; primarily driven by more recurrent BSI)

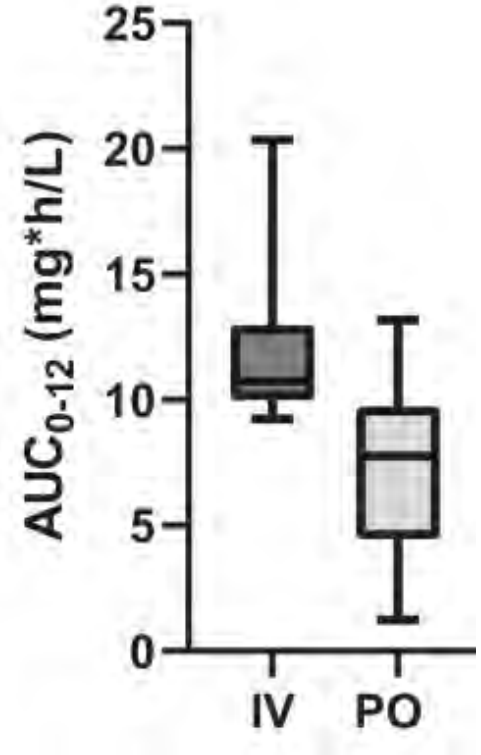


	Usual dose	High dose
Amoxicillin	250-500mg TID	1g TID 1g QID
Amoxicillin-Clavulanate	500/125mg TID 875/125mg BID	875/125mg TID
Cephalexin	500mg QID	1g TID
Cefadroxil	500mg BID	1g BID
Cefuroxime	500mg BID	500mg TID 1g BID

Who might not be a good candidate for PO switch?

- Patients not able to tolerate oral medications (intractable N/V)
- Patients with extensive bowel resection
- (for oral beta-lactams): patients who are unlikely to tolerate maximum-dose oral BLs or who have risk factors for relapse infection / treatment failure

Drug levels achieved with ciprofloxacin 400mg IV versus 750mg PO in 18 patients with short bowel syndrome. From Korzilius et al, JAC 2023



Monitoring response to therapy: **follow-up blood cultures are not routinely needed in GNR bacteremia**

Should patients with GNR BSI receive follow-up blood cultures (FUBC) to demonstrate control of the bacteremia?

Most FUBC (~90%) in Gram-negative bacteremia are negative.
Recognized risk factors for positive FUBC include:

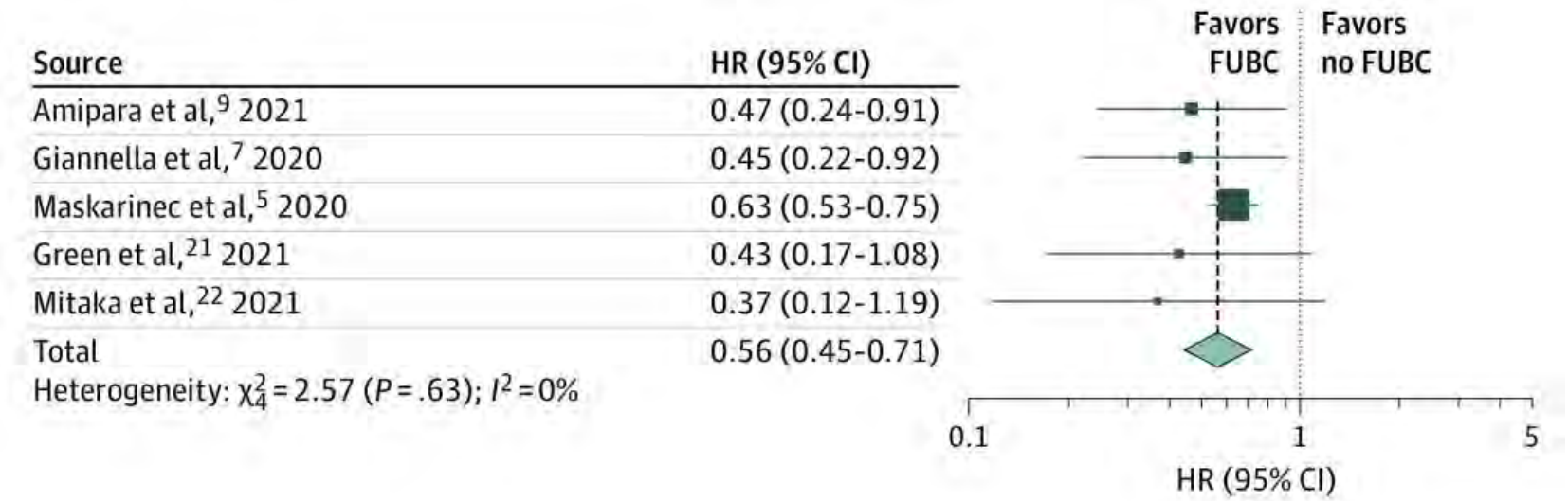
- ESRD and/or presence of a central venous catheter
- Infections with MDR pathogens and/or inappropriate empiric abx therapy
- Unfavorable clinical response at 24hr and/or uncontrolled source of infection

Meta-analyses show that:

- Having a received a FUBC is associated with lower in-hospital and 30-day mortalities, but also longer LOS and antibiotic treatment durations
- Having a positive FUBC is associated with higher mortality

Ong CMI 2024; Gatti CMI 2023; Thaden JAMA IM 2022

Thaden JAMA IM 2022: meta-analysis of studies associating FUBC and in-hospital mortality in GNR BSI



Study:	Population:	% FUBC (+)	Controlled for survival bias?
Amipara 2021	606 adults with community-acquired BSI	7	Yes; excluded deaths within 72hr
Giannella 2020	1576 adults with GNR BSI at a large university hospital	39	Yes; treated FUBCs as a time-dependent covariate and matched patients w/wo FUBC by initial survival time
Maskarinec 2020	1702 adults with GNR BSI within a university health system	20	Yes; treated FUBCs as a time-dependent covariate
Green 2021	159 adults with *P. aeruginosa* BSI at a large university hospital	7	Yes; treated FUBCs as a time-dependent covariate
Mitaka 2021	381 adults with GNR BSI from four large NYC hospitals	10	Yes; excluded deaths within 72hr

Newer studies suggest no mortality benefit to obtaining FUBC in GNR BSI

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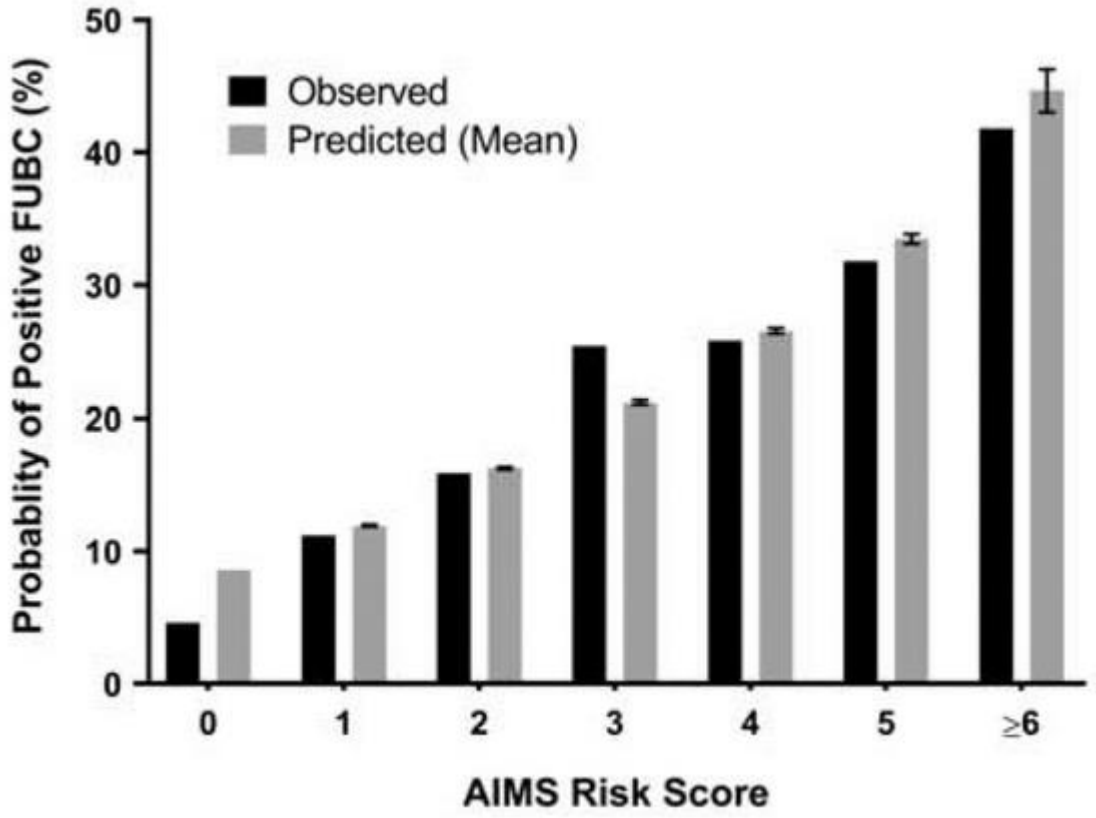
Study:	Population:	% FUBC (+)	Finding
Elamin 2022	482 adults with GNR BSI at a single US community hospital	4	**No association between FUBC & mortality**; longer LOS and longer abx durations given in pts receiving FUBC
Yildiz 2023	812 adults with GNR BSI at a large university hospital	14	**No association between FUBC & mortality**; longer abx durations given in pts receiving FUBC
Ranganath 2024	206 neutropenic adults with GNR BSI at the Mayo Clinic	9	**No association between FUBC & mortality**; longer LOS and longer abx durations given in pts receiving FUBC
Ong 2024	**34,100** adults with GNR BSI in the Ontario health system	11	**No association between FUBC & mortality**; longer LOS and fewer days alive outside the hospital in pts receiving FUBC

Maskarinec CMI 2020: AIMS score predicts (+) FUBC in GNR BSI

Variable	Point allocation
Antibiotics	
days to effective therapy (≥1)[a]	1
Infection source	
endovascular	3
gastrointestinal	1
genitourinary	1
other[b]	3
Medical comorbities	
cardiac device present	1
corticosteroid use	1
hemodialysis dependence	1
Species	
Serratia species	2
AIMS RISK SCORE	**TOTAL (0-9)**

[a]refers to duration in days between initial blood culture and effective antibiotic therapy

[b]refers to infections with identifiable sources that did not fit into predefined categories



Bottom line: even if FUBC is sometimes valuable, routinely obtaining FUBC is unlikely to be high-value care

Key takeaways:

1. **Most patients with GNR bacteremia should be treated for 7 days**
   - Reserve longer courses for patients with:
     - Delayed clinical response (e.g., ongoing fever >3 days into therapy, persistent BSI)
     - An uncontrollable source of infection (e.g., undrainable abscess)
     - Concomitant infection needing longer tx (e.g., osteoarticular, CNS, or device infections)

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- FQ and TMP/SMX are great for this; oral beta-lactams are an option but may benefit from higher doses and/or longer total or initial-IV durations

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