Clinical Trials in Bacterial Diseases That May Change Your Practice

Julie Ann Justo, PharmD, MS, FIDSA, BCPS
Clinical Associate Professor, University of South Carolina College of Pharmacy
Infectious Diseases Clinical Pharmacy Specialist, Prisma Health-Midlands
Infectious Diseases Pharmacy Fellowship Director, Prisma Health/USC COP
@julie_justo

Disclosures

- Dr. Justo has the following disclosures:
  - Entasis Therapeutics, Gilead Sciences, and Shionogi (advisory boards)
  - Spero Therapeutics (speaker)
  - Vaxart (stock ownership)

Objectives

- Discuss recent bacterial infection trials and their effects on current clinical practice

Outline

	Topic	Trials
	Antimicrobial Selection	GRACE-VAP Trial
	Medical Management	Meta-Analysis of Follow-Up Blood Cultures in Gram-negative Bloodstream Infections
	Dosing	SABATO Trial ZeNix Trial
	Duration	SHINE Trial
	Novel & Investigational Agents	Fecal microbiota spores, live-brpk (Vowst®) Fecal microbiota suspension, live-jslm (Rebyota®) Cefepime/enmetazobactam Sulbactam/durlobactam

Original Investigation | Critical Care Medicine

Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients With Ventilator-Associated Pneumonia

The GRACE-VAP Randomized Clinical Trial

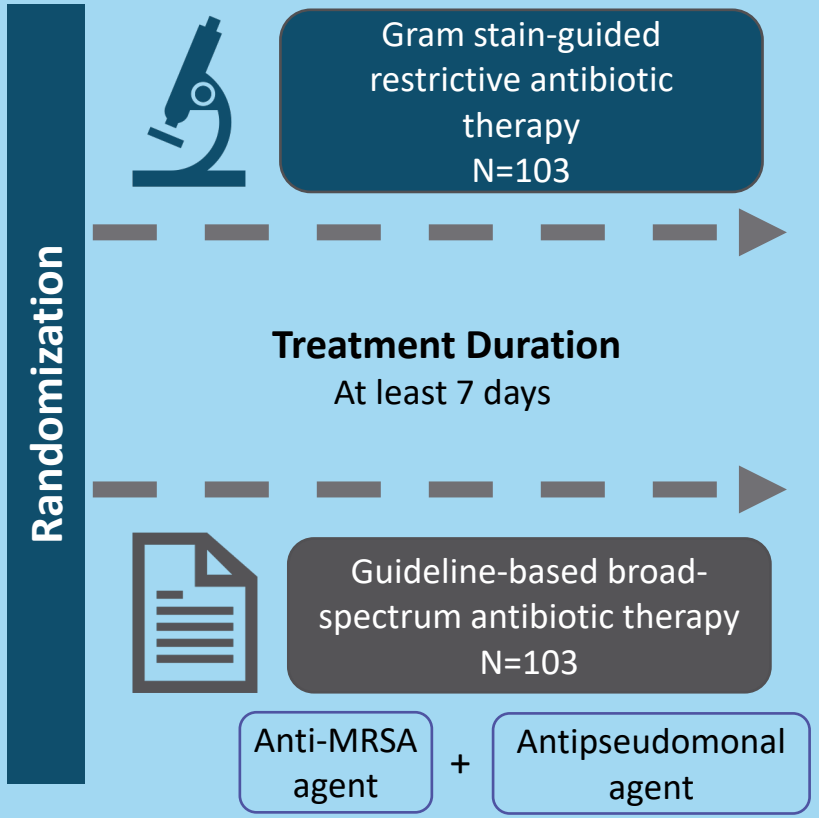
Study Population

Adults & adolescents (aged ≥15 yr) with ventilator-associated pneumonia

- N=206 pts (68.4% male)
- Median (IQR) 69 yr (54-78 yr)

Study Design

- Multicenter: 12 ICUs in Japan
- Open-label
- Non-inferiority (20% margin)
- Randomized controlled trial



1º Outcome

Clinical Response Rate at Test-of-Cure (all met):

- Complete therapy ≤14 d
- Radiograph improved or stable
- Resolution of s/sx
- No antibiotic readministration

Blinded adjudication committee for all endpoints

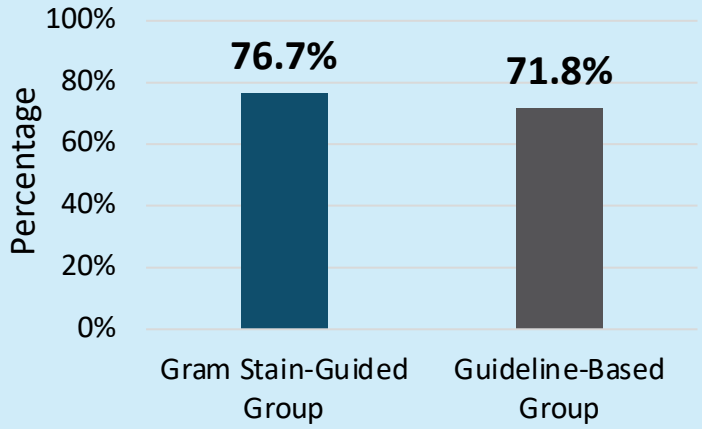
Yoshimura J, et al. *JAMA Netw Open*. 2022;5(4):e226136. doi:10.1001/jamanetworkopen.2022.6136

GRACE-VAP: Results

1º Outcome

Clinical Response Rate

Risk Difference 0.05
(95%CI, –0.07 to 0.17)
P < 0.001 for noninferiority



2º Outcomes

28-day Mortality

13.6% Gram stain-Guided group

17.5% Guideline-based Group

p=0.44

- 28-day ICU-free & ventilator-free days also comparable

Coverage with Initial Antibiotic Therapy

86.4% Gram stain-Guided group

92.2% Guideline-based Group

p=0.18

Gram Stain-Guided Group with:

Antipseudomonal Agent Use

↓30.1%
(95%CI, 21.5 to 39.9%)
P < .001

Anti-MRSA Agent Use

↓38.8%
(95%CI, 29.4 to 48.9%)
P < .001

Yoshimura J, et al. *JAMA Netw Open*. 2022;5(4):e226136. doi:10.1001/jamanetworkopen.2022.6136

How will this change your practice?

- Gram stain-guided restrictive antibiotic therapy noninferior to guideline-based empiric antibiotic therapy for VAP
- May reconsider a “one-size-fits-all” approach to empiric antibiotic therapy for VAP
  - Discuss with critical care colleagues, acknowledge these were endotracheal aspirates
  - Potential stewardship initiative, especially for ICUs with ↑↑ broad-spectrum antibiotic use
- Limitations:
  - Significantly escalation in gram stain-guided group
  - May not be generalizable to institution with ↑ severity of illness and/or antimicrobial resistance
    - Few patients with sepsis (34%), even fewer with septic shock (4%)
    - Frequency of multidrug-resistant gram-negatives low (<10%), none isolated in trial

Yoshimura J, et al. *JAMA Netw Open*. 2022;5(4):e226136. doi:10.1001/jamanetworkopen.2022.6136

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Original Investigation | Infectious Diseases

Association of Follow-up Blood Cultures With Mortality in Patients With Gram-Negative Bloodstream Infections

A Systematic Review and Meta-analysis

Population

Hospitalized adult patients with gram-negative bloodstream infection (GN BSI)

Study Selection

Search through March 11, 2022:

- Standard databases (e.g. Medline, Embase)
- IDWeek conferences
- ASHE journal
- ClinicalTrials.gov

1º Outcome

In-hospital or 30-day mortality

Key Question 1 (KQ1)

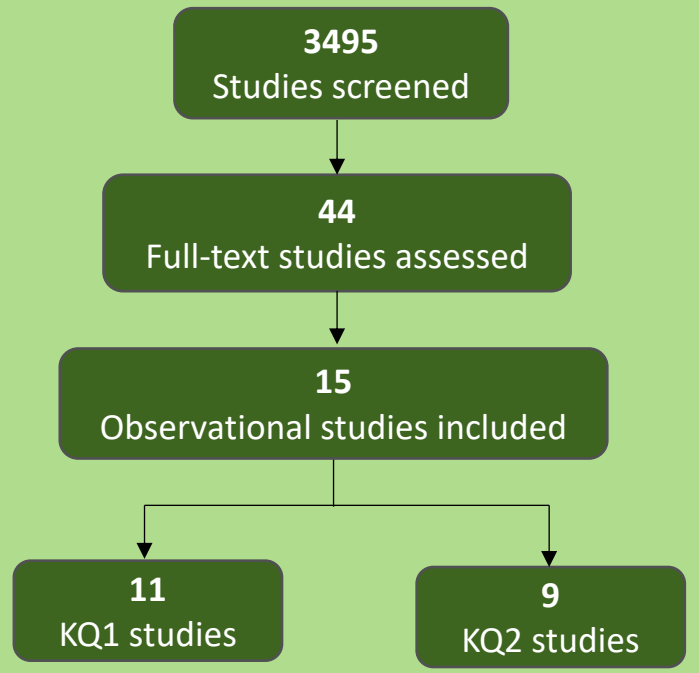
Are follow-up blood cultures (FUBC) associated with ↓mortality?

Key Question 2 (KQ2)

Are (+) FUBC associated with ↑mortality vs. (-) FUBC?

Primary Analysis: Studies must have adjusted for acute illness in patients (e.g. matching, statistical adjustment)

Included Studies



- FUBCs generally 24h-7d after index culture

ASHE = Antimicrobial Stewardship and Healthcare Epidemiology

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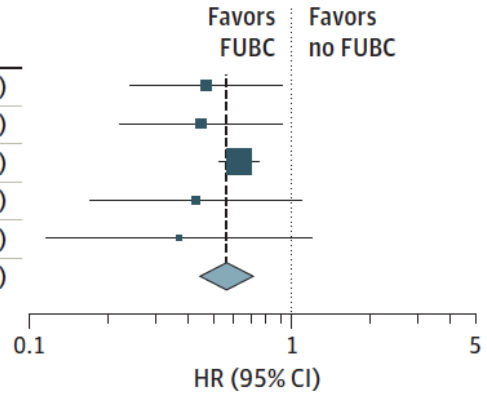
Thaden JT, et al. *JAMA Netw Open*. 2022;5(9):e2232576. doi:10.1001/jamanetworkopen.2022.32576

Follow-Up Blood Cultures in Gram-Negative Bloodstream Infections: Results

Key Question 1.
Association of Obtaining FUBC with Mortality

Source	HR (95% CI)
Amipara et al,[9] 2021	0.47 (0.24-0.91)
Giannella et al,[7] 2020	0.45 (0.22-0.92)
Maskarinec et al,[5] 2020	0.63 (0.53-0.75)
Green et al,[21] 2021	0.43 (0.17-1.08)
Mitaka et al,[22] 2021	0.37 (0.12-1.19)
Total	0.56 (0.45-0.71)

Heterogeneity: $\chi^2_4 = 2.57$ ($P = .63$); $I^2 = 0\%$



Significantly ↓ **mortality with FUBC** vs. no FUBC

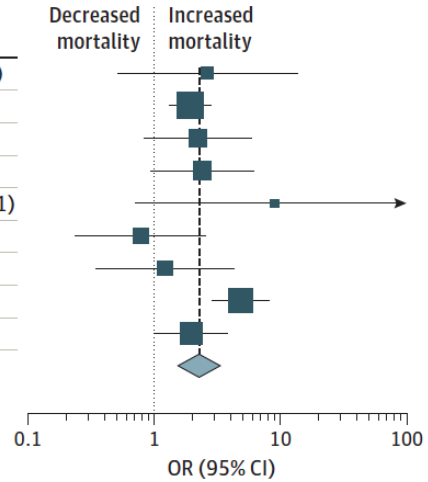
HR 0.56 (95% CI 0.45-0.71)

- N=5 studies met criteria (adequate adjustment)
- Little heterogeneity (thought small number of studies)

Key Question 2.
Association of (+) FUBC with Mortality

Source	OR (95% CI)
Amipara et al,[9] 2021	2.64 (0.51-13.55)
Maskarinec et al,[5] 2020	1.93 (1.33-2.80)
Chan et al,[11] 2021	2.22 (0.83-5.93)
Wiggers et al,[8] 2016	2.40 (0.93-6.19)
Groft et al,[32] 2021	9.00 (0.71-113.81)
Spaziante et al,[28] 2020	0.78 (0.24-2.53)
Mitaka et al,[29] 2020	1.21 (0.34-4.31)
Kim et al,[30] 2022	4.87 (2.90-8.17)
Kang et al,[31] 2013	1.98 (1.03-3.81)
Total	2.27 (1.54-3.34)

Heterogeneity: $\chi^2_8 = 14.48$ ($P = .07$); $I^2 = 45\%$



- Only 2 studies met criteria of adequate adjustment → no meta-analysis performed on KQ2
- Exploratory analysis (n=9 studies) indicated ↑ mortality with (+) FUBC vs. (-) FUBC

Thaden JT, et al. *JAMA Netw Open*. 2022;5(9):e2232576. doi:10.1001/jamanetworkopen.2022.32576

How will this change your practice?

- Consider a more systematic approach to obtaining FUBC in patients with GN BSI
- Limitations:
  - Randomized clinical trial data lacking
  - Relatively small number of studies in meta-analysis
  - Mechanism of morality benefit with FUBC not well characterized
  - Limited subgroup analyses to identify groups who could safely avoid FUBC
  - Impact of logistics/workflow in healthcare not well characterized

Thaden JT, et al. *JAMA Netw Open*. 2022;5(9):e2232576. doi:10.1001/jamanetworkopen.2022.32576

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Staphylococcus aureus Bacteremia Antibiotic Treatment Options (SABATO) Trial

Population

Hospitalized adult patients with **low-risk** *S. aureus* bloodstream infection (SAB)

Low-risk (ALL):

- (-) FUBC after 24-96 hr
- No s/sx metastatic infection
- IV catheters removed by 4 days
- No prosthetic heart valve or grafts
- Not severely immunosuppressed

Study Design

- Randomized trial
- Open-label
- Non-inferiority

5-7 d
IV antibiotics

Randomization

7-9 d
Oral Switch Therapy

Follow-Up
Days 30 & 90

7-9 d
IV Standard Therapy

Follow-Up
Days 30 & 90

1º Outcome

90-d SAB-Related Complication (composite):

- Relapsing bacteremia
- Deep-seated SA infection
- Attributable mortality

2º Outcomes

- Length of stay
- Survival
- Complications of IV therapy
- *Clostridioides difficile*-associated diarrhea

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Kaasch A, et al. ECCMID. 2022 April 25.
ClinicalTrials.gov. NCT01792804. https://clinicaltrials.gov/ct2/show/NCT01792804

Staphylococcus aureus Bacteremia Antibiotic Treatment Options (SABATO) Trial: Results

Population

5331 patients screened
→ 213 enrolled

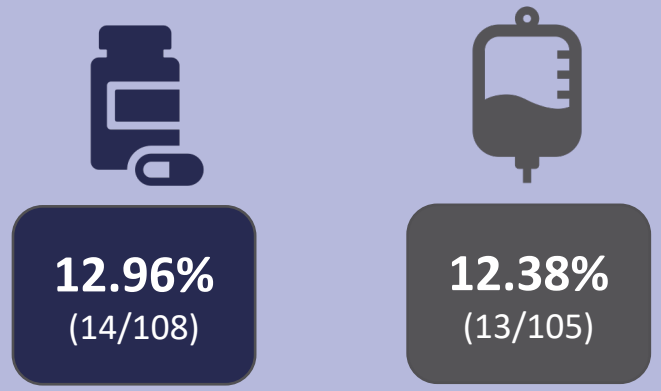
- Only 5% MRSA
- Sources primarily venous catheters & SSTIs

Oral Switch Therapy Options

Oral Switch Therapy	First-line	Alternative
MSSA	TMP/SMX 1 DS PO Q12h	Clindamycin 600mg PO Q8h
MRSA	TMP/SMX 1 DS PO Q12h	Linezolid 600mg PO Q12h

1º Outcome

90-day SAB-Related Complication



Oral switch **non-inferior** to IV standard therapy

2º Outcomes

- ↓ **length of stay** by median 4 days (p=0.02)

- ↔ 90-day mortality (7% vs. 5%, p=0.6)

- ↔ Complications of IV therapy (8% vs. 18%, p=0.1)

- ↔ *C. difficile* associated diarrhea (2% vs. 1%, p=0.6)

Kaasch A, et al. ECCMID. 2022 April 25.
ClinicalTrials.gov. NCT01792804. https://clinicaltrials.gov/ct2/show/NCT01792804

How will this change your practice?

- More support to consider expanding SAB treatment options beyond parenteral therapy (inpatient and outpatient)
- May optimize transitions of care in select SAB patients
- Limitations:
  - Full publication pending
  - Low-risk patients remain the minority of SAB cases
  - Few MRSA cases
  - Limited oral regimens specifically evaluated, mainly TMP/SMX

Thaden JT, et al. *JAMA Netw Open*. 2022;5(9):e2232576. doi:10.1001/jamanetworkopen.2022.32576

ZeNix Trial: Bedaquiline-Pretomanid-Linezolid (BPaL) Regimens for Drug-Resistant Tuberculosis

- Evaluated **low-dose linezolid 600 mg PO daily** as part of BPaL triple therapy
- N=181 patients aged > 14 years with drug-resistant tuberculosis

	Low-Dose Therapy Linezolid 600 mg x 26 weeks	vs.	Standard Therapy Linezolid 1200 mg x 26 weeks
Effectiveness:	**91%** Favorable Outcome		**93%** Favorable Outcome
Safety:	**24%** ↓ Peripheral Neuropathy **2%** ↓ Myelosuppression		**38%** Peripheral Neuropathy **22%** Myelosuppression

New Regimens

B	Bedaquiline
Pa	Pretomanid
L	Linezolid
±M	Moxifloxacin

- WHO Rapid Communication[2] (May 2022): Recommended **low-dose as preferred** for linezolid-containing in BPaLM & BPaL regimens for drug-resistant tuberculosis
- WHO Drug-Resistant Tuberculosis Guideline Update[3] (Dec 2022): **BPaLM x 6 months** recommended as preferred regimen for drug-resistant tuberculosis (vs. 9- or 18-month regimens)

1. Conradie F, et al. *N Engl J Med*. 2022;387:810-823. doi:10.1056/NEJMoa2119430.
2. WHO. Rapid Communication. 2022 May 2. https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2.
3. WHO. Drug-Resistant TB Guidelines. 2022 Dec 15. https://www.who.int/publications/i/item/9789240063129.

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SHINE Trial: Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

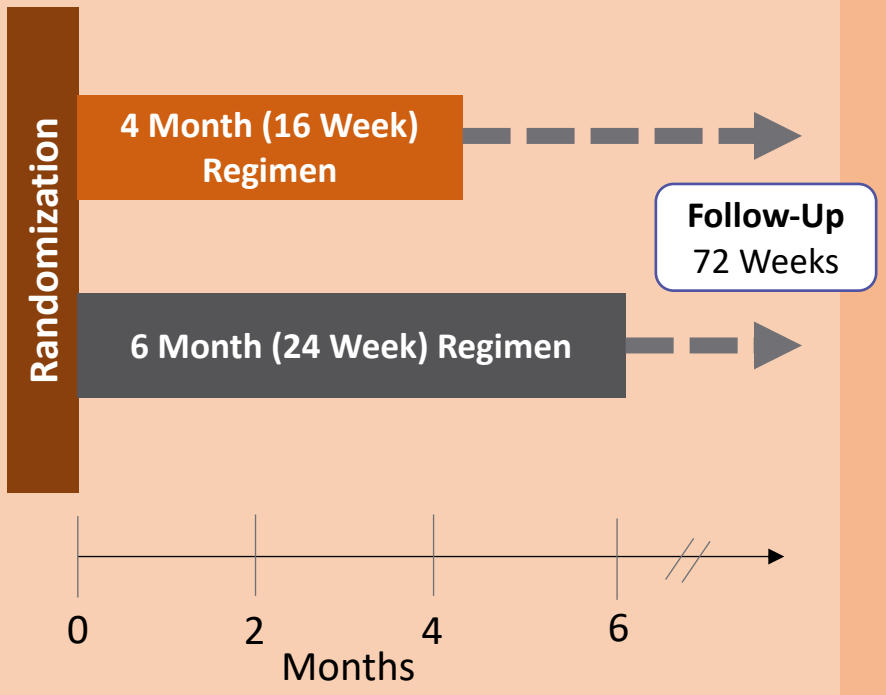
Population

Nonsevere, symptomatic, drug-susceptible tuberculosis in children aged <16 years

- N=1204 pts (52% male, 11% HIV+)
- Median (range) 3.5 yr (2 mo-15 yr)

Study Design

- Randomized trial
- Open-label
- Non-inferiority (6% margin)
- Multicenter
- Parallel-group

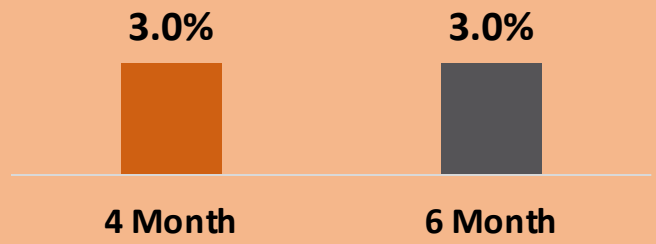


Treatment: Rifampin, isoniazid, pyrazinamide, ± ethambutol (using fixed dose combinations)

1º Outcome

Unfavorable Status

Adjusted Difference -0.4%
(95%CI, –2.2 to 1.5)



2º Outcomes

- Comparable ≥ Grade 3 Adverse Event (3% vs. 3%)

Now preferred regimen for 3 mo to 16 yr in WHO Guidelines for Drug-Susceptible Tuberculosis Treatment (May 2022)[2]

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1. Turkova A, et al. *N Engl J Med*. 2022;386:911-922. doi:10.1056/NEJMoa2104535.
2. WHO. 2022 May 24. https://www.who.int/publications/i/item/9789240048126.

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Novel Agents

Clostridioides difficile Infection (CDI) – 2 new FDA-approved products!

- Fecal microbiota spores, live-brpk (Vowst®); formerly SER-109
  - 4 capsules PO once daily x 3d
  - Live Firmicutes bacterial spores given after antibiotics
  - Superior to placebo in preventing CDI recurrence at 8 weeks[1]
- Fecal microbiota suspension, live-jslm (Rebyota®); formerly RBX2660
  - Human fecal microbiota 150 mL suspension for enema delivery
  - Superior to placebo in preventing CDI recurrence at 8 weeks[2]

1. Feuerstadt P, et al. *N Engl J Med*. 2022;386:220-229. doi:10.1056/NEJMoa2106516
2. FDA. VRBPAC Committee Meeting Announcement. 2022 Sept 22. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-22-2022-meeting-announcement

Investigational Agents

Gram-Negative Bacterial Infections

- Cefepime/enmetazobactam (Phase 3)
  - Includes novel beta-lactamase inhibitor with activity against ESBLs
  - Evaluated for treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis (AP) due to gram-negative urinary pathogens
  - **Treatment Arms:**
    - Cefepime/enmetazobactam 2 G/0.5 G IV Q8h as a 2-hr infusion x 7 days
    - Piperacillin/tazobactam 4 G/0.5 G IV Q8h as a 2-hr infusion x 7 days
  - **Clinical Cure with Microbiological Eradication:**
    - **79.1%** cefepime/enmetazobactam vs. 58.9% piperacillin-tazobactam (difference 21.2%, 95% CI 14.3-27.9)
  - Cefepime/enmetazobactam met noninferiority and superiority criteria for clinical cure
  - Limitations: Few minorities included, only 18% ESBL-producing pathogens

Kaye KS, et al. *JAMA*. 2022;328:1304-1314. doi:10.1001/jama.2022.17034

Investigational Agents

Gram-Negative Bacterial Infections

- Sulbactam/durlobactam (Phase 3)
  - Studied vs. colistin therapy in patients with *Acinetobacter baumannii-calcoaceticus* complex (ABC) infections
  - 28-day all cause mortality in carbapenem-resistant ABC cohort:
    - **19%** for sulbactam/durlobactam vs. 32.3% for colistin
  - Clinical cure rates:
    - **61.9%** for sulbactam/durlobactam vs. 40.3% for colistin
- Promising potential agent for CRABC infections

Contagion Live. 2022 Apr 26. https://www.contagionlive.com/view/novel-antibiotics-for-resistant-pathogens-results-of-attack-trial-for-sulbactam-durlobactam

Honorable Mentions

- iDIAPASON trial: RCT on 8 vs. 15 days of antibiotics for *P. aeruginosa* VAP
- TARGET trial: RCT examining piperacillin-tazobactam therapeutic drug monitoring in sepsis
- CAMERA2 post-hoc analysis of risk factors for nephrotoxicity
- IV Vitamin C in sepsis associated with increased risk of death and persistent organ dysfunction
- Temporal temperature measurement not as accurate as oral measurement in Blacks
- RAIN trial: IV to PO antibiotic switch in neonates with comparable outcomes & decreased hospital stay vs. IV alone
- NORAPP trial: Antibiotic prophylaxis may not be necessary in transperineal prostate biopsies
- Time to appropriate antibiotics and 30-day mortality
- Administer beta-lactam prior to vancomycin as first dose therapy for bloodstream infections
- Oral fluoroquinolones and TMP/SMX vs. oral beta-lactams for GN BSI
- Impact of organism reporting from endotracheal aspirate cultures on antimicrobial prescribing practices in mechanically ventilated patients
- Beta-lactam plus doxycycline for CAP decreases mortality
- NABOGO trial: Ertapenem for anogenital gonorrhea

Honorable Mentions

- Bouglé A, et al. Intensive Care Med. 2022 Jul;48(7):841-849. doi:10.1007/s00134-022-06690-5. Epub 2022 May 13.
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Learning Assessment Question

How will the preliminary results from the recent SABATO trial, which evaluated IV to PO therapy switch for low-risk *S. aureus* bloodstream infection (SAB), be *most likely* to change your practice?

A. Switch from IV to PO antibiotic therapy will become standard of care for all SAB patients
B. Switch from IV to PO antibiotic therapy may optimize transitions of care options for select SAB patients
C. Clarifies optimal oral dosing for SAB across wide variety of antibiotics
D. Clarifies optimal oral dosing in obese SAB patients

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@julie_justo
justoj@cop.sc.edu