![ARLG - Antibacterial Resistance Leadership Group]

Antibacterial Resistance Leadership Group (ARLG)

Fast Antibiotic Susceptibility Testing for Gram-Negative Bacteremia (FAST) Trial

## 8th Annual Texas Medical Center Antimicrobial Resistance and Stewardship Conference: Jan 16, 2025

Principal Investigator – Ritu Banerjee, MD, Ph.D

We need faster blood culture diagnostics

- **Sepsis due to bloodstream infections**
  - 30% mortality with ineffective treatment
  - $15 billion in hospital costs (US)
- **Blood cultures**
  - Organism ID and antimicrobial susceptibility testing (AST) results >2 days AFTER a positive culture
- **Early treatment** is critical but empiric
  - Ineffective = poor outcomes
  - Overtreatment = drug resistance, AEs
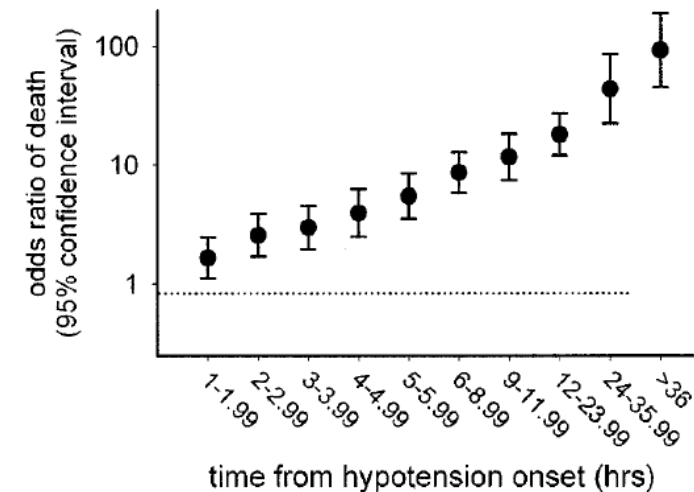
Background Study– <u>RA</u>pid <u>ID</u>entification and <u>S</u>usceptibility testing for <u>G</u>ram <u>N</u>egative bacteremia (RAPIDS GN) trial
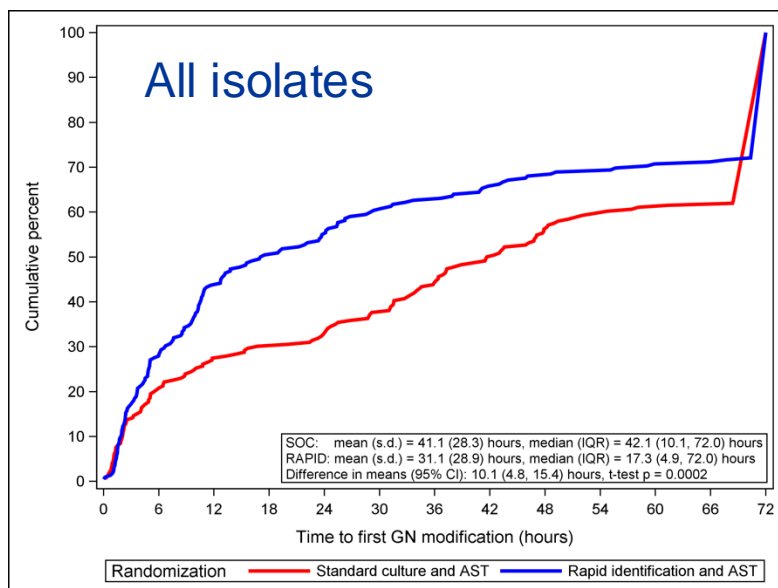
- **Hypothesis**: Rapid _phenotypic_ AST methods enable optimal management of GN bacteremia

- **Multicenter, prospective RCT** in 2 US sites to evaluate antibiotic use and outcomes among patients with **GNB bacteremia** who have blood culture evaluated using standard methods vs. rapid ID/AST

- Randomized to either:
  - Standard culture and AST (SOC) [N=226] or
  - Rapid identification and AST using Pheno System (Accelerate Diagnostics) and SOC [N=222]

- Both arms had antibiotic stewardship review
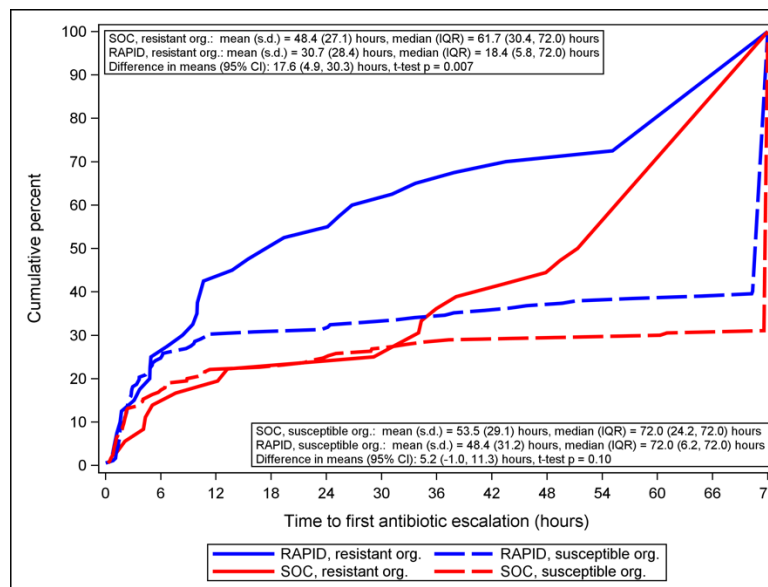- Primary outcome: Time to antibiotic change

Results from RAPIDS GN
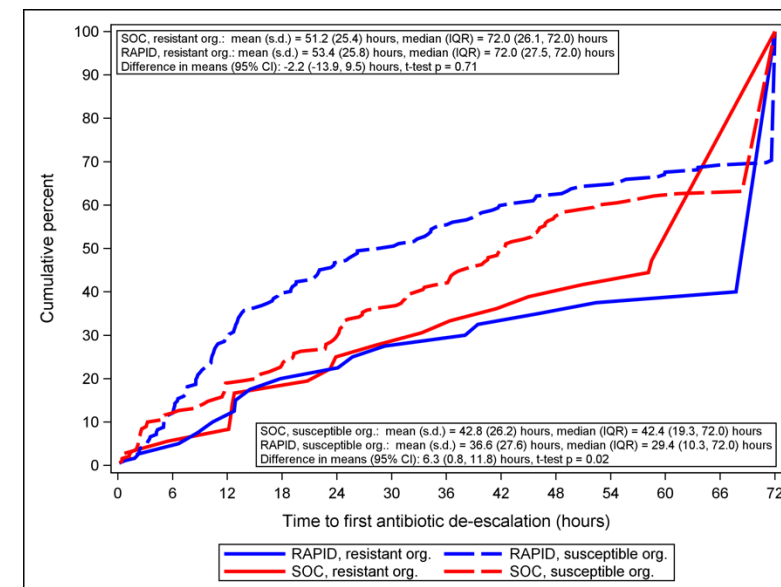# Antibiotic changes vary by testing method and resistance
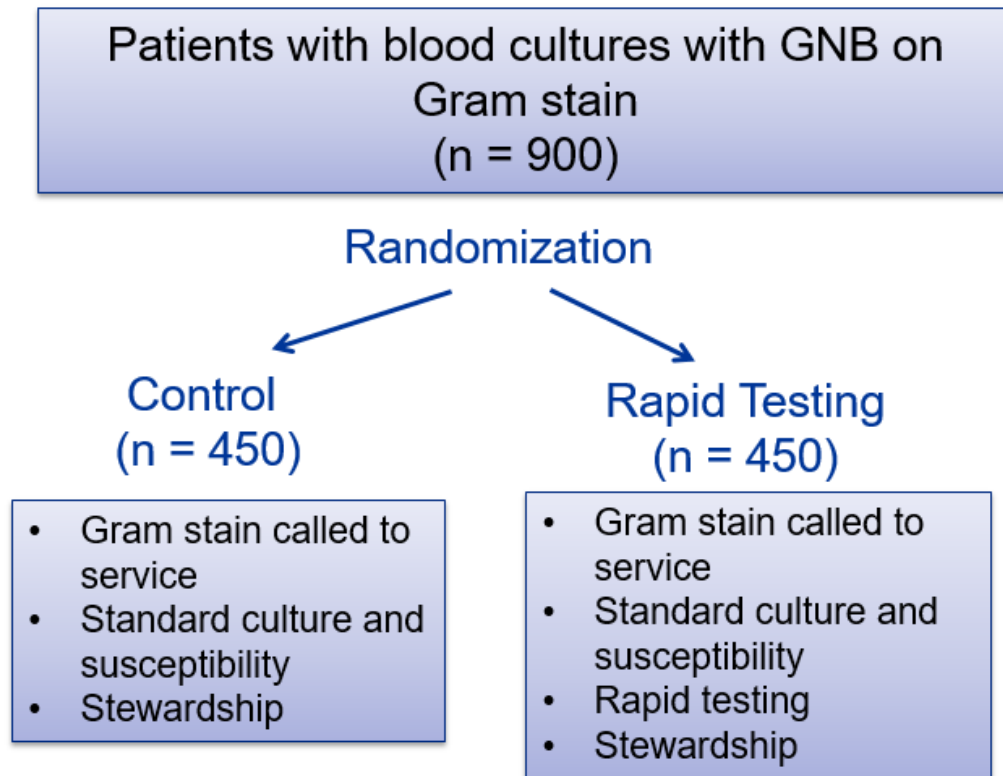
Conclusions from RAPIDS GN

- Rapid _phenotypic_ AST methods implemented with stewardship can optimize treatment of GNB bloodstream infections

- Antibiotic modifications occurred **faster with rapid testing** than SOC

- **Limitations:**
  - **Not powered to detect differences in clinical outcomes**
  - **Low rates of MDR GNB**
  - **Costly rapid AST method**

Fast Antibiotic Susceptibility Testing for Gram-negative bacteremia (FAST)

- **Hypothesis:** Rapid *phenotypic* AST methods implemented with stewardship can optimize treatment and improve outcomes of GNB bloodstream infections

- **Objective:** To compare **clinical outcomes** among patients with GNB BSI who have isolate AST determined using rapid AST method (VITEK Reveal™) vs. SOC methods *in areas with high resistance rates*

Multisite, multinational, prospective RCT

Patients with blood cultures with GNB on Gram stain (n = 900)

Randomization

Control (n = 450)
- Gram stain called to service
- Standard culture and susceptibility
- Stewardship

Rapid Testing (n = 450)
- Gram stain called to service
- Standard culture and susceptibility
- Rapid testing
- Stewardship

- Participants with Gram-negative bacilli (GNB) bloodstream infection will be randomized to either:
  - Standard culture and AST (SOC) or
  - Rapid AST in addition to SOC

- Both arms will receive stewardship consultation per SOC

- Enroll 900 patients with GN BSI

Rapid Metabolomic-Based AST: VITEK REVEAL™

- Approved in Europe *and US*
- Measures changes in volatile organic compounds emitted during bacterial growth
- Mean TAT ~5 hours
- Does not provide ID
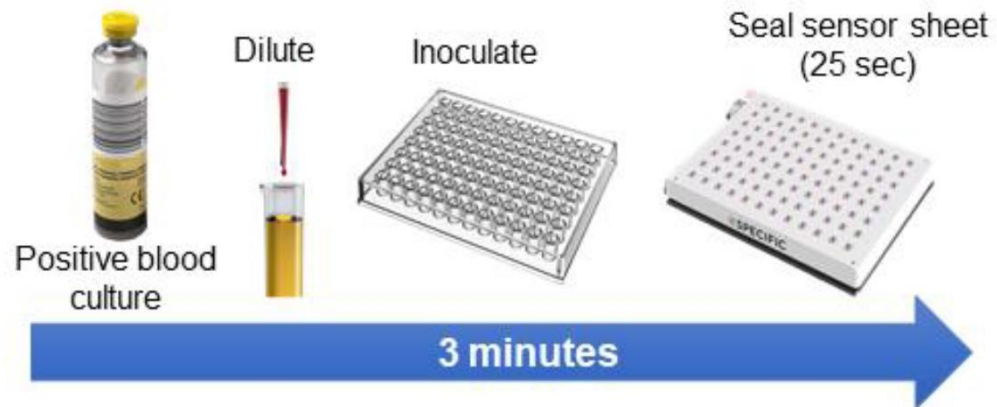
Eligibility Criteria

- **Inclusion criteria**
  - Positive blood culture with Gram stain showing GNB
  - Hospitalized at the time of randomization

- **Exclusion criteria**
  - Positive blood culture for GNB within prior 7 days (if known at time of randomization)
  - Deceased at time of randomization
  - Gram-positive bacilli, Gram-negative cocci, multiple morphologies of GNB, and/or yeast detected on Gram stain of blood culture
  - Previous enrollment in this study

Endpoints

- **Primary** – Desirability Of Outcome Ranking (DOOR) at 30 days
  - Alive no deleterious events
  - Alive with 1 to 3 deleterious events
  - Death

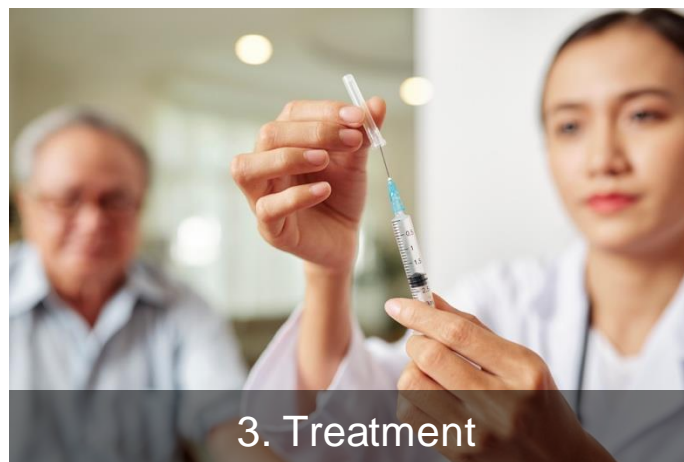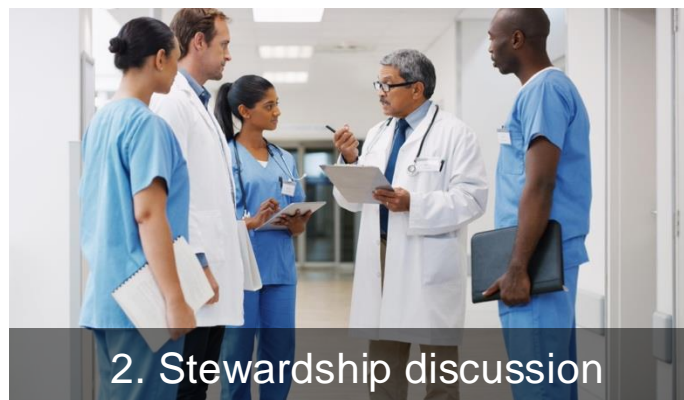| Deleterious Events include any of the following		
Unsuccessful discharge: • Not discharged from index hospitalization • Readmission	Lack of clinical response: • Relapse of bacteremia with the same species causing the index infection • Local suppurative complications not present at randomization • Seeding distant sites with infecting organism after randomization	Undesirable events • Acquisition of hospital-acquired infection – C. difficile – Multidrug resistant organisms (MDROs) • Post-randomization renal failure defined by RIFLE criteria: – Three-fold or greater increase in serum creatinine – New renal replacement therapy

- **Secondary**
  - All-cause in-hospital mortality up to 30d
  - LOS in hospital and ICU up to 30d
  - Acquisition MDRO/*C. difficile* up to 30d
  - Time to abx modification in the first 72h
  - Time to effective antibiotic treatment within 72h

- **Exploratory**
  - Discrepancies between REVEAL and SOC
  - Changes in antibiotics that match at least one AS recommendation

Study Flow

1. Lab testing

2. Stewardship discussion

3. Treatment

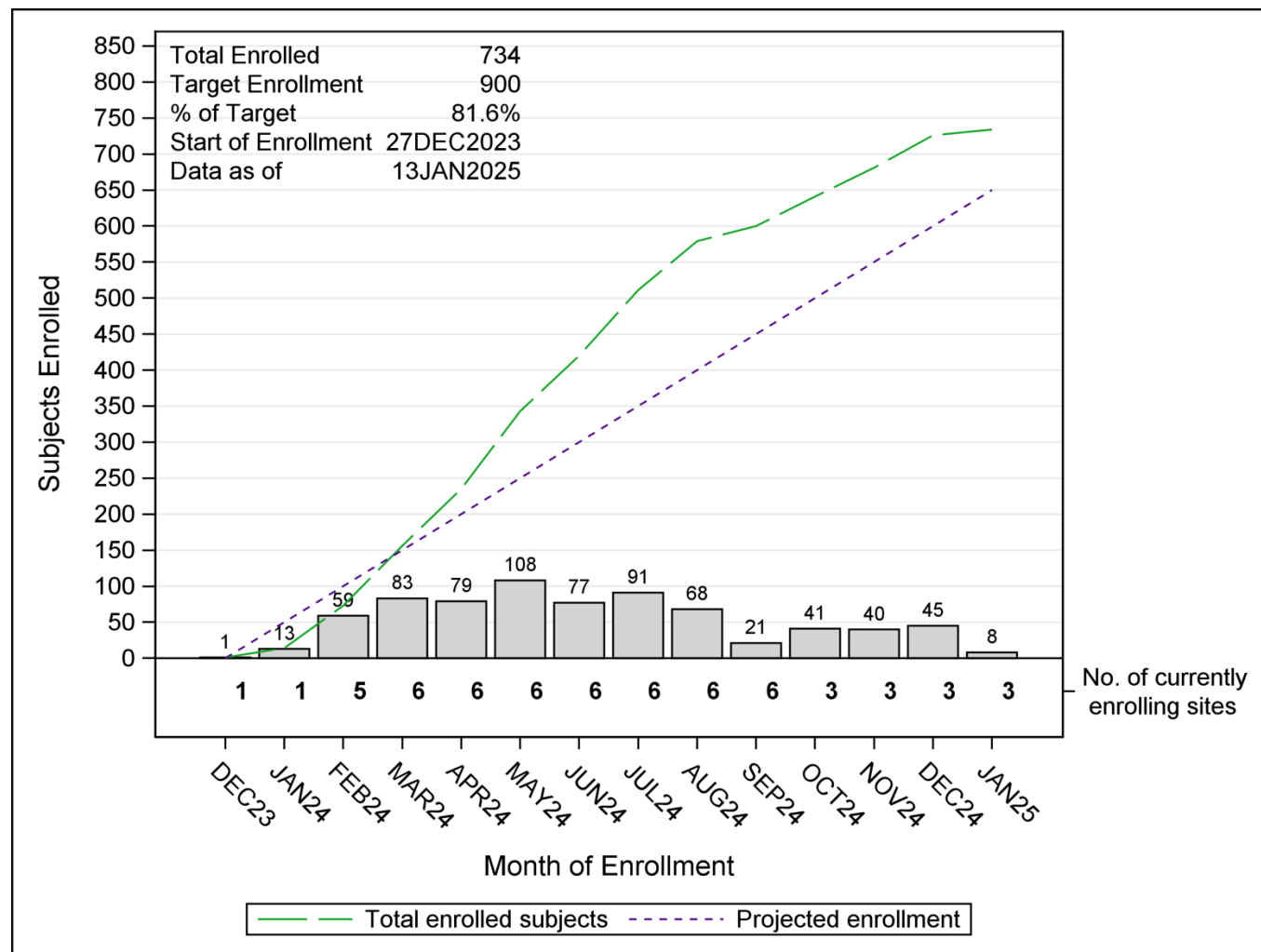4. Clinical Outcomes

Sites

1 site

2 sites

3 sites

1 site

MDR GN prevalence
Lab capacity
ASP
Rapid ID method
REVEAL regulatory approval

Total accrual by month, updated 13-Jan 2025

Accrual by country, updated 13-Jan 2025

Site	# randomized
Spain*	63
Israel*	298
Greece	331
India	42
Total	734 (82% of 900)

*Enrollment at these sites was capped in Aug 24

Baseline characteristics by country, 15-Dec 2024

Characteristic[1]	Spain (N=62)	Israel (N=291)	Greece (N=285)	India (N=20)	Total (N=658)
Age in years [median (Q1, Q3)]	74 (65, 82)	76 (67, 83)	72 (60, 81)	53 (36, 65.5)	74 (65, 82)
Male sex N (%)	37 (60%)	166 (57%)	158 (55%)	13 (65%)	374 (57%)
ICU at enrollment N (%)	13 (21%)	29 (10%)	54 (19%)	7 (35%)	103 (16%)
Qpitt > 0 N (%)	29 (47%)	78 (27%)	187 (66%)	12 (60%)	306 (46%)
Charlson score [median (Q1, Q3)]	5 (4, 7)	5 (4, 7)	4 (3, 6)	3 (0, 4)	5 (3, 6)
Immunocompromise N (%)	16 (26%)	68 (23%)	77 (27%)	3 (15%)	164 (25%)

[1]Among subjects with complete data

Microbiology by country, 15-Dec 2024

Organism characteristics[1,2]	Spain (N=62)	Israel (N=291)	Greece (N=285)	India (N=20)	Total (N=672)
Monomicrobial	60 (97%)	277 (96%)	239 (91%)	15 (100%)	591 (94%)
Cephalosporin-resistance[3]	11 (18%)	102 (38%)	98 (43%)	9 (60%)	220 (38%)
Carbapenem-resistance	1 (2%)	4 (1%)	87 (35%)	5 (42%)	97 (16%)

[1]Among eligible subjects with complete data; missing data in 36 in Greece, 5 in India, 1 in Israel
[2]Subject-level data
[3]Ceftriaxone, ceftazidime, or cefuroxime

Select organisms by country, updated 15-Dec 2024

Organism*	Spain (N=64)	Israel (N=307)	Greece (N=330)	India (N=20)	Total (N=721)
On-panel	62 (97%)	249 (81%)	245 (83%)	10 (67%)	566 (83%)
E. coli	39 (61%)	147 (48%)	77 (26%)	5 (33%)	268 (39%)
K. pneumoniae	13 (20%)	48 (16%)	76 (26%)	1 (7%)	138 (20%)
P. aeruginosa	4 (6%)	20 (7%)	25 (9%)	2 (13%)	51 (8%)
P. mirabilis	1 (2%)	20 (7%)	21 (7%)	0	42 (6%)
A. baumanii	0	4 (1%)	30 (10%)	0	34 (5%)
E. cloacae	2 (3%)	3 (1%)	7 (2%)	2 (13%)	14 (2%)
S. typhi	0	0	0	3 (20%)	3 (0%)
S. marcescens	0	2 (1%)	7 (2%)	0	9 (1%)

*Isolate-level data; some subjects had >1 isolate

Challenges/Delays

- COVID-19

- Specific Dx bought by bioMérieux

- Contracting delays

- Reagent shipment delays

- Geopolitical conflict

Acknowledgements

- ARLG/DCRI

- bioMerieux
- Parexel
- Participating sites