Impact of Rapid Identification and Phenotypic Results on Clinical, Economic, and Antimicrobial Stewardship Outcomes in Patients with Gram-Negative Bacteremia

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Background

- Gram-negative bacilli (GNB) bacteremia is associated with significant morbidity, healthcare spending, and challenge clinically with increasing antimicrobial resistance.[1-3]
- Timely and effective antibiotic therapy is a critical determinant of clinical outcome.
  - Risk of mortality increases 7.6% with each hour delaying administration in septic shock.[4]
  - In the United States, approximately 1 in 5 patients receive ineffective empiric therapy which is independently associated with increased risk of mortality regardless of antimicrobial resistance, sepsis, or septic shock.[5]
- Broad-spectrum antibiotics, such as antipseudomonal β-lactams, improve the odds of adequate coverage but carry risk of causing collateral harm.
  - Empiric exposure beyond 48 hours is an independent risk factor for new *Clostridioides difficile* infection (CDI).[6]
  - Risk of emergence of antimicrobial resistance increases 4% with each additional day of empiric exposure beyond 48 hours.[7]
- Molecular rapid diagnostic tests (mRDT) enable earlier identification (ID) of pathogens and are associated with improved time to effective therapy, improved clinical outcomes, and lower hospital costs compared to conventional antimicrobial susceptibility testing (AST) methods alone.[8,9]
- Accelerate Pheno™ (Accelerate Diagnostics, Tucson, AZ) is a novel system that provides both ID and AST results directly from a positive blood culture sample in roughly 8 hours.

Objective

Evaluate the impact of Accelerate Pheno™ (AP) on clinical, economic, and antimicrobial stewardship (AMS) outcomes in patients with GNB bacteremia.

Methods

- Single-center, quasi-experimental study compared outcomes pre-/post- AP to a historical standard of mRDT (BioFire® FilmArray® BCID Panel, bioMérieux, Durham, NC) and conventional AST (VITEK®2, bioMérieux) with pharmacist-driven AMS intervention.
  - Periods: November 4, 2019 – July 4, 2020 (PRE); November 4, 2020 – July 4, 2021 (POST)

Inclusion criteria

- Admitted inpatients at least 18 years of age
- Positive blood culture with an on-AP-panel GNB
  - *Acinetobacter baumannii*, *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa*, *Serratia marcescens*

Exclusion criteria

- Pregnant
- Positive blood culture with >1 organism
- Palliative care, hospice care, or death before final AST results
- Positive blood culture with the same organism and source within 7 days

Outcomes

Primary

- Time to targeted antibiotic therapy (TTT)

Secondary

- Time to first intervention (TFI-) following Gram stain (GS), ID, and AST results
- Antipseudomonal days of therapy (DOT)
- Antibiotic intensity score (AIS) total at 96 hours following GS result
- Hospital and ICU length of stay (LOS)
- Hospital-acquired CDI
- Inpatient all-cause mortality
- Hospital costs for antibiotics and microbial testing

Statistical Analysis

With alpha set *a priori* at 0.05, a minimum of 132 bacteremic episodes per arm was required to achieve 80% power for detecting a 10-hour decrease in TTT.[10] Analyses were performed in SPSS (IBM Corp., Armonk, NY) using the Mann-Whitney U test for all nonparametric continuous data and using the Chi-square or Fisher's exact test for all nominal data.

Results

Figure 1: Enrollment

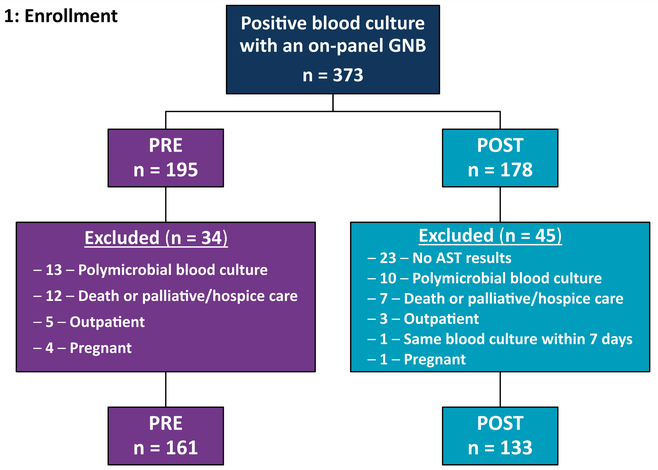


Table 1: Baseline Characteristics

Characteristic	PRE (n = 161)	POST (n = 133)	*P* value
Age, median years (IQR)	73 (64–81)	71 (64–80)	0.26
Female sex, n (%)	83 (52)	66 (50)	0.74
Hospitalization in prior 30 days, n (%)	25 (16)	31 (23)	0.09
Pitt bacteremia score, median (IQR)	1 (0–2)	1 (0–3)	0.054
ESBL isolate, n (%)	13 (8)	11 (8)	0.95
ID consult, n (%)	118 (73)	101 (76)	0.6
Pharmacist intervention, n (%)	69 (43)	77 (58)	< 0.05
Intervention accepted, n (%)	62 (90)	66 (86)	0.45

ESBL: Extended-spectrum β-lactamase; ID: Infectious diseases

Table 2: Primary and Secondary Outcomes

Outcome	PRE (n = 161)	POST (n = 133)	*P* value
TTT, median h (IQR)	50 (44–92)	28 (14–55)	< 0.05
TFI-GS, median h (IQR)	3.7 (NA)	1.6 (1.2–2.3)	0.28
TFI-ID, median h (IQR)	1.5 (0.5–4.2)	1.3 (0.6–3.5)	0.78
TFI-AST, median h (IQR)	9.1 (4.2–32)	6.3 (1.5–22)	0.1
Antipseudomonal DOT, median days (IQR)	2 (0–4)	1 (0–4)	0.37
AIS, median (IQR)	8 (3–9)	6 (4–9)	0.44
Hospital LOS, median days (IQR)	4.4 (3.1–6.4)	4.6 (3.1–7)	0.67
ICU LOS, median days (IQR)	2 (1.5–3.5)	2 (0.9–3.9)	0.9
Hospital-acquired CDI, n (%)	2 (1)	4 (3)	0.42
Inpatient all-cause mortality, n (%)	7 (4)	9 (7)	0.36
Antibiotic costs†‡, median (IQR)	$89.14 (63–133)	$97.14 (55–133)	0.86
Microbial testing costs‡, median	$119.15	$156.79	< 0.05

TTT: Time to targeted therapy; TFI-: Time to first intervention following; GS: Gram stain; NA: Not applicable; ID: Identification; AST: Antimicrobial susceptibility testing; DOT: Days of therapy; AIS: Antibiotic intensity score; LOS: Length of stay; ICU: Intensive care unit; CDI: *Clostridioides difficile* infection
† Priced at wholesale acquisition cost
‡ Values adjusted to reflect the relative cost difference rather than actual costs

Table 3: Microbiologic Result Turnaround Time

Result	PRE (n = 161)	POST (n = 133)	*P* value
Blood Cx Collection to GS*, median h (IQR)	15.1 (13–20)	15.7 (14–20)	0.33
GS to ID, median h (IQR)	1.3 (1.2–1.6)	2.4 (2–3.6)	< 0.05
ID to AST, median h (IQR)	43 (38–47)	6 (5–11)	< 0.05
GS to AST, median h (%)	45 (39–48)	9 (8–15)	< 0.05

Cx: Culture; GS: Gram stain; ID: Identification; AST: Antimicrobial susceptibility testing
*All blood cultures both PRE and POST were incubated in BACT/ALERT® 3D (bioMérieux)

Figure 2: Time To Targeted Therapy

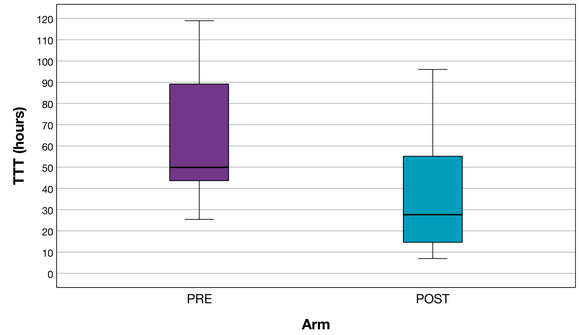
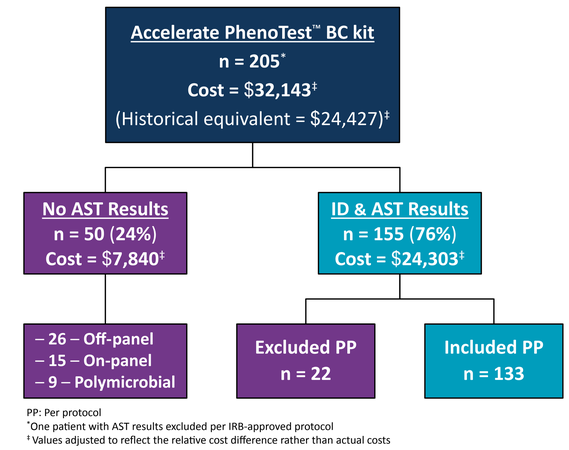


Figure 3: AP Performance



PP: Per protocol
*One patient with AST results excluded per IRB-approved protocol
‡ Values adjusted to reflect the relative cost difference rather than actual costs

Discussion

- Similar results have been reported in previous literature on AP.[10-12]
  - Improved time to targeted/optimal therapy
  - Clinical outcomes comparable to those of mRDT ID coupled with AMS intervention
  - Complete ID and AST in 75% of GNB blood cultures, and at least 10% off-panel GNB
- Additional education, AP result-based guidelines, and automated notification of AP AST results likely had an impact on pharmacists to intervene more POST-AP.
- Findings may not be generalizable to institutions with differing patient populations, rates of GNB species or resistance, antibiotic formularies, laboratory or AMS practices.

Conclusion

Implementation of Accelerate Pheno™ to an established AMS program was associated with improved time to targeted antibiotic therapy and higher microbial testing costs. Clinical, AMS, and other economic outcomes were unchanged.

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