# Impact of Rapid Antimicrobial Susceptibility Testing in Gram-Negative Rod Bacteremia: a Quasi-experimental Study

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**ABSTRACT** Clinical justification for rapid antimicrobial susceptibility testing (AST) in Gram-negative rod (GNR) bacteremia is compelling; however, evidence supporting its value is sparse. We investigated the impact of rapid AST on clinical and antimicrobial stewardship outcomes in real-world practice. We performed a before-and-after quasi-experimental study from February 2018 to July 2019 at a tertiary hospital of the 24-h/day, 7-day/week implementation of the direct Vitek 2 AST method from positive blood culture broth for GNR bacteremia with electronic isolate-specific de-escalation comments and daytime antibiotic stewardship program (ASP) intervention. The primary outcome was time to appropriate antibiotic escalation or de-escalation, and secondary outcomes included time to oral antibiotic stepdown, hospital length of stay (LOS), all-cause 30-day mortality, 7-day incidence of acute kidney injury (AKI), and 30-day incidence of *Clostridioides difficile* infection (CDI). A total of 671 GNR isolates were included from 643 adult patients. Among patients for whom antibiotic change occurred after rapid AST result, rapid AST was associated with a trend in decreased time to escalation or de-escalation (hazard ratio, 1.22; 95% confidence interval [CI], 0.99 to 1.51; $P = 0.06$), with median times of 52.3 versus 42.2 h. Secondary outcomes were similar in both groups and include median time to oral antibiotic stepdown, LOS, all-cause mortality, and incidence of AKI and CDI. Rapid AST led to improved stewardship measures but did not impact clinical patient outcomes. These results highlight that multiple variables in addition to the timing of the AST result contribute to clinical outcome and that further intervention may be required to clinically justify rapid AST implementation.

**KEYWORDS** antibiotic stewardship, Gram-negative bacteria, bacteremia, rapid diagnostic tests

Gram-negative rod (GNR) bacteremia and sepsis are associated with significant morbidity and mortality that increase with delay in effective antibiotic therapy (1). Rapid methods for organism identification directly from positive blood cultures have emerged over the last decade, including matrix-assisted laser desorption–ionization–time of flight (MALDI-TOF) and rapid multiplexed PCR panels, with turnaround time of 1 to 5 h (2–4); however, standard phenotypic antimicrobial susceptibility testing (AST) requires 2 to 4 days given the time required for subculture and AST (5). As such, rapid AST methods directly from positive blood cultures have been developed, which include the FDA-cleared Accelerate Pheno system (6–8) and short incubation disk diffusion (9, 10). Rapid nucleic acid tests have also been developed for the identification of certain resistance mechanisms (4, 11, 12), but due to technical limitations and complexity of

resistance mechanisms, they do not currently capture the full antimicrobial resistance profiles found in GNRs for which rapid phenotypic testing is necessary. Rapid AST methods were developed with the goals of optimizing the timing of initiation of appropriate antibiotics, reducing time to antibiotic de-escalation, facilitating timely transition to oral antibiotics, and limiting adverse patient outcomes and emergence of antibiotic resistance, all significant antibiotic stewardship program (ASP) objectives (13). However, little is known about the real-world clinical impact of these rapid AST procedures and whether the expense and effort associated with their implementation is justified by improved patient outcomes.

Vitek 2 (bioMérieux, Marcy l'Étoile, France) is an automated instrument that is FDA cleared for AST from isolated bacterial colonies. The Stanford Health Care Clinical Microbiology Laboratory developed and validated a simple and rapid sample processing method for Vitek 2 AST directly from BD Bactec FX (Becton, Dickinson, Franklin Lakes, NJ) blood culture bottles (BCBs) positive for GNRs (14). Hands-on time is about 10 min per sample, and mean turnaround time from AST setup to results is 9 h for *Enterobacterales* (formerly *Enterobacteriaceae*) and 12 h for *Pseudomonas aeruginosa* (7). Vitek 2 direct AST was implemented for routine care in November 2018. Here, we present the findings of our investigation on the impact of rapid AST on ASP measures and clinical outcomes in patients with GNR bacteremia in real-world clinical practice.

## MATERIALS AND METHODS

**Ethics.** This work was conducted as part of a hospital-sponsored quality improvement project, and thus institutional review board (IRB) approval was not required.

**Study design.** This study was a before-and-after quasi-experimental study at Stanford Health Care (SHC) to compare ASP measures and clinical outcomes of direct Vitek 2 testing in patients with GNR bacteremia. The retrospective period included cases from 8 February 2018 to 9 October 2018, and the prospective period included cases from 1 November 2018 to 15 July 2019. Data collection was performed from 1 November 2018 to 30 August 2019, retrospectively for the preintervention period and prospectively for the intervention period. The primary outcome was the time from positive blood culture to appropriate escalation or de-escalation (based on antibiogram result and the protocol in Table S1 in the supplemental material), and secondary outcomes included time to oral antibiotic stepdown, all-cause 30-day mortality, length of stay (LOS), 7-day incidence of acute kidney injury (AKI), and 30-day incidence of *Clostridioides difficile* infection (CDI).

**Study population.** Consecutive adult (defined as ≥18 years old) inpatients at SHC with bloodstream infection (BSI) with *Enterobacterales* or *Pseudomonas aeruginosa* were included (see Table S2 in the supplemental material). Positive blood cultures with these organisms were included from all shifts. Stanford Hospital is a 613-bed adult tertiary care academic hospital with extensive programs for cancer care and hematopoietic stem cell and solid organ transplant. Exclusion criteria included patients with a previous BSI with the same organism in the preceding 7 days, blood cultures with mixed morphologies on Gram stain, and patients who died within 48 h of the positive blood culture Gram stain. Blood cultures that were only recognized to be polymicrobial after Gram stain were included in the study and analysis. Similarly, individuals with ≥1 positive blood culture with GNR were included in the study and analysis if at least 7 days had elapsed between the 2 collections.

**AST and ASP.** All procedures were completed at the SHC Clinical Microbiology Laboratory by licensed technologists. Blood cultures were collected and incubated in the BD Bactec FX system. Once positive, a Gram stain was performed, reported in the electronic medical records (EMR) system, and called to the ordering provider within 1 h. Prior to the direct Vitek 2 implementation, all phenotypic AST was performed from rapid subculture (2 to 4 h for *Enterobacterales* and up to 6 h for *Pseudomonas aeruginosa*), followed by the standard setup on the MicroScan WalkAway *plus* system (Beckman Coulter, Brea, CA), with a total AST turnaround time of 1 to 2 days (preintervention). On 1 November 2018, the laboratory implemented direct Vitek 2 AST for all *Enterobacterales*- and *Pseudomonas aeruginosa*-positive blood cultures using a processing method previously described (intervention) (14). In brief, organism identification was performed by direct MALDI-TOF extraction from positive blood culture broth on a Bruker Biotyper instrument (Bruker, Billerica, MA) using a laboratory-developed lysis and differential centrifugation procedure (14). This procedure provides organism identification results within 30 min and is batched in the laboratory workflow such that results are available within 4 h. In parallel, the same steps of lysis and differential centrifugation were performed from positive blood culture broth, leading to a bacterial suspension that is set up on the Vitek 2 AST-GN81 card. Blood culture identification and susceptibility testing results were reported in the EMR system but not called to the ordering provider.

The ASP group at SHC during the study period consisted of two infectious disease (ID) physicians and two infectious disease pharmacists who provided services during regular working hours (8 a.m. to 5 p.m.) on weekdays. Comments specific to the isolate AST profile were developed and integrated into the Epic EMR system for real-time electronic reporting with AST results in addition to an email alert to the ASP group (Table S1). Emails were sent in real-time for each direct Vitek 2 AST result in the study. If sent during off-hours, the email would be read and acted on by the ASP team the next workday during regular

working hours. Definitions of antibiotic escalation and de-escalation were established for this study (see Table S3 in the supplemental material). During working hours, the ASP group reviewed the case and communicated treatment recommendations directly with the treating team if appropriate. Patients for whom the infectious diseases service was already consulted and cases for which appropriate antibiotic change based on AST result and ASP assessment had already been performed by the primary team prior to case review were not approached by ASP.

**Data collection.** Chart review was performed by three users for the ASP data (W.A., E.M., and L.M.) and by two users for the microbiological data (B. E. and C.A.H.). All data were reviewed by one user (C.A.H.). Data points collected included demographic and clinical characteristics, microbiologic data, ASP intervention data, admission details, and patient outcome data.

**Data analysis.** The primary outcome was time to appropriate escalation and de-escalation in hours (time between Gram stain result to the first antibiotic change). Secondary outcomes included (i) time to oral antibiotic stepdown (time between Gram stain and oral antibiotic change for patients initially receiving intravenous [i.v.] antibiotics), (ii) LOS in hours (time between Gram stain to hospital discharge), (iii) all-cause 30-day mortality, (iv) incidence of AKI at 7 days (defined as a ≥0.3 rise in creatinine within 48 h), and (v) CDI incidence at 30 days (defined as predicted toxin-positive *C. difficile* PCR testing [15] with a compatible clinical syndrome).

**Statistical analysis.** Statistical analysis was performed using R version 3.5.0. Time to escalation or de-escalation, time to oral antibiotic stepdown, and LOS were assessed by Cox proportional hazards regression analysis in both unadjusted and adjusted models, including the *a priori*-determined potential confounders of age, sex, Charlson comorbidity index, infection source, active empirical therapy, and febrile neutropenia. Censoring was performed based on mortality and on individuals who underwent antibiotic escalation or de-escalation before availability of AST results. All-cause 30-day mortality, AKI incidence, and CDI incidence were analyzed by logistic regression analysis, both crude and adjusted for the same potential confounders as above. A statistical threshold of $P \leq 0.05$ was considered significant, and a complete case analysis was performed.

Assuming a two-sided alpha error of 0.05, power of 80%, and censorship rate of 0.01, and based on a time to de-escalation and escalation of 60 and 48 h in the preintervention and intervention groups, the required sample size per group was calculated to be 320 patients per group. A larger total number of individuals per group was screened to ensure enough samples to account for exclusions in each group and lack of antibiotic de-escalation or escalation after rapid AST result.

**Data availability.** The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

## RESULTS

A total of 671 GNR bloodstream infections from 643 unique patients were included in total, with 336 samples in the preintervention group and 335 in the intervention group (Fig. 1). Clinical and demographic characteristics were similar in both groups, with the exceptions of a higher proportion of urinary infections and individuals in the emergency department in the intervention group and a higher proportion of active empirical antimicrobial therapy based on the AST result in the preintervention group (Table 1). About half of patients were immunocompromised (51.1%), most commonly from solid organ malignancy (26.4%), leukemia or lymphoma (14.8%), solid organ transplant (6.6%), or being recipients of a bone marrow transplant (1.9%). Across both groups, urinary source of infection was most common, followed by intraabdominal source. Median time from blood culture positivity to AST result communication in the preintervention group to ASP was 24.1 h (interquartile range [IQR], 21.5 to 29.4) for *Enterobacterales* and 25.8 h (IQR, 20.9 to 29.3) for *Pseudomonas aeruginosa*, compared to 12.3 h (IQR, 10.4 to 17.2) and 16.3 h (IQR, 14.7 to 19.4), respectively, in the intervention group.

The 4 most common pathogens in both groups were *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* complex, and *Pseudomonas aeruginosa* (Fig. 2). The most common antimicrobial agent administered empirically at the time of Gram stain was piperacillin-tazobactam (46.2%), followed by ceftriaxone (18.0%) and cefepime (12.8%). Recommended antibiotics for de-escalation included ceftriaxone, ciprofloxacin, or trimethoprim-sulfamethoxazole (TMP-SMX), depending on the isolate susceptibility profile (Table S1) and individual patient characteristics. Primary and secondary outcomes in the preintervention and intervention groups are shown in Table 2. Results were similar between the adjusted and unadjusted models for all endpoints. There was a trend for shorter time to appropriate escalation or de-escalation in the intervention group (hazard ratio [HR], 1.22; 95% CI, 0.99 to 1.51; $P = 0.06$), with median times of 52.3 versus 42.2 h (Fig. 3). When restricted to cases with an ASP interventional recommendation that was followed by the primary team, median time to appropriate escalation
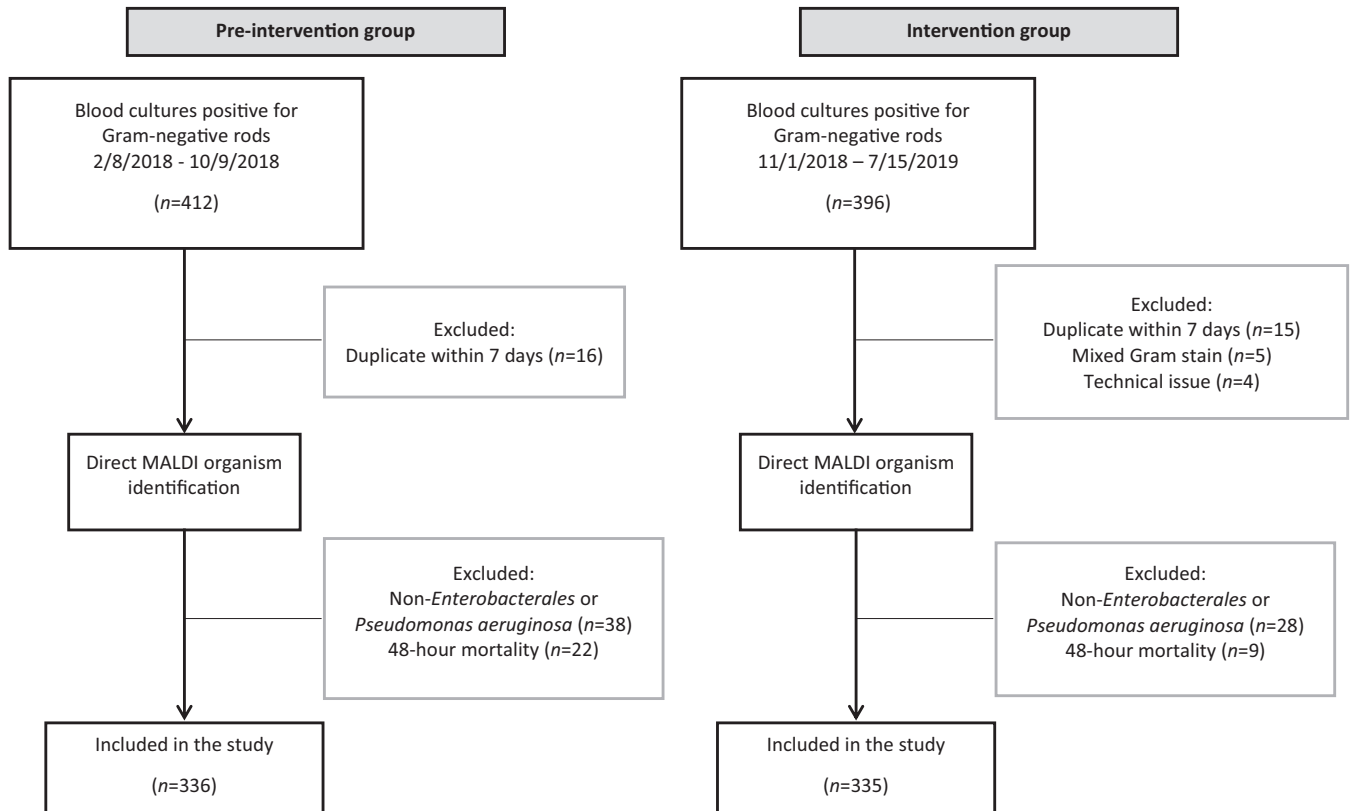
**FIG 1** Schematic overview of blood culture selection for the preintervention and intervention groups.

or de-escalation in the intervention group was reduced compared to that in the intervention group as a whole (HR, 1.68; 95% CI, 1.25 to 2.26; $P = 0.001$), with median times of 52.3 versus 38.4 h. Antibiotic escalation occurred in a similar time frame in both groups, with median times of 46.6 versus 45.0 h. The most commonly used antibiotic for escalation was oral ciprofloxacin (9.4%), followed by ertapenem (8.1%) and meropenem (7.3%). Antibiotic escalation was more frequent in the intervention subgroup of 47 ceftriaxone-nonsusceptible *E. coli* and *K. pneumoniae* isolates than in the rest of the intervention group (54.0 versus 30.2%; $P = 0.0001$). There was a trend for a shorter time to antibiotic de-escalation in the intervention group, with median times of 52.2 versus 43.4 h. The most commonly used antibiotic for de-escalation was cefepime (15.3%), followed by oral ciprofloxacin (9.4%) and oral levofloxacin (3.1%). Oral ciprofloxacin was used for both escalation and de-escalation, based on the definitions in Table S3. Time to oral antibiotic stepdown was similar in both groups, and the most commonly used agents for oral antibiotic stepdown were ciprofloxacin (55.7%), levofloxacin (17.9%), amoxicillin-clavulanic acid (11.3%), and TMP-SMX (6.9%).

Secondary outcomes were similar in the two groups and included LOS (HR, 1.02; 95% CI, 0.87 to 1.19; $P = 0.8$), with median times of 96.1 h in the preintervention group versus 115.2 h in the intervention group. In addition, the two groups showed a similar 7-day incidence of AKI (17.3% in the preintervention versus 13.1% in the intervention group; $P = 0.1$), all-cause 30-day mortality (7.1% versus 4.8%; $P = 0.2$), and 30-day CDI incidence rate (2.1% versus 1.8%; $P = 0.8$).

Prior to the start of the rapid method, the ASP was minimally involved in real-time review and/or therapeutic recommendations for GNR bacteremia. In contrast, the ASP group directly intervened for therapeutic recommendations in 114 (34.0%) of cases in the intervention group. Of these, the acceptability of recommendations was high, with 97 (85.1%) of their recommendations being followed. The remaining recommendations were not followed mainly due to physician preference (64.7%) or treatment of concur-

**TABLE 1** Demographic characteristics in the preintervention and intervention groups

| Demographic characteristic[c] | Preintervention (n = 336) | Intervention (n = 335) | P value (LR)[d] |
|---|---|---|---|
| Sex, male (no. of patients [%]) | 178 (53.0) | 176 (52.5) | 0.9 |
| Age (yrs) (mean [SD]) | 63.9 (18.2) | 63.1 (17.7) | 0.5 |
| Charlson comorbidity index (mean [SD]) | 5.2 (2.8) | 5.1 (3.0) | 0.9 |
| Immunocompromised (no. of patients [%]) | 171 (50.9) | 172 (51.3) | 0.9 |
| | | | |
| Source of bacteremia (no. of patients [%]) | | | 0.04 |
| Urinary | 117 (34.8) | 131 (39.1) | |
| Intra-abdominal | 106 (31.6) | 104 (31.0) | |
| Central venous catheter | 19 (5.7) | 15 (4.5) | |
| Respiratory | 19 (5.7) | 21 (6.3) | |
| Surgical site infection | 23 (6.9) | 5 (1.5) | |
| Other | 10 (3.0) | 19 (5.7) | |
| Unknown | 42 (12.5) | 40 (11.9) | |
| | | | |
| Patient location at time of blood culture draw (no. of patients [%]) | | | 0.001 |
| Emergency department | 210 (62.5) | 225 (67.2) | |
| Inpatient ward | 89 (26.5) | 75 (22.4) | |
| Intensive care unit | 16 (4.8) | 11 (3.3) | |
| Other | 21 (6.3) | 24 (7.2) | |
| | | | |
| Mixed (polymicrobial) growth (no. of patients [%]) | | | 1 |
| Yes | 35 (10.4) | 34 (10.1) | |
| No | 301 (89.6) | 301 (89.9) | |
| | | | |
| Empiric antibiotic therapy (no. of patients [%]) | | | 0.3 |
| Piperacillin-tazobactam | 157 (46.7) | 153 (45.7) | |
| Ceftriaxone | 52 (15.5) | 69 (20.6) | |
| Cefepime | 44 (13.1) | 42 (12.5) | |
| | | | |
| No. (%) of isolates susceptible | | | |
| Ceftriaxone | 263 (78.3) | 248 (74.0) | 0.2 |
| Ceftazidime[a] | 288 (85.7) | 293 (88.0) | 0.4 |
| Ciprofloxacin | 278 (82.7) | 256 (76.4) | 0.04 |
| TMP-SMX | 247 (73.5) | 226 (67.5) | 0.1 |
| | | | |
| Empirical antibiotic active against the GNR (no. of patients [%])[b] | | | 0.4 |
| Yes | 311 (92.6) | 294 (87.8) | |
| No | 25 (7.4) | 32 (9.6) | |
| | | | |
| Escalation (no. of patients [%]) | 118 (35.1) | 122 (36.4) | 0.7 |
| De-escalation (no. of patients [%]) | 151 (44.9) | 151 (45.1) | 1 |
| No antibiotic escalation or de-escalation (no. of patients [%]) | 67 (19.9) | 62 (18.5) | 0.6 |

[a]Missing data for 2 isolates in intervention group.
[b]Missing data for 9 isolates in intervention group.
[c]Empirical, antibiotic at or around the time of Gram stain; GNR, Gram-negative rod; TMP-SMX, trimethoprim-sulfamethoxazole. No missing data were present unless otherwise noted.
[d]LR, logistic regression.

rent febrile neutropenia (17.7%). The ASP group did not intervene in 221 (66.0%) cases. This was due to the infectious disease (ID) team already consulting on the case (31.2%), the treating team having made the appropriate antibiotic change per ASP review prior to ASP involvement (20.4%), or the patient no longer being hospitalized at the time of ASP review (22.2%).

## DISCUSSION

The recognition that early initiation of appropriate antibiotic therapy is associated with improved outcomes in patients with serious infections, as well as the fact that early de-escalation reduces exposure to unnecessarily broad antibiotic therapy, has led to a desire to shorten the time required to complete antimicrobial susceptibility testing (16–20). This has generated growing interest and technology development designed to shorten the turnaround time of antimicrobial susceptibility testing for positive blood cultures as adoption of the rapid methods may facilitate achievement of important ASP targets. Implementation of rapid AST systems, however, requires significant investment
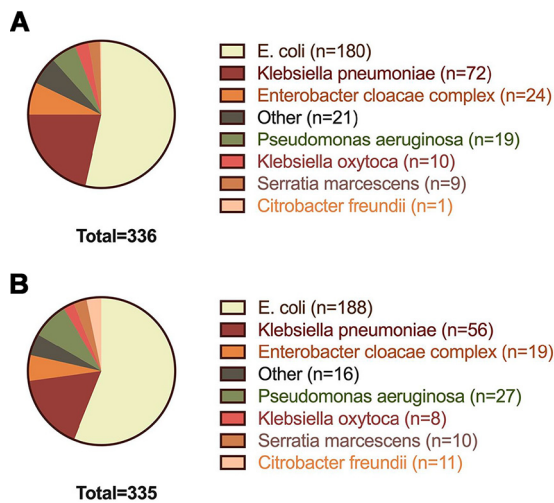
**FIG 2** Gram-negative rod species distribution in the preintervention (A) and intervention (B) groups.

of resources in instrument acquisition, reagent costs, and staffing. Given the paucity of evidence regarding GNR bacteremia, it is currently unclear if the clinical impact of rapid testing justifies the testing cost. Antimicrobial prescribing is a complex process influenced by multiple variables in addition to timing of AST result availability. These include availability of expert clinical advice by, e.g., ASP teams, willingness of the treating team to modify therapy, severity of clinical illness, drug allergies, potential adverse effects, and a number of host factors, such as immunocompromise (21). Thus, understanding the role that each of these variables plays in facilitating improved outcomes with rapid direct AST may be essential for justifying clinical implementation of rapid AST.

In this study, we showed that implementation of rapid AST for GNR bacteremia with isolate-specific de-escalation comments provided electronically and part-time ASP intervention was associated with a trend toward reduction in time to appropriate escalation and de-escalation of therapy but no changes in clinical outcomes. Thus, a bundled approach with more intensive ASP intervention may be required to leverage the full potential of rapid AST technology. The Pheno system (Accelerate Diagnostics Inc., Tucson, AZ) was the first rapid phenotypic AST commercial platform to receive FDA clearance, and it produces AST results within 7 h (6–8). Similarly, rapid disk diffusion

**TABLE 2** Primary and secondary outcomes in the preintervention and intervention groups

| Outcome parameter[a] | Preintervention | Intervention | Unadjusted HR[b] (Cox) or OR (LR)[c] | Unadjusted P value (Cox or LR)[c] | Adjusted[d] HR (Cox) | Adjusted[d] P value (Cox or LR) |
|---|---|---|---|---|---|---|
| Time to appropriate escalation or de-escalation in h (median [95% CI]) | 52.3 (48.2–60.0) | 42.2 (37.4–48.0) | 1.24 (1.02–1.51) | 0.03 | 1.22 (0.99–1.51) | 0.06 |
| Time to appropriate escalation in h (median [95% CI]) | 46.6 (37.9–64.4) | 45.0 (33.0–60.7) | 1.23 (0.96–1.57) | 0.1 | 1.28 (0.98–1.68) | 0.08 |
| Time to appropriate de-escalation in h (median [95% CI]) | 52.2 (47.5–60.6) | 43.4 (37.4–54.5) | 1.27 (0.92–1.74) | 0.1 | 1.17 (0.83–1.65) | 0.4 |
| Time to oral antibiotic stepdown in h (median [95% CI]) | 105.8 (87.2–147.4) | 132.3 (102.8–195.7) | 0.92 (0.74–1.14) | 0.4 | 0.87 (0.69–1.10) | 0.2 |
| LOS in h (median [95% CI]) | 96.1 (86.0–107.2) | 115.2 (99.8–127.9) | 1.02 (0.87–1.19) | 0.8 | 0.92 (0.77–1.09) | 0.4 |
| 30-day all-cause mortality (no. [%]) | 24 (7.1) | 16 (4.8) | 0.65 (0.34–1.25) | 0.2 | 0.83 (0.39–1.77) | 0.6 |
| 7-day AKI incidence (no. [%]) | 58 (17.3) | 44 (13.1) | 0.72 (0.47–1.11) | 0.1 | 0.82 (0.51–1.31) | 0.4 |
| 30-day C. difficile incidence (no. [%]) | 7 (2.1) | 6 (1.8) | 0.86 (0.29–2.58) | 0.8 | 1.08 (0.32–3.60) | 0.9 |

[a]AKI, acute kidney injury; CI, confidence interval; LOS, length of stay.
[b]HR, hazard ratio; Cox, Cox proportional hazards model.
[c]OR, odds ratio; LR, logistic regression.
[d]Adjusted for age, sex, Charlson comorbidity index, empirical active therapy, infection source, and febrile neutropenia.
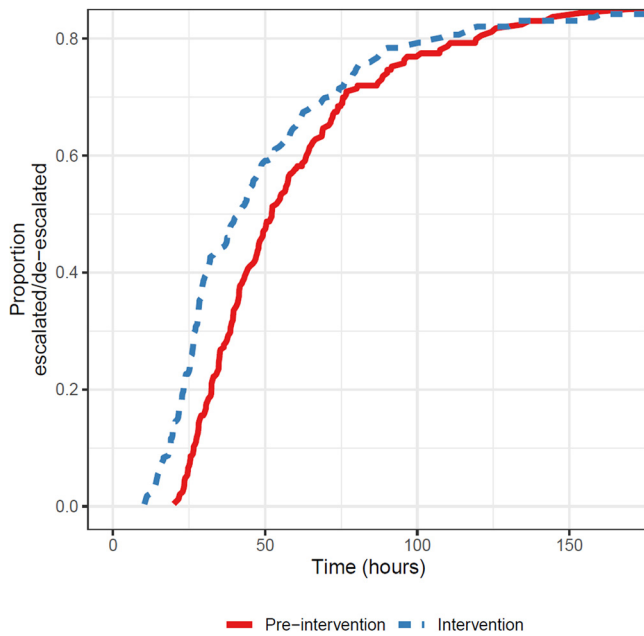
**FIG 3** Kaplan-Meier curves of time to appropriate escalation or de-escalation of antibiotic therapy.

testing methods from positive blood culture broth have been developed (9, 10, 22, 23). Real-world impact on patient outcomes has been examined in small studies that included Gram-negative bacteremia and showed improved time to optimal antimicrobial therapy but no change in clinical outcomes or antibiotic consumption (24–26). Selection of positive blood cultures from the daytime shift only and a dedicated team of investigators with full ASP intervention may explain shorter intervals for antibiotic change. Other published studies have considered the theoretical benefit of rapid testing with the Accelerate Pheno system and projected it to be beneficial (8, 27–30); however, this may not reflect real-world challenges in implementation of rapid AST strategy.

Approximately half of the participants included in this study were immunocompromised, including due to solid organ malignancy and leukemia or lymphoma; these two patient populations are at high risk for febrile neutropenia and bloodstream infection (31–33). Clinicians are often reluctant to de-escalate antibiotic therapy in neutropenic patients with bacteremia. Thus, patient characteristics, as well as clinician practice, are important factors to consider in assessing the clinical impact of rapid AST. Multicenter studies with representation of community hospitals are needed to measure the clinical impact of rapid AST in different patient settings, as impact may be greater in lower-risk populations. Furthermore, this study used rapid subculture-based AST in the preintervention period; greater impact would be expected in settings with AST methods with a longer turnaround time and/or with higher rates of drug-resistant GNR isolates.

In this study, the intervention subgroup with ceftriaxone-nonsusceptible *E. coli* or *Klebsiella pneumoniae* isolates was significantly more likely to have undergone antibiotic escalation compared to the rest of the intervention group (54.0 versus 30.2%), most commonly to a carbapenem antibiotic. The MERINO trial demonstrated a significant reduction in 30-day mortality in bloodstream infection patients treated with meropenem compared to piperacillin-tazobactam for such isolates (34). This finding bears important implications for antimicrobial stewardship, as patients who would previously have been considered candidates for antibiotic de-escalation are now maintained or escalated on a carbapenem antibiotic, limiting the potential impact of full phenotypic rapid AST. In addition, recent data support shortening duration of therapy for uncom-

plicated GNR bacteremia to 7 days, which should also be considered in assessing the overall impact of rapid AST testing (35).

This study's main strength is its comprehensive nature in presenting the largest number of Gram-negative rod isolates in a rapid AST clinical impact study to date, representing diverse clinical settings and patient populations with a high proportion of immunocompromised hosts and real-world conditions. The primary outcome analysis was restricted to individuals with an antibiotic change occurring after AST result availability, which better assesses the impact of the rapid AST method itself. In addition, this study assesses impact of the direct Vitek 2 procedure, a method that is inexpensive, robust, and broadly relevant, given it makes use of an instrument that is already widely in use in many laboratories. Furthermore, the multipronged approach was designed to optimize clinical impact and enable full potential of the method. This study showed the effectiveness of individual case-by-case email communication with an ASP and the feasibility of pursuing rapid testing continuously on all laboratory shifts.

However, this study presents limitations. First, this quasi-experimental study design cannot account for confounding factors or changes in practice over time the same way a prospective, randomized controlled trial would have. Furthermore, since this intervention was rolled out as a bundled approach, we were unable to isolate the impact of the rapid AST method alone. Previously published data have shown a positive impact from approaches combining a rapid diagnostic for identification and AST with either ASP, ID pharmacist, or fellow intervention (11, 24, 36, 37), with this combination approach yielding better results than those with conventional testing with ASP intervention alone (24) or with the rapid diagnostic method alone (11, 24). Second, the study was powered statistically for the primary outcome only. Nonetheless, the secondary clinical outcomes were considered important to include, given that they may reveal trends that warrant further assessment in future studies. The lack of clinical impact is consistent with that seen in previous studies (24, 25, 38). Third, ASP intervention was only performed during regular weekday working hours, which may contribute to the prolonged time to appropriate antibiotic change. Delay in time to escalation may also occur from delay in switch to oral ciprofloxacin from ceftriaxone, a common clinical scenario in this study. Given that ASP involvement in this study was associated with a lower time to antibiotic change, an intensified ASP approach may have led to greater clinical impact (39). Fourth, the direct Vitek 2 method is at least 2 h slower than the Accelerate Pheno System; thus, more rapid intervention could have been possible with this technology. However, in the case of both techniques, real-world turnaround time is slower (an additional 3 to 7 h) than published validation results (6, 8, 14, 38). Finally, this study used an AST method in the preintervention period that provided results within 1 to 2 days, which may have limited clinical impact compared to a more standard method with a 2- to 4-day turnaround time.

In summary, this study showed that the impact of rapid AST testing led to improved antibiotic stewardship measures but did not impact length of stay and other clinical outcome measures. These results highlight that variables in addition to the timing of AST result, including antibiotic stewardship program availability, contribute to clinical outcome and that further investigation is needed to identify key factors that may increase the clinical impact of rapid AST.

## SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1**, PDF file, 0.1 MB.

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