



Concise Communication

Impact of direct disk-diffusion testing on time to optimal antibiotic therapy

Tulip A. Jhaveri MBBS^{1,2} , Ahmad Taqi PharmD, BCIDP^{3,4}, Jeffrey C. Pearson PharmD, BCIDP^{3,a} and Sanjat Kanjilal MD MPH^{5,6,a} 

¹Division of Infectious Diseases, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, ²Division of Medical Microbiology, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, ³Department of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts, ⁴Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University, Kuwait, ⁵Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Healthcare Institute, Boston, Massachusetts and ⁶Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

We evaluated the impact of preliminary blood-culture antibiotic susceptibility testing on time to optimal antibiotic therapy in a cohort of 503 patients with monomicrobial bloodstream infections. The median time from blood-culture collection to optimal antibiotics was 17 hours earlier in the preliminary antibiotic susceptibility testing group.

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Bloodstream infections (BSIs) are a major cause of morbidity and mortality, with an incidence rate of 200 per 100,000 person years and 85,000 deaths annually in North America.¹ Initiation of empiric treatment should occur as soon as possible after patient triage. The choice of antibiotic must account for the risk of antimicrobial resistance while also avoiding unnecessary use of broad-spectrum therapy.² Reducing the time to report antibiotic susceptibilities for blood cultures is one of the most effective tools available to reduce adverse outcomes associated with under- or overtreatment. Accordingly, there is great interest in reducing the time to reporting of antibiotic susceptibility testing (AST) to guide treatment decisions in those with BSIs.^{3,4}

One method to shorten the time to reporting AST is to test directly from newly positive blood cultures, referred to as preliminary blood-culture susceptibility testing.⁵ This method is considered preliminary due to the possibility of polymicrobial infection and the unknown size of the inoculum. Thus, the utility of preliminary AST from blood-culture bottles reflects a tradeoff between reductions in the time to reporting results and the potential for errors. In June 2020, our clinical microbiology laboratory

discontinued the practice of preliminary blood culture AST to conserve resources in the setting of the COVID-19 pandemic. We utilized this opportunity to evaluate the impact of performing preliminary blood culture susceptibility testing on the time to reporting of results and initiation of optimal antibiotic therapy.

Methods

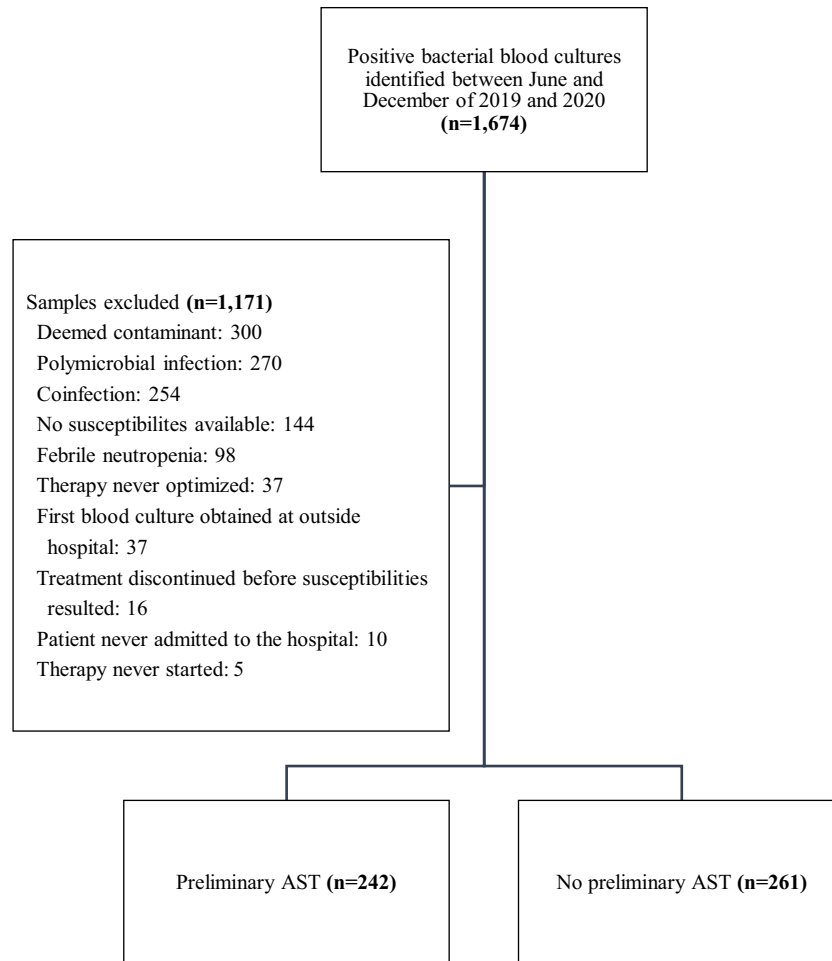
We conducted a single-center, retrospective analysis of adult inpatients with bloodstream infections from June to December 2019 (preliminary AST group) and June to December 2020 (no preliminary AST group). The clinical microbiology laboratory utilized the BacT/Alert Virtuo automated blood culture incubation system (bioMérieux, Marcy-l'Étoile, France) with FAN Plus bottles during the study period. Species identification was performed by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-TOF) using VITEK MS (bioMérieux). Preliminary blood culture susceptibility testing was performed by disk diffusion using 0.5 mL media drawn from a positive, previously vented, blood-culture bottle and plated onto Mueller-Hinton agar within 8 hours. Final AST was performed using VITEK 2 system (bioMérieux). Individuals who had at least 1 positive blood culture were evaluated for eligibility. We excluded patients with polymicrobial bacteremia, coinfection at a different site with another pathogen, or when positive blood cultures were deemed to be the result of contamination. Blood cultures were deemed contaminated if they grew coagulase-negative *Staphylococcus* spp, *Micrococcus* spp, *Bacillus* spp, or *Corynebacterium* spp from 1 of 4 blood-culture bottles and were considered such by the primary team. A full list of criteria is provided in Figure 1.

Author for correspondence: Tulip A. Jhaveri, MBBS, Division of Infectious Diseases, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216. E-mail: tjhaveri@umc.edu. Or Jeffrey C. Pearson, PharmD, Department of Pharmacy, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115. E-mail: jcpearson@bwh.harvard.edu

^aAuthors of equal contribution.

PREVIOUS PRESENTATION. Preliminary data were presented as an oral abstract (<https://www.abstracksonline.com/pp8/#!/9286/presentation/4846>) at the World Microbe Forum on June 21, 2021, held virtually.

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Polymicrobial infection: more than one bacterial species identified in blood culture

Coinfection: confirmed infection with a different bacterial species in a non-blood culture

Fig. 1. Study flow diagram.

The primary end point was median time from blood-culture collection to optimal antibiotic therapy in those with versus those without preliminary AST results. Optimal therapy was defined as receiving an antibiotic that was of the narrowest possible spectrum yet effective in treating the pathogen. A list of optimal antibiotics by pathogen is found in Supplementary Table S1. Secondary end points included median time to reporting of bacterial species and susceptibilities first reported in both groups. We also calculated rates of major errors (MEs) and very major errors (VMEs) between preliminary and final AST results for each antibiotic–pathogen combination with at least 30 samples over the study period. Statistical comparisons were performed using the Mann-Whitney *U* and χ^2 tests for continuous and categorical variables, respectively. The study was deemed exempt from approval by the Mass General Brigham Institutional Review Board.

Results

Of 1,674 unique patients with positive blood cultures during the study period, 503 patients met the inclusion criteria: 242 patients had preliminary AST performed and 261 had no preliminary AST (Fig. 1). The most common organisms isolated were *S. aureus* (119 of 503, 24%), *E. coli* (110 of 503, 22%), and *K. pneumoniae* (37 of 503, 7%). The distribution of organisms was similar between the

2 groups except for *K. pneumoniae*, which appeared more often in the groups with no preliminary AST (10% vs 5%; $P = .02$) (Supplementary Table S2). The median time to optimal therapy was 48 hours (interquartile range [IQR], 36–68) in the preliminary AST group compared to 66 hours (IQR, 50–77) in the group with no preliminary AST ($P < .01$) (Table 1). The median time to species identification between groups was similar, with the preliminary AST group being 42 hours (IQR, 36–47) versus 43 hours (IQR, 36–53) in the group with no preliminary AST, however the median time to report susceptibilities was 41 hours (IQR, 36–47) in the preliminary AST group compared to 64 hours (IQR, 58–70) in the group with no preliminary AST ($P < .01$). In those who had preliminary AST, MEs occurred in patients with 8 of 1,491 susceptible isolates (0.5%; 95% CI, 0.2%–1.1%) and VMEs occurred in patients with 11 of 332 resistant isolates (3.3%; 95% CI, 1.7%–5.8%). The most common ME occurred with cefepime and *Escherichia coli* (5 of 52, 10%) and VMEs with clindamycin and *Staphylococcus aureus* (9 of 18, 50%) (Supplementary Table S3).

Discussion

Preliminary blood-culture AST is a simple laboratory method intended to provide early insight into antibiotic susceptibilities for patients with BSIs. Although the advent of modern automated

Table 1. Time from Blood Culture Collection to Identification of Species, Reporting of Susceptibilities, and Initiation of Optimal Antibiotic Therapy

End Point	Time From Collection of Blood Cultures, Median Hours [IQR]		P Value
	Preliminary AST 2019 (n=242)	No Preliminary AST 2020 (n=261)	
Species identification reported	41.5 [36.1–47.3]	42.6 [36.3–52.8]	.05
Initial susceptibilities reported	41.2 [35.5–46.9]	64.2 [57.7–70.1]	<.01
Optimal antibiotic therapy initiated	48.2 [36–68]	66.2 [49.6–77]	<.01

Note. IQR, interquartile range; AST, antibiotic susceptibility testing.

blood culture incubation and AST systems has led many microbiology laboratories to discontinue preliminary AST, our results suggest that the practice still has potential value when other more expensive rapid testing techniques are not available. In this population, compared to final blood-culture AST, preliminary results were significantly quicker, though with notable limitations for specific pathogen–drug combinations.

Rapid molecular AST diagnostics have become key in treating patients with bacteremia. The average turnaround time to identify an organism and the presence of resistance genes on multiplex blood-culture identification panels generally ranged from 13 to 15 hours. However, genotypic methods have their own set of limitations,⁶ chief among them being cost. Phenotypic methods, such as preliminary blood-culture AST, could provide a relatively rapid and cost-effective alternative for performing susceptibilities. Several reports have described the performance characteristics of direct preliminary susceptibility testing^{7–10}; this study expands on the published literature to evaluate its impact on time to optimal antibiotic therapy.

Early administration of effective antibiotic therapy is independently associated with increased survival in patients with bloodstream infections.¹¹ However, selection of an overly broad-spectrum regimen is associated with drug toxicities and promotion of antibiotic resistance. In patients with BSIs, a fine balance is required between the need for aggressive broad-spectrum antibiotic treatment and the potential harm associated with antibiotics.¹² The faster turnaround times and reliability of preliminary AST, with subsequent earlier optimization of antibiotics as demonstrated in our study, reinforce its potential for routine use in clinical microbiology laboratories.

Our study had several limitations. Our analysis was retrospective in nature; therefore, there is the possibility for hidden confounding, including the impact of the COVID-19 pandemic, which may have biased the median time for clinicians to change antibiotics. Notably, however, the laboratory times to report species were similar before and during the pandemic. Second, with our strict inclusion criteria, the impact of preliminary AST was likely overestimated. Lastly, this single-center study performed at a tertiary-care, academic medical center; hence, patient mix, microbiology laboratory infrastructure, and provider practices may differ from other medical settings.

In summary, for patients with BSIs, time from blood-culture collection to optimal therapy was significantly reduced with preliminary blood-culture AST. However, additional studies are needed to better characterize the overall clinical impact of preliminary AST on patient outcomes, specifically when compared to potentially faster genotypic testing methods.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ash.2023.128>

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