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Early Detection of Antibiotic Resistance in Positive Blood Cultures: A Study from a Tertiary Care Center in India

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ABSTRACT

Background and objectives: Conventional culture and sensitivity methods take around 48 hours to generate antibiotic sensitivity results after a blood culture is flagged as positive by automated systems. However, it is imperative to initiate early targeted antibiotic therapy for effective management of sepsis and to reduce morbidity, mortality, and cost of treatment. This study aimed to evaluate the direct sensitivity test (DST) as a potential tool to obtain quicker antibiotic susceptibility results from positive BacT/ALERT blood culture vials and the VITEK-2 system (the reference method).

Methods: Blood culture bottles flagged as positive by BacT/ALERT were Gram-stained. Cultures with polymicrobial growth were excluded from the study. The isolates were then simultaneously cultured and processed for the DST using the disk diffusion method. Agreements or errors were interpreted according to the Clinical and Laboratory Standards Institute's guidelines.

Results: Among 76 Gram-positive isolates, we observed 99.2% essential agreement between the DST and AST. The rate of minor and major errors was 4.04% and 1.18%, respectively. Among 75 Gram-negative isolates, we observed 98.99% essential agreement between the DST and AST. The rate of minor and major errors was 4% and 2%, respectively. No very major error was seen in either Gram-negative or -positive isolates.

Conclusions: The DST results are available earlier than the AST results, which can ultimately help in the early initiation of targeted antibiotic therapy.

Keywords: Drug Resistance, Microbial, blood culture, Sepsis.

INTRODUCTION

"Sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream, which leads to signs of systemic illness in remote organs," this was the first scientific definition of sepsis proposed by Dr. Schottmuller in 1914. Sepsis is among the most common causes of death in hospitalized patients. The mortality rate due to sepsis is in the same range as that of myocardial infarction i.e. ranging from 10% to 50% despite advances in critical care medicine (1). Early and reliable diagnosis is imperative because of the remarkably rapid progression of sepsis into a life-threatening condition. The international guidelines for the management of severe sepsis and septic shock also recommend that appropriate antimicrobial therapy be administered within 1 hour of recognition of severe sepsis or septic shock (2).

The reference method for positive blood cultures involves Gram staining, which is followed by the subculture of blood culture broth onto agar media plates. Plates are then incubated overnight aerobically at 37 ºC to obtain isolated colonies. A standardized inoculum is made from these colonies, which are used for conventional antibiotic susceptibility testing (AST). This whole procedure usually takes 48 hours to get AST results.

Direct susceptibility testing (DST) is a standard and well-established diagnostic work-up of bloodstream infections from positive blood culture broths (3, 4). The results of DST are available 18-24 hours after a blood culture was signaled positive by the BacT/ALERT compared to 36-48h for conventional AST. Thus, obtaining results 24 hours earlier than the conventional AST (5, 6). Outcome-based studies on the effect of rapid reporting of susceptibility results have shown a decrease in the number of laboratory tests and procedures ordered as well as in the length of stay, healthcare costs, and modification of antimicrobial therapy (7, 8). In this study, we evaluated DST from positive BacT/ALERT blood culture vials as a potential tool to obtain antibiotic susceptibility results earlier compared to the reference method.

MATERIALS AND METHODS

This was a prospective study that was conducted in a tertiary care hospital from February to August 2016. Blood cultures bottles [FA (adult) and PF (pediatric)] (bioMerieux, France) that were flagged as positive by the BacT/ALERT system (bioMerieux, France) were used in the study. Positive blood culture bottles were first analyzed by Gram staining (Himedia, India) and then subcultured on solid media (Himedia, India). Blood cultures with polymicrobial growth in the Gram stain and later subcultures were excluded from the study.

A total of 151 positive blood cultures were included in the study out of which 76 were uni-microbial Gram-positive cocci and 75 were uni-microbial Gram-negative bacilli. All broths were simultaneously cultured and processed for DST using the disk diffusion method as described by standards of the British Society of Antimicrobial Chemotherapy guidelines for AST (9). Zone sizes were then recorded and interpreted according to the Clinical and Laboratory Standards Institute's guidelines (10). Conventional AST of all isolates was performed with a pure overnight subculture on the VITEK-2 system (bioMerieux, France) according to the manufacturer′s instructions (the reference method).

Escherichia coli ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* ATCC 29213 were used as the control strains. The susceptibility results obtained by DST (test method) were compared to those obtained by the conventional AST by VITEK-2 (reference method). Categorical agreement or "no error", essential agreement or "minor errors", major errors, and very major errors were calculated as follows: essential agreement or "minor errors" (percentages of agreement obtained when minor discrepancies are ignored, i.e. "reference method" is sensitive or resistant and "test method" is intermediate; alternatively, "reference method" is intermediate and "test method" is sensitive or resistant). Categorical agreement or "no error" ("test method" and "reference method" susceptibility results agree using the respective criteria). Major errors ("reference method" is sensitive and "test method" is resistant; the percentage of major errors was calculated only for susceptible isolates). Very major errors ("reference method" is resistant and "test method" is sensitive; the percentage of very major errors was calculated only for resistant isolates (11).

RESULTS

A total of 151 bacterial strains isolated from the blood culture bottles were compared for DST and AST by VITEK-2. Among these, 76 isolates were Gram-positive and 75 were Gram-negative (Figure 1). Coagulase-negative *Staphylococcus* (CoNS; 78.9%) was the most common Gram-positive and *Escherichia coli* (44%) was the most common Gram-negative microorganism.

Results of DST were available 18-24 hours after a blood culture was signaled positive by the BacT/ALERT compared to 36-48 hours for AST results, secondary to overnight incubation required to produce isolated colonies. Thus, the DST results were available 18-24 hours sooner than the AST results.

Table 1- Correlation of DST and AST among Gram-positive isolates

Bacteria	Antibiotic	Vitek-2 Susceptibility test			Direct Susceptibility test									
					Essential agreement		Categorical agreement		Minor error		Major error		Very major error	
		S	I	R	No.	%	No.	%	No.	%	No.	%	No.	%
S. aureus (n=4)	Gentamicin (n=4)	4	0	0	4	100	4	100	0	0	0	0	0	0
	Ciprofloxacin (n=4)	4	0	0	4	100	3	75	1	25	0	0	0	0
	Cefoxitin (n=4)	4	0	0	4	100	4	100	0	0	0	0	0	0
	Linezolid (n=4)	4	0	0	4	100	4	100	0	0	0	0	0	0
	Vancomycin (n=4)	2	0	2	4	100	4	100	0	0	0	0	0	0
	Trimethoprim/sulfamethoxazole (n=2)	0	0	2	2	100	2	100	0	0	0	0	0	0
CoNS (n=60)	Gentamicin (n=36)	28	4	4	36	100	34	94.4	2	5.5	0	0	0	0
	Ciprofloxacin (n=32)	18	2	12	32	100	31	96.9	1	3.1	0	0	0	0
	Cefoxitin (n=42)	26	0	16	42	100	42	100	0	0	0	0	0	0
	Erythromycin (n=44)	22	2	20	43	97.7	41	93.2	2	4.5	1	4.5	0	0
	Penicillin (n=36)	12	2	22	36	100	35	97.2	1	2.7	0	0	0	0
	Linezolid (n=40)	32	2	6	39	97.5	36	90	3	7.5	1	3.1	0	0
	Teicoplanin (n=14)	12	0	2	14	100	14	100	0	0	0	0	0	0
	Vancomycin (n=34)	28	0	6	34	100	34	100	0	0	0	0	0	0
	Tetracycline (n=10)	8	1	1	9	90	9	90	0	0	1	12.5	0	0
	Trimethoprim/sulfamethoxazole (n=40)	24	2	14	40	100	38	95	2	5	0	0	0	0
Enterococcus spp. (n=8)	Gentamicin (n=4)	4	0	0	4	100	4	100	0	0	0	0	0	0
	Vancomycin(n=4)	2	0	2	4	100	3	75	1	25	0	0	0	0
	Linezolid (n=8)	6	0	2	8	100	7	87.5	1	12.5	0	0	0	0
	Penicillin (n=8)	0	0	8	8	100	8	100	0	0	0	0	0	0
	Teicoplanin (n=6)	3	0	3	6	100	6	100	0	0	0	0	0	0
	Levofloxacin (n=4)	3	1	0	4	100	4	100	0	0	0	0	0	0
S. pneumoniae (n=4)	Trimethoprim/sulfamethoxazole (n=4)	2	0	2	4	100	3	75	1	25	0	0	0	0
	Linezolid (n=4)	4	0	0	4	100	3	75	1	25	0	0	0	0
	Penicillin (n=4)	2	0	2	4	100	4	100	0	0	0	0	0	0

S: sensitive; I: intermediate; R: resistant

The correlation of sensitivity patterns from DST as compared to that from the reference method (VITEK-2) for Gram-positive isolates are shown in table 1. For 76 Gram-positive isolates (396 antimicrobial-organism combinations), we observed 99.2% essential agreement between DST and AST. Three antimicrobial-organisms combinations did not show essential agreement. In addition, DST yielded 16 (4.04%) minor, 3 (1.18%) major, and no very major errors. In CoNS (n=60), no very major errors were seen. Most major errors were detected in tetracycline (12.5%), erythromycin (4.54%), and linezolid (3.12%). Maximum minor errors were found in linezolid (7.5%), gentamicin (5.5%), trimethoprim/sulfamethoxazole (5%), erythromycin (4.5%), and ciprofloxacin (3.1%).

In other Gram-positive isolates (n= 16), no very major and major errors were seen (Figure 2). There was one minor error detected in *Staphylococcus aureus* (n=4) for ciprofloxacin, two in *Enterococcus spp*. one

each for linezolid (n= 8) and vancomycin (n=4), and two minor errors in *Staphylococcus pneumoniae*one each for linezolid (n=4) and trimethoprim/sulfamethoxazole (n=4).

The correlation of sensitivity patterns of DST with the reference method (VITEK-2) for *Enterobacteriaceae*, *Pseudomonas spp.*, and *Acinetobacter spp.* Are shown in table 2. For all 75 Gram-negative isolates (398 antimicrobial-organisms combinations), we observed 98.99% essential agreement between DST and AST.

Four antimicrobial combinations did not show essential agreement. In addition, DST yielded 16 (4%) minor, 4 (2%) major, and no very major errors.

Table 2- Correlation of DST and AST among Gram-negative isolates

Bacteria	Antibiotic	Vitek-2 Susceptibility test			Direct Susceptibility test									
					Essential agreement		Categorical agreement		Minor error		Major error		Very major error	
		S	I	R	No.	%	No.	%	No.	%	No.	%	No.	%
Enterobacteriaceae (n=61)	Imipenem (n=48)	33	0	15	48	100	46	95.8	2	4.1	0	0	0	0
	Meropenem(n=50)	39	0	11	50	100	50	100	0	0	0	0	0	0
	Gentamicin(n=40)	19	2	19	40	100	37	92.5	3	7.5	0	0	0	0
	Tigecycline (n=28)	20	8	0	28	100	26	92.9	2	7.1	0	0	0	0
	Ciprofloxacin (n=49)	8	3	38	48	97.9	47	95.9	1	2	1	12.5	0	0
	Trimethoprim /sulfamethoxazole (n=24)	18	0	6	23	95.9	23	95.9	0	0	1	5.5	0	0
	Ceftazidime (n=30)	13	0	17	30	100	30	100	0	0	0	0	0	0
	Levofloxacin (n=8)	5	0	3	7	87.5	7	87.5	0	0	1	12.5	0	0
	Piperacillin/ Tazobactam (n=49)	25	2	22	49	100	47	95.9	2	4	0	0	0	0
Pseudomonas spp. (n=6)	Imipenem (n=6)	0	0	6	6	100	6	100	0	0	0	0	0	0
	Meropenem (n=4)	2	0	2	4	100	4	100	0	0	0	0	0	0
	Gentamicin (n=4)	4	0	0	4	100	4	100	0	0	0	0	0	0
	Ceftazidime (n=6)	3	0	3	6	100	6	100	0	0	0	0	0	0
	Levofloxacin (n=6)	0	0	6	6	100	3	50	3	50	0	0	0	0
	Piperacillin-Tazobactam (n=6)	3	3	0	6	100	6	100	0	0	0	0	0	0
Acinetobacter spp. (n=8)	Amikacin (n=6)	3	0	3	6	100	6	100	0	0	0	0	0	0
	Imipenem (n=8)	3	0	5	7	87.5	6	75	1	12.5	1	33.3	0	0
	Meropenem (n=8)	0	0	8	8	100	8	100	0	0	0	0	0	0
	Piperacillin-Tazobactam (n=8)	0	0	8	8	100	8	100	0	0	0	0	0	0
	Ceftazidime (n=6)	0	0	6	6	100	4	66.6	2	33.3	0	0	0	0
	Tigecycline (n=4)	2	0	2	4	100	4	100	0	0	0	0	0	0

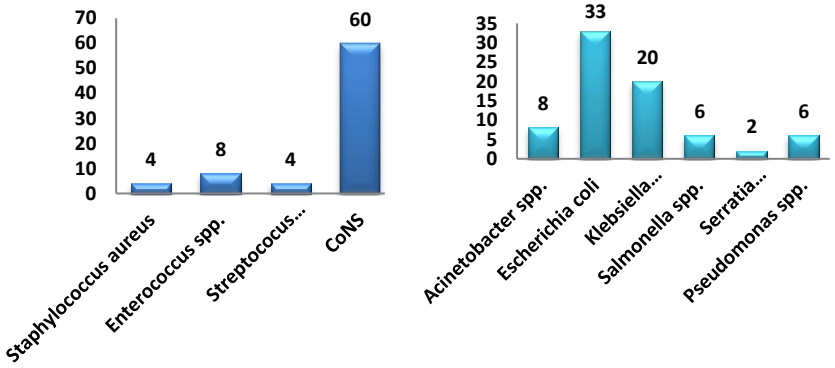

Figure 1- Frequency distribution of Gram-positive (a) and Gram-negative (b) isolate among positive blood cultures available for the DST and AST

In *Enterobacteriaceae* (n=61), no very error major errors were found. Most major errors were detected in the interpretation of ciprofloxacin (12.5%), levofloxacin (12.5%), and trimethoprim/sulfamethoxazole (5.5%). Minor errors were found in gentamicin (7.5%), tigecycline (7.1%), imipenem (4.1%), piperacillin–tazobactam (4%), and ciprofloxacin (2%). In case of *Pseudomonas spp.* (n=6), neither very major error nor major error was seen.

Three minor errors were found in the case of levofloxacin (50%). In *Acinetobacter spp.*, one major error was detected in the interpretation of imipenem (33.3%). Minor errors were found in imipenem (12.5%) and ceftazidime (33.3%). No very major error was seen (Figure 3).

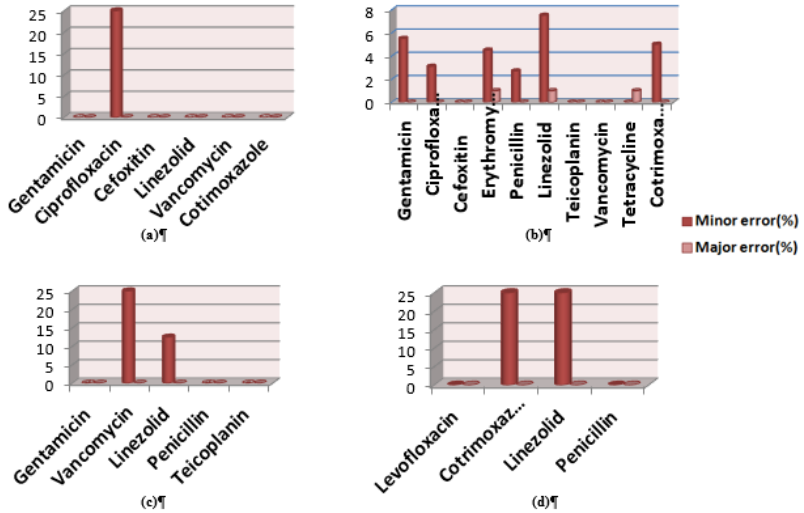

Figure 2- Minor error and major error rates related to *S. aureus* (a), CoNS (b), *Enterococcus spp.* (c), and *S. pneumoniae* (d)

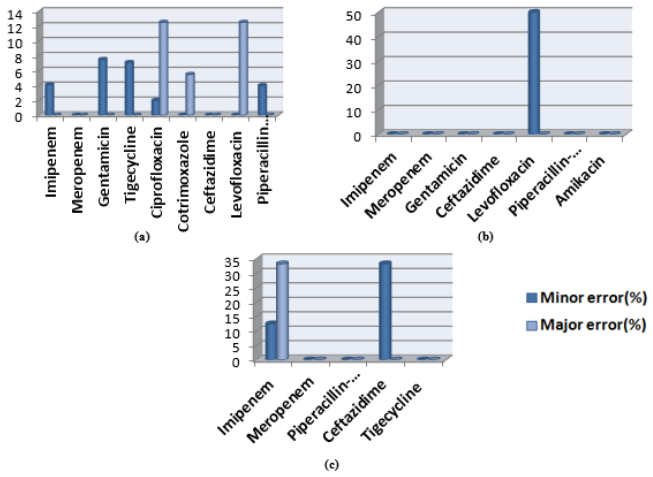

Figure 3- Minor error and major error rates related to *Enterobacteriaceae* (a), *Pseudomonas spp.* (b), and *Acinetobacter spp.* (c)

DISCUSSION

Bacterial bloodstream infections can lead to life-threatening sepsis that requires rapid antimicrobial treatment. Blood culture is the gold standard technique that provides essential information for the diagnosis and appropriate treatment to save the life of affected patients(12). Also, DST of positive blood cultures can help clinicians to tailor antibiotic treatment about 24 hours earlier than the final AST. Shortening the time to results of susceptibility testing of blood culture isolates can significantly reduce morbidity, mortality, and costs (13, 14).

Overall, the DST inoculum is a better representative of bacterial isolates in patients' samples compared to the standard AST

inoculum. Resistant variants of the microorganisms can be picked up by DST as they show visible growth inside the sensitive zone for a particular antibiotic. These resistant clones are Gram-stained first to confirm the purity of lawn cultures of DST plates and then separately tested for antibiotic sensitivity. The final report of antibiotic sensitivity may advise against the use of that particular antibiotic, which although reported sensitive based on standard AST as the resistant variants may be selected during treatment and cause treatment failure. This becomes even more important when dealing with blood cultures of immunocompromised and neutropenic patients.

In this study, a total of 76 Gram-positive cocci and 75 Gram-negative bacilli were included. The numbers are comparable to previously published studies of direct AST with positive blood cultures (11, 15).

Among Gram-positive isolates, CoNS was the most common Gram-positive (78.9%), followed by *Enterococcus spp*. (10.5%), *S. aureus* (5.2%), and *S. pneumonia* (5.2%). Similar results were reported by Wisplinghoff et al. (16). However, Marina et al. (2004) found *S. aureus (*44%) as the most common microorganism followed by *Staphylococcus epidermidis* (32%), CoNS (22%), and *Streptococcus agalactiae* (3%) (17).

The most common Gram-negative bacteria were *E. coli* (44%), *Klebsiella pneumonia* (26.6%), *Acinetobacter spp*. (10.66%), *Salmonella spp.* (8%), *Pseudomonas spp*. (8%), and *Serratia marcens* (2.6%). Similar results were reported in studies by Marina et al. (17) and Goel et al. (11). However, Sonawane et al. found *K. pneumoniae* (22.38%) as the most common Gram-negative bacteria (18).

Our study demonstrated that the DST of Gram-positive isolates performs well with 99.2% essential agreement. Minor and major errors of 4.04% and 1.18% were noted, respectively. No very major error was seen. Moreover, the DST of Gram-negative isolates performs well with 98.99% essential agreement. Minor and major errors of 4% and 2% were noted, respectively. No very major error was seen.

Numerous studies have investigated DST on positive blood cultures, most of them showing good agreement between AST and DST. In line with our results, Goel et al. found that the DST of Gram-negative isolates showed 96.2% essential agreement and 12.5%, 5.3%, and 1.4% minor, major, and very major errors, respectively (11). Chapin et al. reported that the DST of Gram-positive isolates showed 98.0% essential agreement, with 0.3% minor errors, 0 % major errors, and 1.7% very major errors (15). For Gram-negative isolates, they reported 99.0% essential agreement between DST and standard AST with 0.5% minor, 0% major, and 2.0% very major errors. Zappavigna et al. reported that the DST of Gram-negative isolates had a 93.7% correlation with 5.0% minor errors, 0.8% major errors, and 0.5% very major errors (19). However, Marina et al. reported that none of the Gram-positive cocci showed concordant results when comparing the direct and standard methods (17). Of the Gram-negative rods studied, only 62% showed concordant identification between the direct and standard methods with 2.8% minor errors, 2.4% major errors, and 3.2% very major errors. In a study by Rahila et al. on the DST of 116 isolates from BacT/ALERT bottles, 55.17% minor error/categorical error, 15.5% major error, and 0.8% very major errors were observed (20).

CONCLUSION

There is high concordance between the DST and AST. Inoculum size and proper disc strengths (quality) are major variables for proper DST results. It can be concluded that DST is a simple and rapid method of susceptibility testing. When compared to AST, the results of DST are obtained 24 hours earlier, which can help clinicians tailor antibiotic treatment sooner. This can ultimately reduce patient morbidity, mortality, and costs.

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DECLARATIONS

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Ethics approvals and consent to participate

The study was approved by the local ethics committee (registration number: EC/NEW/INST/2021/1556).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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