JOURNAL OF CLINICAL MICROBIOLOGY, June 1989, p. 1342–1345
0095-1137/89/061342-04$02.00/0

Vol. 27, No. 6

Clinical Impact of Rapid Identification and Susceptibility Testing of Bacterial Blood Culture Isolates

GORDON M. TRENHOLME,[1,2]* RAYMOND L. KAPLAN,[1,2,3] PETER H. KARAKUSIS,[1] TERRY STINE,[1] JACK FUHRER,[1] WILLIAM LANDAU,[2,3] AND STUART LEVIN[1]

Section of Infectious Disease, Department of Internal Medicine,[1] Section of Clinical Microbiology, Offices of Consolidated Laboratory Services,[2] and Department of Immunology/Microbiology,[3] Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612

Received 19 October 1988/Accepted 12 February 1989

Two hundred twenty-six patients with bacteremia were prospectively enrolled in a randomized trial that was performed to determine the clinical impact of the receipt of in vitro microbiological data by the physician soon after organism detection as opposed to having the physicians wait until similar data were available by routine methods. Identification and antibiotic susceptibility patterns of 110 isolates were determined by direct inoculation of the Vitek AutoMicrobic system (Vitek Systems, Inc., Hazelwood, Mo.) with a sample from a positive blood culture vial. One hundred sixteen isolates were processed by routine methods. Microbiological results were available within an average of 8.8 h by the direct method versus an average of 48 h by the routine method. In both groups an infectious disease fellow used the information to make therapeutic recommendations to the responsible physician. When compared with that provided by the routine method, the information provided by the direct method was significantly more likely to result in an initiation of antibiotic therapy, a change to more effective therapy, or a change to less expensive therapy. Recommendations were significantly more likely to be followed in patients whose isolates were processed by the direct method versus the routine method. A projected savings of $158 per patient was estimated for the patients who were changed to less expensive therapy or in whom antibiotics were discontinued because results were available sooner. These cost savings, coupled with changes in therapy made for reasons of efficacy, support the usefulness of the earlier reporting of the identity and antibiotic susceptibility patterns of bacterial blood culture isolates.

Approximately 200,000 cases of septicemia occur annually in the United States, with a 40 to 50% mortality rate (12). Over the past few years there has been an emphasis in clinical microbiology laboratories to rapidly identify and determine antimicrobial susceptibility patterns of bacterial isolates from blood cultures. It is believed that if this information is provided more rapidly it will result in more timely and cost-effective therapy in hospitalized patients (V. Lorian and D. B. Louria, Editorial, J. Infect. Dis. **142:** 661–662, 1984). Based on this premise many hospitals have purchased automated or semiautomated systems. While the abilities of many of these systems to produce accurate and rapid results have been studied extensively (3–5, 6, 9–11), the clinical relevance of the information generated has been less well documented (2). One such system, the AutoMicrobic system (AMS; Vitek Systems, Inc., Hazelwood, Mo.), has the ability to identify the organism and determine its antimicrobial susceptibility patterns in 4 to 10 h after the organism is placed in the instrument (1, 6, 8). Preparation of the organism is usually from a 24-h subculture of a positive blood culture vial. We evaluated a procedure which allows the inoculation of the AMS with bacteria obtained directly from a positive blood culture vial. This allowed identification and antimicrobial susceptibility testing of bacterial blood culture isolates to be completed on the same day that the bacteremia was detected in the clinical microbiology laboratory. Using this system, we analyzed the impact of the receipt of in vitro microbiological data by the physician soon after organism detection on the management of patients with bacteremia in our hospital setting.

* Corresponding author.

MATERIALS AND METHODS

Microbiology. All blood culture vials submitted to the clinical microbiology laboratory during an 11-month period were screened for bacterial growth each morning by using the BACTEC 460 system (Johnston Laboratories, Inc., Towson, Md.). Specimens demonstrating 30 or more radioactive units of activity were deemed positive. An aspirate from the positive blood culture vial was Gram stained to confirm the presence of organisms. Specimens from outpatients or pediatric patients, specimens deemed positive on Sunday, and specimens which appeared to be polymicrobial based on Gram stain results were not included in this study. If a patient had multiple positive blood cultures on the same day and there appeared to be similar organisms in each set, based on Gram stain, one set was used for the study procedure. Identification and susceptibility testing were performed by direct inoculation into the AMS (direct method) and by our routine laboratory methodology (routine method).

The procedure for the direct method was as follows. A 10-ml portion was removed from the positive blood culture vial and centrifuged at 125 × *g* for 10 min to sediment blood cells. The supernatant was transferred to a second tube, and the bacteria were sedimented by centrifugation at 2,200 × *g* for 30 min. This bacterial pellet was suspended in 0.5 to 1.0 ml of 0.45% saline, and this suspension was used for inoculation of the Gram-Positive Identification, Gram-Positive Susceptibility, Gram-Negative Identification, and Gram-Negative Susceptibility cards of the AMS according to the Gram stain and the recommendations of the manufacturer. Inoculation of the Gram-Positive Identification card was accomplished by further dilution of the suspended pellet with 0.45% saline to produce a turbidity equivalent to a 0.5

McFarland standard. To inoculate the Gram-Positive Susceptibility card, 200 μl of the suspended pellet was diluted with 1.8 ml of 0.45% saline. To inoculate the Gram-Negative Identification card, a portion of the original suspended pellet was diluted with 0.45% saline to produce a turbidity equivalent to a no. 1 McFarland standard. To inoculate the Gram-Negative Susceptibility card, 50 μl of the no. 1 McFarland standard suspension was diluted with 1.8 ml of 0.45% saline. To inoculate the Gram-Negative Supplemental Susceptibility card, 25 μl of the no. 1 McFarland standard suspension was diluted with 1.8 ml of 0.45% saline. All cards were placed in the AMS immediately after inoculation. To aid in organism identification, the bacterial pellet was used to perform a cytochrome oxidase test on gram-negative rods and to perform a tube coagulase test on gram-positive cocci.

Our routine method was initiated by streaking a portion of the suspended pellet onto a blood agar plate and an eosin-methylene blue agar plate for gram-negative isolates or a blood agar plate for gram-positive isolates in order to obtain colonies for use the next day. The colonies (18 to 24 h old) were used to inoculate either a Micro ID strip (General Diagnostics, Div. Warner-Lambert Co., Morris Plains, N.J.) for oxidase-negative, gram-negative rods or a Microscan Combo panel (American Microscan, Inc., Mahwah, N.J.) for oxidase-positive, gram-negative rods in order to obtain an identification. Prior to the inoculation of a Microscan panel, oxidase-positive, gram-negative rods were screened by using an acetamide agar slant and were tested for growth at 42°C. Isolates which were positive for these two tests were called *Pseudomonas aeruginosa*. Staphylococci were identified by the coagulase test. Coagulase-positive organisms were reported as *Staphylococcus aureus*, and coagulase-negative organisms were identified as *Staphylococcus epidermidis*. All antibiogram determinations were accomplished with Microscan panels, depending on the Gram stain morphology.

When a blood culture vial from a patient was confirmed as containing bacteria by Gram staining, an infectious disease fellow contacted the physician responsible for the patient. The fellow explained the purposes and procedures of the study and asked the physician whether the patient could participate in the study. If the patient was allowed to be enrolled in the study, the organism from the patient was randomly assigned to either the routine or the direct method for identification and antimicrobial susceptibility testing. All isolates assigned to the direct method were also processed by the routine method. In both groups, the physician was informed by an infectious disease fellow of the results of the identification and antimicrobial susceptibility test as soon as they were available. For isolates processed by the direct method, this was the same afternoon or evening as the day the blood culture was determined to be positive. For isolates processed by the routine method, this was the morning or afternoon of the day when the identification and susceptibility testing were completed. The infectious disease fellow recommended initiation or alterations in antimicrobial therapy when appropriate. Antimicrobial agents that demonstrated greater clinical efficacy, cost savings, or the potential for less toxicity were recommended. The impact of these recommendations was analyzed with regard to physician compliance and the cost-effective use of antibiotics.

RESULTS

A total of 226 patients with bacteremia were enrolled in this study; isolates from 110 patients were processed by the direct method and isolates from 116 patients were processed by the routine method. Coagulase-negative staphylococci were the most frequent isolates found, followed by *S. aureus*, *Escherichia coli*, and *P. aeruginosa* (Table 1). Of the 110 isolates processed by the direct method, we were able to identify or determine the antibiotic susceptibility patterns of 109 of them. We were unable to identify nine isolates by the direct method (four *S. aureus* isolates, three *S. epidermidis* isolates, and two *P. aeruginosa* isolates), but antimicrobial susceptibility patterns were determined for eight isolates. We were unable to determine susceptibility patterns by the direct method for seven isolates (four *Streptococcus pneumoniae* isolates, two *Staphylococcus aureus* isolates, and one *Staphylococcus epidermidis* isolate), but we were able to identify six isolates. For the 1 isolate (*S. epidermidis*) of the 110 isolates for which we were unable to identify or determine the susceptibility patterns by the direct method, the results of the Gram stain and the rapid tube coagulase test were available, and thus, this isolate was included in the study. We were able to identify or determine the antibiotic susceptibility patterns of all 116 isolates processed by the routine method. Identification of the blood isolate was completed by the direct method in an average of 10.6 h (range, 4 to 15 h) for gram-positive cocci and in 5.8 h (range, 4 to 18 h) for gram-negative rods. Antibiotic susceptibility testing was completed by the direct method in an average of 6.6 h (range, 4 to 10 h) for gram-positive cocci and 5.9 h (range, 4 to 10 h) for gram-negative rods. Overall, identification of the blood isolate was completed in an average of 8.8 h, and antibiotic susceptibility patterns were available in an average of 6.4 h by the direct method.

TABLE 1. Distribution of isolates randomized to the direct versus routine processing methods

Organism	No. of isolates processed by the:	
	Direct method	Routine method
Staphylococcus epidermidis	33	50
Staphylococcus aureus	32	15
Escherichia coli	14	16
Pseudomonas aeruginosa	4	8
Enterococcal group D streptococci	5	3
Corynebacterium spp.	2	5
Streptococcus pneumoniae	5	1
Viridans group streptococci	1	3
Enterobacter cloacae	3	1
Enterobacter aerogenes	2	2
Streptococcus agalactiae	2	2
Acinetobacter calcoaceticus subsp. *lwoffii*	1	2
Proteus mirabilis	1	2
Citrobacter freundii	0	2
Morganella morganii	2	0
Streptococcus pyogenes	1	1
Providencia stuartii	0	1
Micrococcus sp.	0	1
Yersinia enterocolitica	0	1
Pseudomonas maltophilia	1	0
Serratia marcescens	1	0

At the time of randomization, 208 (92%) patients were already receiving at least one antibiotic to which the isolated organism was susceptible in vitro. The changes in antibiotic therapy related to the information provided by identification and susceptibility testing are shown in Table 2. Information provided by direct processing of isolates was significantly more likely to result in an initiation of antibiotic therapy, a

TABLE 2. Recommendations for antibiotic therapy

Recommendation	No. (%) of recommendations by the:	
	Direct method	Routine method
Initiation of antibiotic therapy	10 (9.1)[a]	0 (0.0)
Change to effective therapy	8 (7.3)[a]	1 (0.9)
Change to less expensive therapy	38 (34.5)[a]	21 (18.1)
Discontinue antibiotics	6 (5.5)	4 (3.4)
No change in therapy recommended	40 (36.4)	64 (55.2)
Recommendation not followed	8 (7.3)[a]	26 (22.4)

[a] Differences were significant ($P < 0.05$) when the direct method was compared with the routine method.

change to more effective therapy, or a change to less expensive therapy than was information provided by routine processing. Only 6 of 40 isolates (15%) from patients for whom no change in therapy was recommended were processed by the direct method, as opposed to 22 of 64 isolates (34.4%) from patients in the routine processing group who were not receiving antibiotics. Recommendations made by the infectious disease fellow were significantly more likely to be followed in the group that was randomized to the direct processing of isolates versus the group that was randomized to the routine processing of isolates. Eighteen patients whose isolates were processed by the direct method were either switched to more effective antibiotic therapy or had antibiotics initiated, compared with only one patient in the routine processing group ($P < 0.5$). Table 3 lists the categories of noncompliance for the 34 patients in whom the recommendations of the infectious disease fellow were not followed. In the 44 patients who were switched to less expensive therapy or in whom antibiotics were discontinued because results were available sooner, a cost savings of $6,952 was realized. This was based on the projected savings if no change in therapy was made until results were available by the routine method.

DISCUSSION

The conclusion of this study is that earlier is better. By using a modification of the AMS procedure, we were able to provide physicians with either identification or antimicrobial susceptibility results on blood culture isolates within an average of 8.8 h after the blood culture vial was found to be positive. This information was given to the physician responsible for antibiotic therapy by an infectious disease fellow. This means of contact was chosen to increase physician use of the laboratory results. By interposing an infectious disease fellow, we were deliberately biasing the study in favor of maximum compliance. Interestingly, we found a high rate of noncompliance (22.4%) with therapeutic recommendations among the physicians who had patients whose isolates were processed by the routine method. We attribute this to the reluctance of physicians to change therapy after 2 or 3 days in patients with an improving status. This significant difference in compliance between the two groups of physicians whose patient cultures were processed by the direct versus the routine method and the receipt of the same information from the same person but at different times by both groups of physicians support the fact that the difference in compliance was caused by the earlier provision of information rather than the involvement of an infectious disease fellow in the transfer of information.

TABLE 3. Categories of noncompliance

Recommendation not followed	No. of recommendations by the:	
	Direct method	Routine method
Change to cost-effective drug(s)	5	16
Discontinue antibiotics	0	8
Institute therapy	1	1
Change to effective therapy	2	1

The usefulness of direct processing of blood culture isolates is dependent on the accuracy of the method involved. Previous reports have indicated that inoculation of the AMS with bacteria obtained directly from a positive blood culture vial is technically feasible and accurate (6, 7). A recent report (7) indicated discrepancies in testing of susceptibility of staphylococci to oxacillin when direct inoculation of the AMS was compared with conventional MICs. In the present study five isolates of *S. epidermidis* processed by the direct method were considered to be resistant to oxacillin and were subsequently found to be susceptible to nafcillin by our routine method. All were confirmed to be resistant to oxacillin on further testing. This may have reflected an inadequate NaCl concentration in the medium that was used for the routine processing method. We found no such problems with isolates of *S. aureus* in our study.

Although 92% of patients received at least one antimicrobial agent to which the blood isolate was susceptible, we were able to show a difference in the initiation of therapy as well as switch to effective therapy. This difference would be expected, in that all physicians were informed that the blood cultures of their patients were positive at the same time; however, identification and antibiograms were available within 8 h for the direct method but not for as long as 48 h by the routine method. Thus, for the group of patients whose isolates were processed by the routine method, their physicians would either start therapy or change therapy when they were informed that the blood culture vials were positive, whereas physicians would wait for the results of the direct method before they made therapeutic changes.

We also were able to show a difference between the two processing methods related to changes to less expensive therapy. The projected cost saving for patients who were changed to less expensive therapy or in whom antibiotics were discontinued was $158 per patient. If we presume that cost-effective changes and the same compliance rate would occur in the group randomized to routine processing of isolates, then 37 additional patients would have benefited, with an estimated overall cost savings of $13,114. Although this is only a small part of the total hospital cost of these patients, these savings should support the additional expense of an instrument to perform rapid identification and susceptibility testing. These cost savings in antimicrobial therapy, coupled with changes in therapy made for efficacy reasons, support the usefulness of earlier reporting of the identity and antibiotic susceptibility patterns of blood culture isolates.

LITERATURE CITED

1. **Backes, B. A., S. J. Cavalieri, J. T. Rudrik, and E. M. Britt.** 1984. Rapid antimicrobial susceptibility testing of gram-negative clinical isolates with the AutoMicrobic system. J. Clin. Microbiol. **19**:744–747.
2. **Doern, G. V., D. R. Scott, and A. L. Rashad.** 1982. Clinical

impact of rapid antimicrobial susceptibility testing of blood culture isolates. Antimicrob. Agents Chemother. **82**:1023–1024.
3. **Goldstein, J., J. J. Guarneri, and J. Scherer.** 1982. Use of the AutoMicrobic system for rapid antimicrobial susceptibility testing of Enterobacteriaceae in a clinical laboratory. J. Clin. Lab. Automat. **2**:329–337.
4. **Hansen, S. L., and P. K. Freedy.** 1983. Concurrent comparability of automated systems and commercially prepared microdilution trays for susceptibility testing. J. Clin. Microbiol. **17**: 878–886.
5. **Kelly, M. T., J. M. Latimer, and L. C. Balfour.** 1982. Comparison of three automated systems for antimicrobial testing of gram-negative bacilli. J. Clin. Microbiol. **15**:902–905.
6. **Moore, D. F., S. S. Hamada, E. Marso, and W. J. Martin.** 1981. Rapid identification and antimicrobial susceptibility testing of gram-negative bacilli from blood cultures by the AutoMicrobic system. J. Clin. Microbiol. **13**:934–939.
7. **Sahm, D. L., S. Boonlayangoor, and J. A. Morello.** 1987. Direct susceptibility testing of blood culture isolates with the AutoMicrobic (AMS). Diagn. Microbiol. Infect. **8**:1–11.
8. **Schifman, R. B., and K. J. Ryan.** 1982. Rapid automated identification of gram-negative bacilli from blood cultures with the AutoMicrobic system. J. Clin. Microbiol. **15**:262–264.
9. **Sewell, D. L., and M. T. Makler.** 1981. Clinical evaluation of the Abbott MS-2 antimicrobial susceptibility testing system. Am. J. Clin. Pathol. **76**:82–85.
10. **Stubbs, K. G., and K. Wicher.** 1977. Laboratory evaluation of an automated antimicrobial susceptibility system. Am. J. Clin. Pathol. **68**:769–777.
11. **Thornsberry, D., J. P. Anhalt, J. A. Washington II, L. R. McCarthy, F. D. Schoenknecht, J. C. Sherris, and H. J. Spencer.** 1980. Clinical laboratory evaluation of the Abbott MS-2 automated antimicrobial susceptibility testing system: report of a collaborative study. J. Clin. Microbiol. **12**:375–390.
12. **Washington, J. A., II, and D. M. Ilstrup.** 1986. Blood cultures: issues and controversies. Rev. Infect. Dis. **8**:792–802.