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ORIGINAL ARTICLE

Impact of rapid diagnosis of *Staphylococcus aureus* bacteremia from positive blood cultures on patient management

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Abstract We have performed a retrospective, before–after comparison of turnaround time and therapy adjustment parameters before and after the introduction of matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) plus *mecA* polymerase chain reaction (PCR) for the identification of methicillin-resistant *Staphylococcus aureus* (MRSA) in positive blood cultures. There were 227 episodes of *S. aureus* bacteremia during the study periods. The pre-MALDI-TOF and post-MALDI-TOF groups included 133 and 94 patients, respectively. The two rapid methods performed sequentially decreased the turnaround time of MRSA identification by nearly 50% (2.06 ± 1.95 vs. 3.95 ± 1.70 days). There was no significant reduction in the length of hospitalization (28.27 ± 32.16 vs. 28.62 ± 28.75 days). In both groups, the adequacy of the empirical antibacterial therapy was similar (59.49% vs. 51.31%), but the optimization of the therapy was more frequent in the post-MALDI-TOF group. Routine implementation of these techniques provides results earlier than conventional methods and increases the proportion of episodes with adequate change of empirical to directed antimicrobial therapy.

Introduction

In the industrialized world, the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is increasing due to epidemic healthcare-associated clones of MRSA [1, 2]. In cases of sepsis due to this microorganism, a quick start of appropriate antibiotic treatment is mandatory [3]. Therefore, the use of empirical glycopeptide antimicrobials is advocated, although there is evidence from randomized controlled [4–6] and observational studies [7–9] that β-lactam therapy is better than glycopeptides for methicillin-susceptible *S. aureus* (MSSA) bacteremia.

Molecular methods are able to differentiate between MSSA and MRSA in blood cultures. These methods have allowed the development of screening tests, which aim to decrease the turnaround time and the adjustment of empirical to directed treatment [10–12]. Recently, protocols for the direct identification of microorganisms from positive blood cultures using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) have successfully reduced the time necessary to identify microorganisms in clinical microbiology laboratories [13]. The combined use of MALDI-TOF and rapid diagnostic tests for the identification of MRSA represents one approach to reduce the turnaround time required to identify MSSA or MRSA from positive blood culture bottles [14–16].

The main objective of this study was to evaluate the impact on patient management of the implementation in the clinical routine of MALDI-TOF for the identification of microorganisms grown in positive blood culture bottles combined with a rapid diagnostic test for detection of the *mecA* gene in bottles with *S. aureus*. A secondary objective was to evaluate the impact on length of hospital stay and the establishment of adequate antimicrobial therapy in patients with bloodstream infections (BSI).

Materials and methods

Study design

This single-center retrospective study was conducted at Hospital Universitario La Paz. All patients from 0 to 102 years

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of age with BSI due to *S. aureus* were included. Patients with BSI due *S. aureus* identified by MALDI-TOF and polymerase chain reaction (PCR)-based detection of methicillin resistance in blood cultures were included over a 13-month period (1st November 2010 to 30th November 2011). This group was compared to a pre-MALDI-TOF control group with both *S. aureus* identification and β-lactam susceptibility performed by conventional methods over 13 months from 1st July 2009 to 31st July 2010.

Previously, the sensitivity and accuracy of *S. aureus* identification by MALDI-TOF mass spectrometry (MS) applied directly from blood culture bottles had been evaluated by comparison with the phenotypic identification. Reliable identification was obtained for 75.8% of the *S. aureus* isolates (score > 1.5) [13].

Microbiology workflow

Blood cultures were incubated in the BACTEC automated blood culture device (BACTEC™, Becton Dickinson, Franklin Lakes, NJ, USA) and BacT/ALERT (bioMérieux, Marcy l'Etoile, France) blood culture bottle systems. All positive blood cultures were routinely subcultivated on three agar plates, sheep blood agar, chocolate blood agar, and *Brucella* blood agar, and incubated overnight.

In our institution, prior to the implementation of the Bruker Biotyper MALDI-TOF (Bruker Daltonik GmbH, Leipzig, Germany) technology in the laboratory routine, the identification of *S. aureus* cultures was performed by conventional methods, including Gram stain and colony morphology. Biochemical identification tests were carried out by standard laboratory methods (e.g., DNase testing and the latex slide agglutination test; Staphytect Plus, Oxoid, Basingstoke, UK) and by VITEK 2 identification cards (bioMérieux, Marcy l'Étoile, France). The susceptibility studies were done using the susceptibility VITEK 2 AST-P588 cards (bioMérieux, Marcy l'Étoile, France), following the manufacturer's instructions.

After the implementation of the Bruker Biotyper MALDI-TOF technology in the laboratory routine, when a blood culture was flagged positive, indicating bacterial growth, a Gram stain was performed and direct identification from positive blood culture bottles was done by MALDI-TOF MS following the protocol established in our institution [13]. When *S. aureus* was identified, the GeneXpert® MRSA/SA BC (Cepheid, Sunnyvale, CA, USA) test was performed [16]. *Staphylococcus aureus* identification was corroborated the following day by the bacterial growth in sheep blood agar and chocolate blood agar.

Identification and antimicrobial susceptibility testing results were routinely reported by telephone between 8:00 AM and 15:00 PM during both periods, pre- and post-MALDI-TOF eras.

Time to results

The average turnaround time values were recovered from the Clinical Microbiology Department database, and defined in all cases from the start of incubation to the input of the results in the database.

Evaluation of clinical impact

The aim of the study was to evaluate the impact on patient management and the clinical impact of rapid identification of *S. aureus* from positive blood culture bottles using MALDI-TOF combined with a rapid diagnostic test for the identification of MRSA and then comparing them with the conventional methods for MRSA detection. Demographic, microbiological, and clinical data evaluated were as follows: age, sex, time to positivity of blood cultures, time to identification of *S. aureus* and methicillin susceptibility results following blood culture positivity, length of hospital stay, source of bacteremia, and the adjustment of antibiotic therapy in patients with *S. aureus* BSI.

Adequate empirical antibiotic therapy was defined as the prescription of active antibiotic, as confirmed by antibiotic susceptibility testing (AST) performed on subcultures.

Antistaphylococcal penicillins or a first-generation cephalosporin were considered optimal treatment for MSSA bacteremia, while vancomycin and daptomycin were considered the optimal therapy for MRSA bacteremia [6].

Adjustment to optimal therapy was considered the change or reduction to antistaphylococcal penicillins or a first-generation cephalosporin for MSSA bacteremia and the change or reduction to vancomycin and daptomycin for MRSA bacteremia.

The antibacterial therapy data of 55 patients, 27.06 % pre-MALDI-TOF era and 20.21% post-MALDI-TOF era, could not be recovered (Table 1).

Statistical analysis

Categorical variables were compared using the Chi-squared or Fisher's exact tests when appropriate and continuous variables were compared using the Mann–Whitney *U*-test. Analyses were conducted using GraphPad Prism software version 5.01 (GraphPad Software, San Diego, CA, USA). A *p*-value of ≤ 0.05 was considered significant.

Results

There were 227 episodes of *S. aureus* bacteremia during the study periods. The pre-MALDI-TOF and post-MALDI-TOF groups included 133 and 94 patients, respectively. False-positive identifications of *S. aureus* with MALDI-TOF MS did not occur.

Table 1 Patient characteristics according to intervention

Characteristic	Pre-MALDI-TOF group (n = 133)	Post-MALDI-TOF group (n = 94)	p-Value
Age (years)	54.71 ± 26.58	59.3 ± 26.6	0.88
Sex (male), n (%)	81 (60.90%)	56 (59.57%)	0.89
Patients with MRSA bacteremia (%)	27.82	26.59	0.88
Length of hospitalization (days)	28.27 ± 32.16	28.62 ± 28.75	0.26
Average time to positivity of blood cultures	2.16 ± 1.51 days	2.08 ± 1.93 days	0.201
Turnaround time to identification and susceptibility	3.95 ± 1.70 days	2.06 ± 1.95 days	< 0.0001
Source of bacteremia			
Intravascular catheter, n (%)	36 (27.06%)	26 (27.65%)	1.0
Skin and soft tissue infection, n (%)	25 (18.79%)	19 (20.21%)	0.86
Infective endocarditis, n (%)	11 (8.27%)	7 (7.44%)	1.0
Osteoarticular infections, n (%)	4 (3.00%)	4 (4.25%)	0.72
Respiratory infections, n (%)	12 (9.02%)	8 (8.51%)	1.0
Urinary tract infections, n (%)	2 (1.50%)	3 (3.19%)	0.65
Others, n (%)	9 (6.76%)	8 (8.51%)	0.61
Unknown, n (%)	34 (25.56%)	19 (20.21%)	0.42
Adequate empirical antibiotic therapy, , n (%)	47 (59,49.%)	39 (51.31%)	0.41
Adjustment to optimal therapy, , n (%)	38 (48.71%)	61 (81.33%)	< 0.0001
Unknown antibacterial therapy data, , n (%)	36 (27.67%)	19 (20.21%)	0.43

The demographic characteristics, including length of hospitalization and source of BSI, were similar in both groups. The most frequent sources of bacteremia were intravascular catheters, skin and soft tissue infections, respiratory infections, and infective endocarditis (Table 1). The number of patients with MRSA bacteremia was similar in both groups (37/133 = 27.82% vs. 25/94 = 26.59%, p = 0.88), as were the mean ages (54.71 ± 26.58 vs. 59.3 ± 26.6 years, p = 0.88) and number of males (60.90% vs. 59.57%, p = 0.89) (Table 1). The average time to positivity of blood cultures was not significantly different between the two groups (2.16 ± 1.51 vs. 2.08 ± 1.93 days, p = 0.201).

Rapid identification of *S. aureus* from the start of incubation to identification and antimicrobial resistance detection using MALDI-TOF combined with PCR had a turnaround time significantly shorter than the phenotypic methods (3.95 ± 1.70 vs. 2.06 ± 1.95 days, p < 0.0001). Therefore, the combined rapid methods decrease the turnaround time to nearly one half by an average of 1.89 days (Table 1).

There was no significant reduction in the length of hospitalization (28.27 ± 32.16 vs. 28.62 ± 28.75 days, p = 0.26) between the two groups, and both had similar rates of adequate empirical antibacterial therapy (59.49% vs. 51.31%, p = 0.41), although the optimization of antibacterial therapy was more frequent in the post-MALDI-TOF group (p < 0.0001) (Table 1).

Discussion

The implementation of rapid diagnostic laboratory techniques provides clinical microbiology laboratories with tools to reduce the turnaround time and the report of correct identification and susceptibility profiles of bacterial pathogens.

Some authors have reported the use of MALDI-TOF MS identification on positive blood cultures, with a grade of concordance between MALDI-TOF and classic microbiological methods of up to 95% [17–22]. In a prospective clinical trial of 218 patients with bacteremia in which MALDI-TOF was used for organism identification and compared with phenotypic methods, the average time to organism identification was 28.8 h shorter with MALDI-TOF (16.3 vs. 45.2 h, p < 0.001) [20].

We did not observe a reduction in the length of hospitalization between both groups. On the other hand, our results suggest that, when microbiological identification and susceptibility data are provided within 2 days of blood culture sampling, clinicians are more likely to change the empirical treatment regimen to optimal therapy. One possible reason for this might be the predisposition of physicians to change therapy when the outcome of the patient is not clear (first 2–3 days after the bacteremia/sepsis). It is more difficult for clinicians to change antibacterial therapy when the patient has a positive clinical and microbiological response, which more frequently occurs after 4 or 5 days of treatment, rather than after 2 days, when the clinical or microbiological response is more difficult

to be evaluated [23, 24]. Therefore, in our study, rapid identification of MRSA and MSSA did not have a measurable impact on length of hospitalization, but did have a positive impact on antimicrobial therapy adjustment, which implies a decrease in the time of optimizing therapy and reduction of the antibacterial spectrum. It can also promote the appropriate use of antimicrobials to improve clinical outcomes by reducing side effects related to the non-optimal antimicrobial therapy (the emergence of resistance, limiting drug-related adverse events, and minimizing the risk of unintentional consequences associated with antimicrobial use) [25].

Our study has one limitation. It was entirely a retrospective analysis, for which some clinical record data could not be recovered.

In conclusion, the use of direct MALDI-TOF on positive blood cultures combined with a rapid diagnostic test for the identification of MRSA provides results earlier than conventional methods, and their implementation in the clinical laboratory routine increased the proportion of adequate adjustments of antimicrobial therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective study is pending of approval by the ethical committee of the University Hospital La Paz.

Informed consent Not required.

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