Journal of Microbiology, Immunology and Infection 56 (2023) 57—63

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Integration of antimicrobial stewardship intervention with rapid organism identification improve outcomes in adult patients with bloodstream infections

Tzu-Ping Weng [a,b], Ching-Lung Lo [a,b], Wen-Liang Lin [d], Jen-Chieh Lee [a], Ming-Chi Li [a,b], Wen-Chien Ko [a,b,c], Nan-Yao Lee [a,b,c,*]

[a] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Center for Infection Control, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[c] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[d] *Department of Pharmacy, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

Received 28 April 2022; received in revised form 23 June 2022; accepted 7 July 2022
Available online 19 July 2022

KEYWORDS
Bloodstream infection;
Antimicrobial stewardship intervention;
MALDI-TOF-MS

Abstract *Background:* Integration of antimicrobial stewardship intervention (ASI) with rapid organism identification has the potential for early customization of antimicrobial therapy and improved clinical outcomes. We aimed to evaluate the impact of this combined approach on antimicrobial therapy-related outcomes in patients with bloodstream infections (BSIs).
Materials and methods: A pre—post quasi-experimental study was conducted to analyze the impact of ASI with organism identification via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) among patients with BSIs. Outcomes were compared to a historic pre-intervention group. The 30-day mortality was the primary endpoint. Secondary outcomes included time to first antibiotic modification, length of hospital stay.
Results: A total of 1004 adult patients with BSIs were included in the final analysis, 519 patients classified into the intervention group and 485 patients in the preintervention group. The patients in the intervention group were younger (66 vs. 70 years, $P = 0.02$). The 30-day crude mortality (14.6% vs. 29.9%, $P < 0.001$) was lower, the time to organism identification (72.25 vs. 83.6 h, $P < 0.001$) and length of hospital stay (12 days vs. 14 days, $P < 0.001$) were shorter in the intervention group. Acceptance of an ASI was associated with a trend toward a

* Corresponding author. Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, 704, Tainan, Taiwan.
E-mail address: nanayao@mail.ncku.edu.tw (N.-Y. Lee).

https://doi.org/10.1016/j.jmii.2022.07.002

reduced 30-day mortality on multivariable analysis (odds ratio 0.33; 95% CI: 0.24—0.47; $P < 0.001$).
Conclusion: The ASI combined with MALDI-TOF-MS approach decreased time to organism identification and time to appropriate antimicrobial therapy would achieve a better clinical outcome in the patients with BSIs.

Introduction

Bloodstream infections (BSIs) are life-threatening diseases associated with increased mortality rates, length of hospital stay, and concomitant cost.[1,2] Prompt organism identification is crucial for optimizing antimicrobial therapy for patients with BSIs. Early initiation of appropriate antimicrobial therapy is associated with better clinical outcomes and reduced healthcare cost.[3—5] Delays in organism identification hinder the ability of clinicians to streamline therapy, resulting in excessive patient exposure to broad-spectrum antimicrobials and subsequent risks of isolates developing antimicrobial resistance.[6]

The gram staining for preliminary organism identification remains the guidance for empiric antimicrobial therapy.[10] The blood cultures are the best approach of organism identification for the patients with BSIs and guarantee whether the antimicrobial treatment is adequate,[7—9,15] but the organism identification remains time-consuming in clinical microbiology laboratories.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) accurately and promptly identifies most bacterial species according to the specific protein profile and represents an attractive alternative to more time-consuming conventional testing methods.[11] Identification of organisms by MALDI-TOF-MS has provided clinical practice in many clinical microbiology laboratories.[12,13]

The antimicrobial stewardship intervention (ASI) was the optimization of proper and timely antimicrobial regimens according to the patient's clinical manifestations, severity of disease, organism identification, and the antimicrobial susceptibility result.[14] The ASI provided timely evaluations for antimicrobial regimens, which would improve the patients' outcomes compared to reporting the microbiology results alone.[16] The integration of MALDI-TOF-MS and ASI into microbiology workflow decreased time to organism identification.[16,17] However, limited data were available for the impact of ASI combined with MALDI-TOF-MS on clinical outcomes of the patients with BSIs.

Therefore, the aim of this study was to evaluate the clinical impact of ASI combined with rapid pathogens identification with MALDI-TOF-MS on clinical and antimicrobial therapy-related outcomes in patients with BSIs.

Materials and methods

Study population and data collection

The study was a pre-post quasi-experimental study conducted at National Cheng Kung University Hospital (NCKUH) in southern Taiwan and received institutional review board approval (B-ER-103-345). Adult patients >20 years of age with a BSI identified via MALDI-TOF-MS over one year period (1 March 2015—29 February 2016) was compared with a historical pre-intervention group with organism identification performed by conventional methods over the same calendar months in the previous year (1 March 2014—28 February 2015). Additionally, patients with a BSI were secondary to organisms not validated for identification by MALDI-TOF-MS at the time of this study required identification by other methods was excluded in both groups.

Microbiology workflow

For both study groups, Gram staining was performed for positive blood cultures, and the preliminary results would be reported electrically to the medical recording system. The VITEK 2 system (bioMe'rieux, Durham, NC, USA) was performed for species identification and antibiotic susceptibility testing (AST) during preintervention period. During intervention period, MALDI-TOF-MS (bioMérieux, Marcy l'Etoile, France) for identification and VITEK 2 (bioMe'rieux, Durham, NC, USA) for AST. Regardless of identification methodology, results were reported to the electronic medical record system in the beginning of the morning shift (Fig. 1).

Antibiotic stewardship intervention workflow

The team of ASI program at the NCKUH consists of two infectious diseases physicians and one clinical pharmacist. An infectious diseases (ID) specialist reviewed notification for all patients with positive blood cultures and provided prescribers with preestablished, evidence-based antibiotic recommendations in accordance with institutional guidelines at the time of Gram stain, organism identification, and antimicrobial susceptibility testing results. The other ID specialist of the ASI monitored a positive blood culture list at least once daily, providing feedback to providers Monday-Friday as part of normal ASI workflow. The prescription of antibiotic agents, indication of treatment, and dosage would be approved by the antimicrobial stewardship team.

Definitions and outcome

Demographic data was retrieved using standard record form from medical charts. Bloodstream infection was defined as the isolation of the organisms in at least one blood culture with a compatible clinical syndrome.

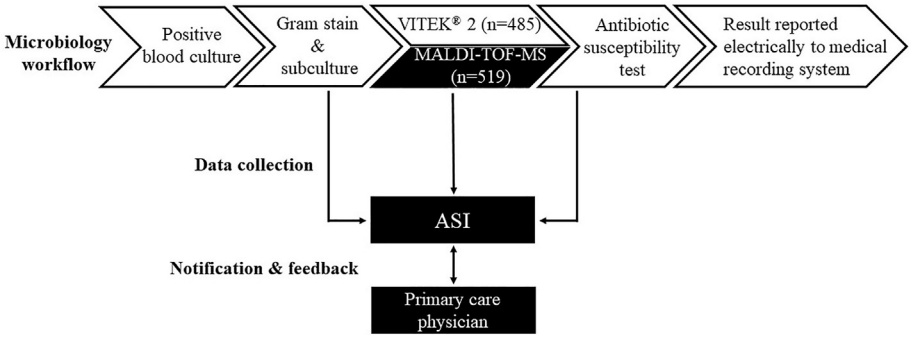

Figure 1. Antimicrobial stewardship intervention and microbiology workflow. Footnote: White boxes represent both pre-intervention and intervention workflow. Black boxes and lines represent added steps to the antimicrobial stewardship intervention workflow for the intervention group.

The multidrug-resistant organism (MDRO) was defined as the bacteria with acquired non-susceptibility to at least one antimicrobial agent in three or more antimicrobial categories, including oxacillin-resistant *Staphylococcus aureus* (ORSA), vancomycin-resistant Enterococcus (VRE), and third-generation cephalosporin-resistant *Enterobacterales*.

The antimicrobial regimens administered within 72 h of onset of the BSI was defined as the empiric therapy, and the regimens administered afterward was regarded as the definite therapy. The combination therapy was defined as more than one antimicrobial regimen. The appropriate therapy was defined as the receipt of the antimicrobial regimens, in which the isolate was *in vitro* susceptible to at least one of the regimens. The escalation and de-escalation of the antimicrobial regimens were defined as the modification of the empiric therapy to a more broad-spectrum and narrow-spectrum regimen within the same class of antimicrobial regimens, respectively.

The study aimed to assess the impact of the combination of ASI and MALDI-TOF-MS on clinical and antimicrobial therapy-related outcomes in the patients with BSIs. The primary outcome measure is crude 30-day mortality, and the secondary outcomes included total hospital length of stay (LOS) after bacteremia onset, and the period of time for organism identification. The severity of bacteremia was graded using the Pitt bacteremia score on the day of bacteremia onset.[23]

Statistical analysis

The data was analyzed by the SPSS software version 22.0 for the Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean values with standard deviation and were compared with Mann—Whitney *U* test or Student *t* test. The categorical variables expressed as the percentages of the case numbers were analyzed and compared with Fisher's exact test or Chi-square test. The independent predictors for the 30-day mortality were identified by means of the logistic regression analysis. Variables with $p \leq 0.1$, determined using univariate analysis, were included for multiple conditioning logistic regression analysis. The Cox proportional hazard model was applied for the comparison of the survival in the both groups, adjusted for the confounding variables. A p value < 0.05 was determined as statistically significant and all of the tests were two-tailed.

Results

A total of 1004 patients with bloodstream infections were included for analysis during both study periods. The pre-intervention group and intervention group included 485 and 519 patients, respectively (Fig. 1).

Demographic characteristics including co-morbidities, clinical status (disease severity) at the time of BSI onset, setting of acquisition (community or hospital acquired), and source of BSI were similar in both groups (Table 1). Patients in the pre-intervention group were slightly older (70 vs 66 years, $P = 0.02$), and were less presented with pneumonia (3.5% vs 7.1%, $P = 0.01$) (Table 1).

There was no significant difference in the rate of acquired MDRO (57% vs. 56.7%, P = 0.92) during both study periods, but the incidence of acquired third-generation cephalosporin-resistant *Enterobacterales* (23.1% vs. 15.1%, $P = 0.001$) was higher while vancomycin-resistant *Enterococcus* species (0.8% vs. 9.7%, $P < 0.001$) was lower in the intervention group. There was no difference of the incidence of ORSA between the two groups (6.4% vs. 4.9%, P = 0.34). Approximately 80% of the patients in both groups received appropriate empiric antimicrobial therapies, but the time to appropriate therapy was significantly shorter in the intervention group (9.5 h vs. 34.7 h, $P < 0.001$). In the multivariable analysis for the variables associated with the 30-day mortality, the patients received the ASI (OR: 0.33, 95% confidence interval [CI]: 0.24—0.47, $P < 0.001$), appropriate antimicrobial therapy (OR: 0.25, 95% CI: 0.09—0.67, $P < 0.001$) demonstrated a better outcome. The patients with pneumonia (OR: 2.25, 95% CI: 1.19—4.26, $P = 0.01$), and critical illness with the Pitt score ≥ 4 (OR: 5.39, 95% CI: 3.86—7.53, $P < 0.001$) were associated with poor prognosis (Table 2).

The survival analysis showed a significantly lower 30-day mortality (14.6% *vs.* 29.9%, $P < 0.001$) and shorter length of hospital stay of survivors (12 days vs. 14 days, $P < 0.001$,

Table 1 Baseline characteristics of the patients with bacteremia.

Characteristics	Pre-intervention group, n = 485	Intervention group, n = 519	*p* values
Age, median (IQR), year	70 (60–78)	66 (56–77)	0.02
Gender, male	258 (53.2)	285 (54.9)	0.59
Route of acquisition			0.76
Healthcare-associated	406 (83.7)	430 (82.9)	
Community-acquired	79 (16.3)	89 (17.1)	
Comorbidity			
Cancer	303 (62.5)	326 (62.8)	0.91
Diabetes mellitus	188 (38.8)	204 (39.3)	0.86
Chronic kidney disease	147 (30.3)	163 (31.4)	0.71
Coronary artery disease	116 (23.9)	131 (25.2)	0.63
Chronic hepatitis	63 (13.0)	69 (13.3)	0.89
Cerebral vascular accident	46 (9.5)	50 (9.6)	0.94
None	29 (6.0)	24 (4.6)	0.34
Multidrug-resistant organism isolate	275 (56.7)	296 (57.0)	0.92
Critical illness (Pitt score ≥4 points)	162 (33.4)	189 (36.4)	0.32
Source of bloodstream infection			
Urinary tract infection	187 (38.6)	185 (35.6)	0.34
Primary bloodstream infection	156 (32.2)	177 (34.1)	0.55
Intra-abdominal infection	49 (10.1)	54 (10.4)	0.88
Vascular catheter-related infection	33 (6.8)	25 (4.8)	0.18
Pneumonia	17 (3.5)	37 (7.1)	0.01
Skin soft tissue infection	43 (8.9)	42 (8.1)	0.73
Appropriate empiric therapy	381 (78.6)	428 (82.5)	0.12
Time to appropriate therapy (hours)	34.7 ± 15.5	9.5 ± 4.7	<0.001
Outcome			
30-day mortality	145 (29.9)	76 (14.6)	<0.001
Overall mortality	164 (33.8)	97 (18.7)	<0.001
Length of hospital stay of survivor after BSI, median (IQR), days	14 (9–24)	12 (8–19)	<0.001

Data are given as numbers (percentages), unless otherwise specified.
Abbreviation: IQR, interquartile range; BSI, bloodstream infection.

Table 1) in the intervention group. There was a significantly higher proportion of cumulative survival in the intervention group ($P < 0.001$, Fig. 2).

In the subgroup analysis, the 30-day mortality was lower in the intervention group with the gram-positive bacteremia (11.8% *vs.* 32.1%, $P < 0.001$), gram-negative bacteremia (15.4% *vs.* 27.6%, $P = 0.001$) and candidemia (30.0% vs. 37.5%, $P = 0.478$), respectively. In the subgroup of the gram-positive bacteremia, the patients with identified coagulase-negative *staphylococcus* in the blood culture accounted for 49.2%. In the subgroup of gram-negative bacteremia, *Escherichia coli* (19.9%) was the most common pathogen, followed by *Klebsiella pneumoniae* (18.9%), *Acinetobacter baumannii* (9.2%), and *Pseudomonas aeruginosa* (7.2%). *Candida albicans* (31.5%) and *Candida tropicalis* (22.5%) accounted for over 50% of candidemia.

The time to organism identification was significantly shorter in the intervention group (72.3 h *vs.* 83.6 h, $P < 0.001$), and was associated with a lower 30-day mortality ($P = 0.06$). The Kaplan–Meier analysis disclosed a significantly shorter time from blood culture positivity to optimal antibiotic therapy for the patients in the intervention group ($P < 0.001$) (Fig. 3).

In the intervention group, the acceptance of advice of antibiotic recommendation by ASI (13.7% vs. 22.0%, $P = 0.09$), or de-escalation (11.1% vs. 19.9%, $P = 0.18$) of the antibiotic therapy was associated with a trend toward reduced 30-day mortality.

Discussion

Our study demonstrated that rapid organism identification by MALDI-TOF combined with ASI decreased time to organism identification and time to effective and optimal therapy, which was associated with a decrease in mortality, shorter length of stay. The ASI combine with MALDI-TOF-MS rapid respond to approach to therapeutic care for BSIs with an early initiation of optimal antimicrobial therapy.[24]

Our finding also highlighted the workflow optimization between microbiology laboratory, ASI members, and primary care physicians in a communication bundle. Because the modification of antimicrobial regimens without ASI may be inappropriate,[18] we optimized our workflow for rapid testing and communication between ASI and primary care physicians to act quickly and accurately according to the identified organism and susceptibility results. Out study demonstrated that the rapid reaction to the results of blood cultures could be tailored to individualized hospital workflow and would have a positive impact on the patients' clinical outcomes.

Table 2 Multivariate logistic regression analysis of the variables associated with the 30-day mortality.

Variables	Survivors (n = 783)	Non-survivors (n = 221)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* values	OR (95% CI)	*p* values
Age; median (IQR), year	67 (57—78)	68 (62—77)	—	0.42		
Male gender	427 (54.5)	116 (52.5)	0.92 (0.68—1.24)	0.59		
Diabetes mellitus	305 (39.0)	87 (39.4)	1.02 (0.75—1.38)	0.94		
Chronic kidney disease	245 (31.3)	65 (29.4)	0.92 (0.66—1.27)	0.62		
Malignancy	497 (63.5)	132 (59.7)	0.85 (0.63—1.16)	0.31		
Chronic hepatitis	108 (13.8)	24 (10.9)	0.76 (0.48—1.22)	0.31		
Pneumonia	34 (4.3)	20 (9.0)	2.19 (1.24—3.89)	0.01	2.25 (1.19—4.26)	0.01
Critical Illness (Pitt score ≥4 points)	210 (26.8)	141 (63.8)	4.81 (3.50—6.60)	<0.001	5.39 (3.86—7.53)	<0.001
Antibiotic stewardship intervention	443 (56.6)	76 (34.4)	0.40 (0.30—0.55)	<0.001	0.33 (0.24—0.47)	<0.001
Multidrug resistant isolates	451 (57.6)	120 (54.3)	0.88 (0.65—1.18)	0.40		
Appropriate antimicrobial therapy	774 (98.9)	211 (95.5)	0.25 (0.10—0.61)	0.003	0.25 (0.09—0.67)	<0.001

Data are given as the numbers (percentages) unless otherwise specified. Ellipses indicate "not available".
Abbreviation: OR, odds ratio; CI, confidence interval; IQR, interquartile range.

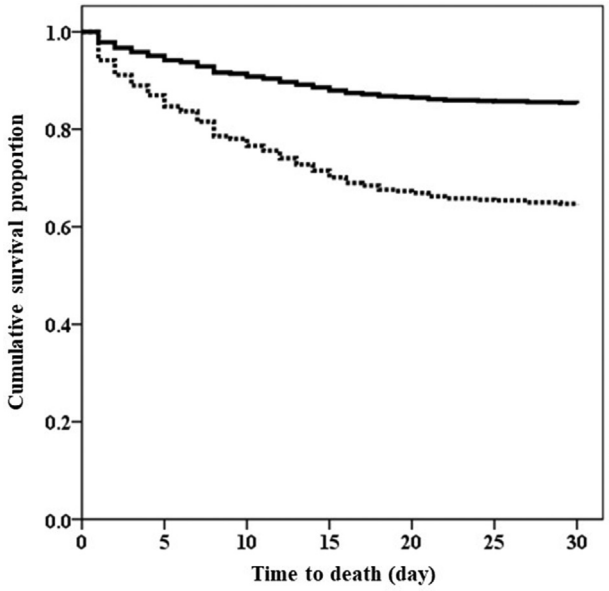

Figure 2. The survival analysis curves for the BSIs in the intervention (solid line) and pre-intervention period (dot line) ($P < 0.001$, log rank test).

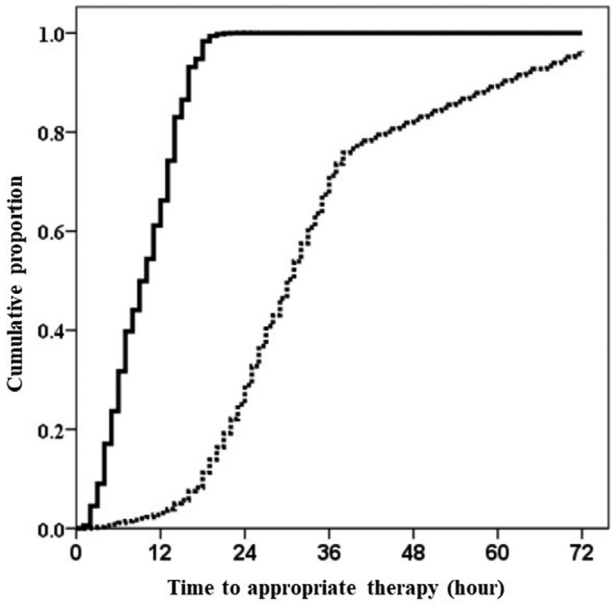

Figure 3. The Kaplan—Meier analysis of the time from blood culture positivity to optimal antibiotic therapy in the intervention (solid line) and pre-intervention period (dot line) ($P < 0.001$, log-rank test).

In our study, the rate of MDRO showed no significant difference between the intervention and pre-intervention groups (57% vs. 56.7%, $P = 0.92$), but the rate of third-generation cephalosporin-resistant *Enterobacterales* (23.1% vs. 15.1%, $P = 0.001$) was higher while vancomycin-resistant *Enterococcus* species (0.8% vs. 9.7%, $P < 0.001$) was lower in the intervention group. The high rate of a resistant strain was probably in relation to the usage of specific antibiotic regimens. The daily defined doses of antibiotics for 1000 persons per day (DID) of ceftriaxone (10047.0 vs. 6773.0) and ceftazidime (15170.3 vs. 13957.8) were higher in 2015, which was the year of patient collection into the intervention group. The DID of vancomycin (10310.3 vs. 9814.5) and teicoplanin (3110.0 vs. 2758.0) were higher in 2014, which was the year of patient collection into the pre-intervention group.

Previous retrospective single-center study in Korea showed that MALDI-TOF-MS would shorter the time to organism identification, but it was not associated with a lower 28-day mortality in the patients with multidrug-resistant bacteremia.[19] The early ID specialist consultation was proved to be associated with better clinical outcomes in the patients with diagnosed infections.[20] The ASI acted as an important role in the prognosis of the patients with BSIs.[21] The patients receiving MALDI-TOF-MS for organism identification of BSIs without the assistance of ASI may not significantly reduce the time to initiate timely effective therapies and lead to lower mortality rates.[22] The acceptance of advice by ASI resulted in a lower 30-day mortality for the patients in the intervention group (13.7% vs. 22.0%, $P = 0.088$) compared with the pre-intervention

group. Among the patients in the intervention group, de-escalation (11.1% vs. 19.9%, P = 0.18) of the empiric therapy didn't lead to a higher 30-day mortality. The results emphasized the importance of the modifications of antimicrobial regimens according to the organism identification, antimicrobial susceptibility report, and the assistance of ASI for the patients with BSIs.

There were several limitations in our study. First, the patients often had multiple comorbidities and advanced age those would be associated an increased risk of mortality. However, we conducted a multivariable regression analysis correcting for age, comorbidities, source of infection, and disease severity to adjust for some of these potential confounding factors. The standard of care for patients with BSI didn't modify during the study periods. Second, the member of ASI (including ID specialists and clinical pharmacists) at our hospital may not be applied in other hospitals to perform ASI efficiently and accurately. The minimal requirement of the personnel for ASI should depend on the patient number, accessible tools for organism identification, antimicrobial susceptibilities, incidence of BSIs and MDROs in each medical facility. Finally, the 30-day mortality may not reflect the long-term survival, and the long-term clinical outcomes in both groups were uncertain.

Conclusion

The target of antibiotic stewardship intervention is to maximize patient outcomes while minimizing the unintended consequences of inappropriate antibiotic use. The ASI combined with MALDI-TOF-MS would decrease the time to organism identification and time to appropriate antimicrobial therapy, and therefore achieve better clinical outcomes in the patients with BSIs.

Financial support

This study was supported by the grants from the Ministry of Science and Technology, Taiwan (MOST 111-2321-B-006-009-).

Author contributions

N.Y.L. and W.C.K. conceived the study. T.P.W., C.L.L., W.L.L., J.C.L. and M.C.L. provided data collection, statistical and analytic support. N.Y.L. and T.P.W. analyzed the data. N.Y.L. and T.P.W. prepared the manuscript. All authors reviewed and edited the manuscript.

Declaration of competing interest

All authors: no conflicts.

References

1. Diekema DJ, Beekmann SE, Chapin KC, Morel KA, Munson E, Doern GV. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *J Clin Microbiol* 2003;**41**:3655—60.
2. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004;**39**:309—17.
3. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. *Clin Infect Dis* 2003;**36**:1418—23.
4. Barenfanger J, Graham DR, Kolluri L, Sangwan G, Lawhorn J, Drake CA, et al. Decreased mortality associated with prompt Gram staining of blood cultures. *Am J Clin Pathol* 2008;**130**:870—6.
5. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis* 2013;**57**(9):1237—45.
6. Gaynes R. The impact of antimicrobial use on the emergence of antimicrobial-resistant bacteria in hospitals. *Infect Dis Clin* 1997;**1**:757—65.
7. Magadia RR, Weinstein MP. Laboratory diagnosis of bacteremia and fungemia. *Infect Dis Clin* 2001;**15**:1009—24.
8. Fabre V, Sharara SL, Salinas AB, Carroll KC, Desai S, Cosgrove SE. Does this patient need blood cultures? A scoping review of indications for blood cultures in adult non-neutropenic inpatients. *Clin Infect Dis* 2020;**71**:1339—47.
9. Opota O, Croxatto A, Prod'hom G, Greub G. Blood culture-based diagnosis of bacteraemia: state of the art. *Clin Microbiol Infect* 2015 Apr;**21**(4):313—22.
10. Haddad G, Bellali S, Takakura T, Fontanini A, Ominami Y, Bou Khalil J, et al. Scanning electron microscope: a new potential tool to replace gram staining for microbe identification in blood cultures. *Microorganisms* 2021;**9**(6):1170.
11. Clark Andrew E, Kaleta Erin J, Amit Arora, Wolk Donna M. Matrix-assisted laser desorption ionization—time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. *Clin Microbiol Rev* 2013;**26**(3):547—603.
12. Vlek AL, Bonten MJ, Boel CE. Direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry improves appropriateness of antibiotic treatment of bacteremia. *PLoS One* 2012;**7**:e32589.
13. Angeletti S, Dicuonzo G, D'Agostino A, Avola A, Crea F, Palazzo C, et al. Turnaround time of positive blood cultures after the introduction of matrix-assisted laser desorption-ionization time-of-flight mass spectrometry. *New Microbiol* 2015;**38**:379—86.
14. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Falck-Ytter YT, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. *Clin Infect Dis* 2016;**62**:e51—77.
15. Opota O, Croxatto A, Prod'hom G, Greub G. Blood culture-based diagnosis of bacteraemia: state of the art. *Clin Microbiol Infect* 2015;**21**(4):313—22.
16. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis* 2013;**57**(9):1237—45.
17. Tan KE, Ellis BC, Lee R, Stamper PD, Zhang SX, Carroll KC. Prospective evaluation of a matrix-assisted laser desorption ionization-time of flight mass spectrometry system in a hospital clinical microbiology laboratory for identification of bacteria and yeasts: a bench-by-bench study for assessing the

impact on time to identification and cost-effectiveness. *J Clin Microbiol* 2012;**50**(10):3301—8.
18. Dellit TH, Owens RC, McGowan Jr JE, Gerding DN, Weinstein RA, Burke JP, et al. Infectious diseases society of America; society for healthcare epidemiology of America. Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;**44**(2):159—77.
19. Mok J, Jo E-J, Eom JS, Kim M-H, Kim KU, Park H-K, et al. Clinical efficacy of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry in patients with multidrug-resistant bacteremia: a single-center study in Korea. *Korean J Intern Med* 2019;**34**(5):1058—67.
20. Schmitt S, McQuillen DP, Nahass R, Martinelli L, Rubin M, Schwebke K, et al. Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. *Clin Infect Dis* 2014;**58**(1):22—8.
21. Maeda M, Takuma T, Seki H, Ugajin K, Naito Y, Yoshikawa M, et al. Effect of interventions by an antimicrobial stewardship team on clinical course and economic outcome in patients with bloodstream infection. *J Infect Chemother* 2016;**22**(2):90—5.
22. Jeon YD, Seong H, Kim D, Ahn MY, Jung IY, Jeong SJ, et al. Impact of matrix-assisted laser desorption/ionization time of flight mass spectrometric evaluation on the clinical outcomes of patients with bacteremia and fungemia in clinical settings lacking an antimicrobial stewardship program: a pre-post quasi experimental study. *BMC Infect Dis* 2018;**18**(1):385.
23. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* 1999;**11**(1):7—12.
24. Delport J, Strikwerda A, Armstrong A, Schaus D, John M. MALDI-ToF short incubation identification from blood cultures is associated with reduced length of hospitalization and a decrease in bacteremia associated mortality. *Eur J Clin Microbiol Infect Dis* 2017;**36**(7):1181—6.