Comparison of semiquantitative and differential time to positivity methods for the diagnosis of central line-associated bloodstream infections in an intensive care unit

Theodoros Karampatakis1,2,*, Katerina Tsergouli2, Ekaterini Karantani2, Anna Diamantopoulou2, Eleni Mouloudi3, Emmanuel Rollides1,4 and Angeliki Karyoti2,4

Abstract

Introduction. Central line-associated bloodstream infections (CLABSIs) adversely affect patients’ hospitalization.

Aim. We compared semiquantitative roll plate (SQRP) and differential time to positivity (DTP) culture methods in diagnosing CLABSIs.

Methodology. A retrospective study was conducted in an intensive care unit (ICU) from January 2013 to August 2014. All ICU patients with suspected CLABSIs were included. Blood cultures were taken, while central venous catheter (CVC) tips were cultured using the roll-tip method. DTP was considered positive if CVC lumen blood cultures became positive at least 2 h prior to concurrently drawn peripheral blood cultures with an identical micro-organism. SQRP method was considered positive when ≥15 c.f.u. of a micro-organism identical to that of blood cultures grew. Measures of diagnostic accuracy were calculated.

Results. SQRP displayed high sensitivity (94.7%), while DTP showed high specificity (82.5%). SQRP combined with DTP displayed 100% sensitivity and negative predictive value.

Conclusion. SQRP and DTP methods should be evaluated in combination.

INTRODUCTION

Central venous catheters (CVCs) are very helpful devices, widely used during hospitalization of critically ill patients [1]. Central line-associated bloodstream infections (CLABSIs) are important complications of their use [2]. According to the Centers for Disease Control and Prevention (CDC), CLABSI is defined as a primary laboratory-confirmed bloodstream infection (BSI) in a patient with a central line placed for >2 calendar days, occurring at the time of, or within 24 h prior to, the onset of symptoms, in cases where the cultured organism is not related to an infection from another site [3]. CLABSIs may have a crucial impact on mortality and cost of patients’ hospitalization [4, 5]. Therefore, the prevention of such infections is of great importance and requires the implementation of optimal practices [2]. CLABSIs frequently necessitate removal of the CVCs [6]. However, studies reveal that in up to 80% of cases, the removed devices are not the source of the patients’ symptoms [7].

Conventional methods that contribute to the diagnosis of CLABSIs include CVC tip cultures using semiquantitative or quantitative methods [8], paired quantitative blood cultures taken through catheter lumen or peripherally and differential time to positivity (DTP) methods [9]. The aim of this study was to compare the semiquantitative roll plate (SQRP) and DTP methods for the diagnosis of CLABSIs in patients of an ICU.

METHODS

This retrospective cohort study was conducted in the nine-bed adult ICU of Hippokration General Hospital of Thessaloniki.
from January 2013 to August 2014. All ICU patients with suspected CLABSIs bearing a CVC were included. CLABSIs were defined according to the CDC criteria [3]. BSIs with data on CVC tip cultures, as well as CVC lumen and peripheral blood cultures were studied.

Blood cultures were taken in aerobic and anaerobic bottles containing 5 ml each and incubated in a BacT/Alert 3D system (Biomerieux, Marcy-l’Etoile, France), while CVC tips were cultured using the roll-tip method [10]. Identification and antimicrobial susceptibility testing was performed by a VITEK 2 automated system (Biomerieux, Marcy-l’Etoile, France). Interpretation results, expressed as sensitivity, intermediate sensitivity and resistance, were determined according to the 2014 Clinical and Laboratory Standards Institute breakpoints [11]. Micro-organisms were considered identical when they were of the same species and had the same antimicrobial susceptibility profile.

DTP was considered positive if CVC lumen blood cultures became positive at least 2 h prior to concurrently drawn peripheral blood cultures with an identical micro-organism, as previously described [12]. DTP was calculated using the BacT/Alert 3D system. The CVC tip was removed approximately 48 h before or after blood cultures were drawn. The SQRP method was considered positive when ≥15 c.f.u. of a micro-organism identical to that of blood cultures grew, as previously described [10]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR) were used as measures of diagnostic accuracy and were calculated as previously described [13], with an exact binomial 95 % confidence interval (CI).

Normality of continuous variables was evaluated using Kolmogorov–Smirnov and Shapiro–Wilk tests according to sample size. Differences in non-normally distributed variables were evaluated using Mann–Whitney U-test, while in normally distributed variables Student’s t-test was used. Categorical variables were compared using Pearson’s chi-square or Fisher’s exact test. The level of statistical significance was set at $P<0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, 22nd version, IBM).

Table 1. Demographic data of patients with CLABSIs and non-CLABSIs

| Parameter                      | Total cohort | CLABSI | non-CLABSI | OR$^a$ (95 % CI) | $P$-value |
|-------------------------------|-------------|--------|------------|-----------------|-----------|
| Patients, $n$ (%)             | 51 (100)    | 19 (37.3) | 32 (62.7) | –               | –         |
| Age (years), median (IQR)     | 56 (17)     | 56 (20) | 55.5 (15) | –               | 0.60$^b$  |
| Sex male, $n$ (%)             | 36 (70.6)   | 11 (57.9) | 25 (78.1) | 0.38 (0.112–1.327) | 0.125$^c$ |
| ICU length of stay (days), mean (sd) | 25.9 (15.9) | 28.5 (20.3) | 24.4 (12.8) | –               | 0.38$^d$  |

$a$, Odds ratio.  
$b$, Mann–Whitney U test.  
$c$, Chi-square.  
$d$, t-test.

![Fig. 1](image-url). Frequencies of isolated pathogens in ICU patients with BSI. Others: single isolates of C. tropicalis, E. cloacae, E. aerogenes, E. faecalis, S. marcescens, S. aureus and S. haemolyticus.
RESULTS
A total of 59 BSIs were evaluated in 51 patients. The demographic data of patients are shown in Table 1. There was no significant association between CLABSI or non-CLABSI and patients’ survival. CLABSI was confirmed in 19 out of 59 BSIs (32.2 %). Overall, 27 out of 59 BSIs (45.8 %) were positive by the SQRP method, while 18 cases (30.5 %) were positive by the DTP method. Median time for DTP in these cases was 5.1 (IQR=20.8) h. Klebsiella pneumoniae was the most frequent pathogen isolated (33.9 %), followed by Acinetobacter baumannii, Candida spp. and Pseudomonas aeruginosa (23.7, 15.3 and 11.9 %, respectively) (Fig. 1).

For the diagnosis of CLABSIs, SQRP displayed high sensitivity (94.7 %) and NPV (96.9 %) reaching percentages similar to previous studies [16]. This means that SQRP, which is commonly used by the majority of laboratories, can adequately preclude a CLABSI itself. The SQRP method presents the inability to culture bacteria from the internal lumen, however other techniques used to solve this problem have not shown any additional advantage [18]. However, the most important limitation of the SQRP method is that its performance requires prior CVC removal.

The combination of SQRP and DTP methods displayed 100 % sensitivity and NPV, a result that is also supported by Gowdorman et al. [16]. Despite the fact that the quantitative method is considered a reference standard [8, 19], it is not implemented in the majority of hospitals. Thus, the combination of negative SQRP and DTP results could rule out CLABSIs, as demonstrated in our study. A limitation of our study was that it was conducted retrospectively and did not include all ICUs of our hospital. In conclusion, when the quantitative method is not available, attempts should be made so that SQRP and DTP methods are evaluated in combination.

DISCUSSION
This study demonstrated the importance of SQRP and DTP methods in diagnosing CLABSIs. The DTP method presented high specificity (82.5 %) reaching levels similar to those shown by Bouza et al. [14]. In practice, this means that a positive DTP result can prove that a BSI is central line-associated and therefore the CVC needs to be removed, apart from cases in which lock therapy is indicated [15]. The clinical utility of the latter can be optimized if using DTP combined with superficial cultures of the skin entry site, as displayed by previous studies [16]. In contrast, a previous study including a very low number of BSIs has revealed that the DTP method is not suitable for the diagnosis of CLABSIs in surgical critically ill patients [17].

SQRP displayed high sensitivity (94.7 %) and NPV (96.9 %) reaching percentages similar to previous studies [16]. This means that SQRP, which is commonly used by the majority of laboratories, can adequately preclude a CLABSI itself. The SQRP method presents the inability to culture bacteria from the internal lumen, however other techniques used to solve this problem have not shown any additional advantage [18]. However, the most important limitation of the SQRP method is that its performance requires prior CVC removal.

The combination of SQRP and DTP methods displayed 100 % sensitivity and NPV, a result that is also supported by Gowdorman et al. [16]. Despite the fact that the quantitative method is considered a reference standard [8, 19], it is not implemented in the majority of hospitals. Thus, the combination of negative SQRP and DTP results could rule out CLABSIs, as demonstrated in our study. A limitation of our study was that it was conducted retrospectively and did not include all ICUs of our hospital. In conclusion, when the quantitative method is not available, attempts should be made so that SQRP and DTP methods are evaluated in combination.

Table 2. Measures of diagnostic accuracy with 95 % CI

|                        | SQRP             | DTP              | SQRP combined with DTP |
|------------------------|------------------|------------------|------------------------|
| Sensitivity % (95 % CI)| 94.7 (71.9–99.7) | 57.9 (33.9–78.9) | 100.0 (79.1–100.0)     |
| Specificity % (95 % CI)| 77.5 (61.1–88.6) | 82.5 (66.7–92.1) | 67.5 (50.8–80.9)       |
| Positive predictive value (PPV) % (95 % CI)| 66.7 (46.0–82.8) | 61.1 (36.1–81.7) | 59.3 (40.8–67.1)       |
| Negative predictive value (NPV) % (95 % CI)| 96.9 (82.0–99.8) | 80.5 (64.6–90.6) | 100.0 (84.5–100.0)     |
| Accuracy % (95 % CI)  | 83.1 (70.9–86.3) | 74.6 (61.7–85.1) | 77.9 (66.5–77.9)       |
| Positive likelihood ratio (LR+) (95 % CI) | 4.21 (2.35–7.56) | 3.31 (1.52–7.18) | 3.08 (1.97–4.81)       |
| Negative likelihood ratio (LR-) (95 % CI) | 0.07 (0.01–0.46) | 0.51 (0.30–0.87) | 0.00 (0.00–0.31)       |
| Diagnostic odds ratio (DOR) (95 % CI) | 62.0 (7.3–530.2) | 6.5 (1.9–22.0)   | 79.4 (4.4–1417.7)      |

Funding information
The authors received no specific grant from any funding agency.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethics statement
The study was carried out in accordance with the Declaration of Helsinki, as revised in 2008 and was approved by the Ethics Committee of Aristotle’s University Medical Faculty. Written informed consent by patients was not deemed necessary by the Ethics Committee for patients’ samples taken for culture.

References
1. Frasca D, Dahyot-Fizelier C, Mimoz O. Prevention of central venous catheter-related infection in the intensive care unit. Crit Care 2010;14:212.
2. Timsit JF, Rupp M, Bouza E, Chopra V, Kärpänen T et al. A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill. Intensive Care Med 2018;44:742–759.

3. Horan TC, Gaynes RP. Surveillance of nosocomial infections. Appendix A-1: CDC definitions of nosocomial infections. In: Mayhall CG (editor). Hospital Epidemiology an Infection Control, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2004. pp. 1659–1702.

4. Siempos II, Kopterides P, Tsangaris I, Dimopoulos I, Armaganidis AE. Impact of catheter-related bloodstream infections on the mortality of critically ill patients: a meta-analysis. Crit Care Med 2009; 37:2287–2292.

5. Nuckols DA, Kortan P, Newton M, Chynoweth D, Bishop N et al. Economic evaluation of quality improvement interventions for bloodstream infections related to central catheters: a systematic review. JAMA Intern Med 2016;176:1843–1854.

6. Lucet JC, Bouadma L, Zahar JR, Schwebel C, Geoffroy A et al. Infectious risk associated with arterial catheters compared with central venous catheters. Crit Care Med 2010;38:1030–1035.

7. Brun-Buisson C. Suspected central venous catheter-associated infection: can the catheter be safely retained? Intensive Care Med 2004; 30:1005–1007.

8. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. Clin Infect Dis 2009; 49:1–45.

9. Catton JA, Dobbins BM, Kite P, Wood JM, Eastwood K et al. In situ diagnosis of intravascular catheter-related bloodstream infection: a comparison of quantitative culture, differential time to positivity, and endoluminal brushing. Crit Care Med 2005; 33:787–791.

10. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977;296:1305–1309.

11. CLSI. Performance Standards for Antimicrobial Susceptibility Testing, Twenty-Fourth Informational Supplement M100–S24. USA: CLSI, Wayne, PA; 2014.

12. Blot F, Nitenberg G, Chachaty E, Raynard B, Germann N et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. Lancet 1999;354:1071–1077.

13. Šimundić AM. Measures of diagnostic accuracy: basic definitions. EJIFCC 2009;19:203–211.

14. Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C et al. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis 2007;44:820–826.

15. Freire MP, Pierrotti LC, Zerati AE, Benites L, da Motta-Leal Filho JM et al. Role of lock therapy for long-term catheter-related infections by multidrug-resistant bacteria. Antimicrob Agents Chemother 2018;62 [Epub ahead of print 27 08 2018].

16. Gowdaman JR, Jeffries P, Lassig-Smith M, Stuart J, Jarrett P et al. A comparative assessment of two conservative methods for the diagnosis of catheter-related infection in critically ill patients. Intensive Care Med 2013;39:109–116.

17. Rijnders BJ, Verwaest C, Peetermans WE, Wilmer A, Vandecasteele S et al. Difference in time to positivity of hub-blood versus nonhub-blood cultures is not useful for the diagnosis of catheter-related bloodstream infection in critically ill patients. Crit Care Med 2001; 29:1399–1403.

18. Bouza E, Alvarado N, Alcalá L, Sánchez-Conde M, Pérez MJ et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis 2005;40:1096–1100.

19. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 2005;142:451–466.

---

**Five reasons to publish your next article with a Microbiology Society journal**

1. The Microbiology Society is a not-for-profit organization.
2. We offer fast and rigorous peer review – average time to first decision is 4–6 weeks.
3. Our journals have a global readership with subscriptions held in research institutions around the world.
4. 80% of our authors rate our submission process as ‘excellent’ or ‘very good’.
5. Your article will be published on an interactive journal platform with advanced metrics.

Find out more and submit your article at microbiologyresearch.org.