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Influence of a resin-based blood culture medium on the time to clearance of methicillin-susceptible *Staphylococcus aureus* bloodstream infection – A retrospective cohort study

Nicolas Gürtler [a,*,1], Anthea Denz [a,1], Adrian Egli [c,d], Andreas F. Widmer [b], Michael Osthoff [a,d]

[a] Division of Internal Medicine, University Hospital Basel, Basel, Switzerland
[b] Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
[c] Division of Clinical Microbiology, University Hospital Basel, Basel, Switzerland
[d] Department of Biomedicine, University Basel, Basel, Switzerland

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ABSTRACT

We evaluated the improved sensitivity and time to detection of new resin-based blood culture (BC) media in *Staphylococcus aureus* bloodstream infection. We observed a significantly longer duration of bacteremia and shorter time to detection compared to traditional charcoal-based BC media, which may influence diagnostic work-up and treatment duration.

Staphylococcus aureus remains a leading cause of bloodstream infections (BSI) associated with considerable morbidity and mortality. (Laupland, 2013; Lopez-Cortes et al., 2013) Blood cultures (BC) are the gold standard for the diagnosis and management of *S. aureus* BSI (SA-BSI). Repeated sampling of BC is recommended to determine clearance and inform about a complicated disease course. Median time to clearance is 3–4 days for methicillin-susceptible (MSSA) and 8–9 days for methicillin-resistant (MRSA) SA-BSI. (van Hal et al., 2012) According to international guidelines intravenous antibiotic treatment should continue for at least 2 weeks for uncomplicated and up to 4–6 weeks for complicated SA-BSI. (Liu et al., 2011; Thwaites et al., 2011)

In the past, BC media have been supplemented with charcoal particles to adsorb antimicrobial agents. Recently, resin containing BC bottle have been introduced, which are superior to charcoal-containing media in terms of pathogen detection and time to positivity. (Gibb et al., 1998; Lee et al., 2013) In particular, sensitivity was improved in patients, who received antibiotic treatment for up to 48 hours before BC sampling. (Kirn et al., 2014; Lee et al., 2013; Mitteregger et al., 2013; Zadroga et al., 2013)

However, this improved detection rate may arbitrarily prolong the time to clearance of SA-BSI, which has not yet been investigated.

In this study we reviewed Patients with a first MSSA SA-BSI episode during 2011–2013 (charcoal-based cohort) and between January 2015 and April 2016 (resin-based cohort) and admitted to our tertiary care hospital. Patients with MRSA bacteremia were excluded to limit further bias. The period was chosen according to the time of introduction of the resin-based BC bottles in 2014. The Ethics Committee of Northwestern and Central Switzerland approved the study (EKNZ 2016–279).

In the first cohort (2011–2013), rapid processing of the charcoal-based BC was ensured 24/7 using the same BC system (biomerieux BacT/ALERT®, Marcy l'Etoile, France) with at least one pair of aerobic/anaerobic bottles (bioMérieux BacT/ALERT® FA/FN) processed. In the second cohort (2015–2016), the same procedures were applied with a resin-based BC system (bioMérieux BacT/ALERT® Plus) with at least one pair of aerobic/anaerobic bottles (biomerieux BacT/ALERT® FA/FN Plus) processed. In both cohorts, BC were routinely incubated for 6 days. The primary endpoint was the time to clearance of SA-BSI, defined as the difference between the time that the first positive BCs were drawn, and the time, that the first (persistently) negative BCs were collected. A power calculation indicated that at least 80 patients using resin-based media and 160 patients using charcoal-based BC media are required to detect a difference of 1.5 days in the mean

Abbreviations: BC, blood culture; BSI, bloodstream infections; SA-BSI, *S. aureus* BSI; MSSA, methicillin-susceptible; MRSA, methicillin-resistant; CB, charcoal-based; RB, resin-based; IQR, interquartile range; TTP, time-to-positivity.

* Corresponding author. Tel.: +41-61-56-53-17; fax: +41-61-265-53-90.
E-mail address: nicolas.guertler2@usb.ch (N. Gürtler).

[1] Nicolas Gürtler and Anthea Denz contributed equally to this study.

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Table 1
Clinical characteristics and outcome according to blood culture media used.

	Resin-based BC media N = 99	Charcoal-based BC media N = 195	*P*-value
Age in years, mean (SD)	62.1 (16.3)	62.2 (17.0)	0.8
Male sex, n (%)	68 (68.7)	139 (71.3)	0.6
Central venous line, n (%)	19 (19.2)	38 (19.5)	0.9
Intravenous drug users, n (%)	10 (10.1)	33 (16.9)	0.1
Vascular implants, n (%)	19 (19.2)	35 (17.9)	0.8
Orthopedic implants, n (%)	19 (19.2)	49 (25.1)	0.3
Immunosuppression, n (%)[1]	18 (18.2)	24 (12.3)	0.2
Surgery during the last month, n (%)	13 (13.1)	40 (20.5)	0.1
Focus of infection			
Endocarditis/intravascular, n (%)	41 (41.4)	75 (38.5)	0.6
Bone and joint, n (%)	21 (21.2)	25 (12.8)	0.06
Respiratory, n (%)	5 (5.1)	11 (5.6)	0.8
Skin and soft tissue, n (%)	13 (13.1)	27 (13.8)	0.8
Other or unknown, n (%)	19 (19.2)	57 (29.2)	0.06
Empirical treatment[2]			
β-Lactams, n (%)	93 (93.9)	183 (93.8)	0.9
Vancomycin, n (%)	2 (2.0)	8 (4.1)	0.4
Other, n (%)[3]	13 (13.1)	31 (15.9)	0.5
Targeted i.v. combination therapy[4]			
Daptomycin, n (%)	23 (23.2)	27 (13.8)	0.04
Rifampin, n (%)	13 (13.1)	9 (4.6)	0.009
Aminoglycosides, n (%)	16 (16.2)	40 (20.5)	0.4
Charlson Comorbidity Score mean (SD)	2.2 (2.2)	2.5 (2.1)	0.4
Pitt Bacteremia Score, mean (SD)	0.7 (1.2)	1.1 (1.2)	0.04
I.v. antibiotic combination therapy, n (%)	30 (30.3)	53 (27.2)	0.6
Length of hospital stay in days, median (IQR)	22 (16–34)	26 (18–38)	0.1
Duration of i.v. antibiotic therapy in days, median (IQR)	29 (17–36)	27 (16–34)	0.2

Abbreviations: BC, blood culture; i.v., intravenous; SD, standard deviation; IQR, interquartile range; [1]treatment with at least 5 mg prednisone equivalent per day in the last 7 days or classical immunosuppressive agents, chemotherapeutics or monoclonal antibodies; Pitt Bacteremia Score is a widely used severity-of-illness score, which is mainly used to estimate short-term mortality in bloodstream infections and is not pathogen-specific. [2]Empirical therapy at time of first positive blood culture. [3]Mostly empirical combination therapy with aminoglycosides and/or rifampin. [4]Additional intravenous targeted therapy after identification of *S. aureus*.

duration of bacteremia (85% power, standard deviation 3.5 days), and hence the analysis periods were chosen accordingly.

All variables were analyzed with chi-square, Wilcoxon-Mann–Whitney-Test or the Student's t-test where appropriate. All testing was two-tailed, and an alpha level of 5% was considered to be statistically significant. We used SPSS 22 software for all statistical calculations (SPSS; IBM, Chicago, IL, U.S.A.).

A total of 294 patients with MSSA SA-BSI were included, 195 in the charcoal-based (CB) and 99 in the resin-based (RB) cohort. Baseline characteristics in the two cohorts were similar. (Table 1).

Time to clearance of bacteremia was significantly longer in the RB cohort compared to the CB cohort (median 3.7 (interquartile range (IQR) 2.0–5.8) vs. 2.5 (IQR 1.3–4.0) days, $P < 0.001$) (Fig. 1). The difference remained significant when excluding patients in whom the first negative BC was drawn more than 3 days after the last positive BC (median 2.9 vs. 1.7 days, $P < 0.001$).

The median number of blood culture bottles per day averaged over the period starting from the first positive until the first persistently negative was similar (3.1 (IQR 2.3–4.1,) vs. 3.2 (IQR 2.3–4.4) bottles, RB vs. CB cohort, $P = 0.3$).

Median time-to-positivity (TTP) of the first positive blood culture was shorter in the RB cohort (14.0 (IQR 11.3–16.4) vs. 15.0 (IQR 12.1–19.2) hours, $P = 0.01$). Intravenous treatment and duration of admission were similar. (Table 1).

Previous studies have shown that RB media are superior to CB media in terms of sensitivity and time to detection for SA-BSI within the first 48 hours of antibiotic treatment. (Gibb et al., 1998; Kirn et al., 2014; Lee et al., 2013; Mitteregger et al., 2013; Zadroga et al., 2013) In line, we demonstrate a shorter median TTP for the first positive BC, although the difference was less pronounced compared to studies using a defined and equal filling volume of blood. Additionally, we extend these findings to BC sampled after more than 48 hours of antibiotic treatment demonstrating for the first time, that the time to clearance of MSSA SA-BSI is more than 24 hours longer when using RB compared to CB BC media.

The length of bacteremia is relevant for the diagnostic work-up as positive follow-up blood cultures after 72–96 hours predict a complicated disease course, and some experts advocate to count the duration of intravenous treatment from the first negative blood culture. (Fowler et al., 2003; Holland et al., 2014) Hence, an improved sensitivity of follow-up BCs may lead to more patients requiring a diagnostic work-up for complicated disease and a longer treatment. In fact, multiple positive BCs after starting active antibiotic therapy commonly trigger a search for an intravascular or metastatic source of SA-BSI, that may be a result of the more sensitive RB BC media rather than of a true prolonged bacteremia. In the present study, the median duration of treatment was two days longer in the RB cohort ($P = 0.2$). However, our study was not powered for this outcome, and the difference in the time to clearance was only small in relationship to a total treatment duration of 2–6 weeks.

Limitations of our study include its single-center nature using data from an established cohort study. The two cohorts may not be fully

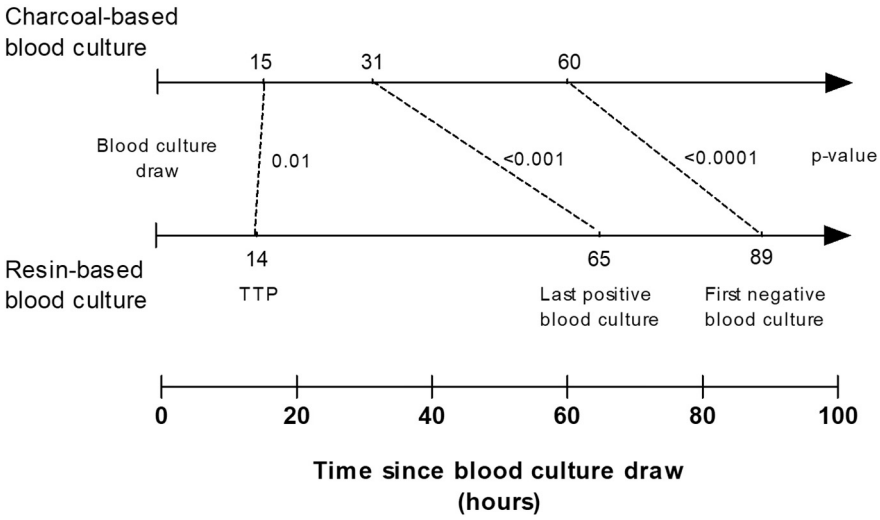

Fig. 1. Timeline of blood culture results in hours since first positive blood culture draw. Abbreviations: TTP, time to positivity.

comparable, and the amount of blood used for incubating the BCs was not routinely recorded. We were also not able to ascertain any differences in diagnostic work-up associated with a prolonged bacteremia. Strengths include a standardized diagnostic and treatment algorithm with active involvement of our infectious diseases team in every single SA-BSI, that should have markedly reduced confounding due to different diagnostic evaluation and treatment in the two groups, and treatment strategies for MSSA SA-BSI have not changed during the study period. This also includes a recommendation of when and how many BC have to be drawn.

In conclusion, duration of MSSA *S. aureus* bacteremia was 1.2 days longer when using resin-based BC media compared to charcoal-based BC media. Duration of SA-BSI in previous studies may be biased by the type of BC media used, which may influence diagnostic work-up and treatment duration.

Declarations

Conflict of interest
The authors declare that they have no competing interests.
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Access to data

The data used and analyzed in this work is available from the corresponding author on reasonable request.

Contribution

MO designed the study. NG and AD collected all data. NG performed the statistical analysis. AD and MO drafted the manuscript, which was further edited by NG, AW, AE and MO. All authors were involved in the interpretation of data, critical revision of the manuscript for important intellectual content, and read and approved the final manuscript.

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