



Onset of symptoms, diagnostic confirmation, and occurrence of multiple infective foci in patients with *Staphylococcus aureus* bloodstream infection: a look into the order of events and potential clinical implications

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Abstract

Purpose Data on the systemic dissemination in *Staphylococcus aureus* bloodstream infection (SAB) remain sparse. We investigated the timing and the sequence of clinical symptoms, diagnostic confirmation, and occurrence of multiple infective foci in relation to three major infective foci.

Methods From 2006 to 2011, all adult patients with first-time SAB in Cologne and Freiburg, Germany were followed prospectively. The study was restricted to patients with short-term central venous catheter (CVC)-related SAB, vertebral osteomyelitis (VO), and infective endocarditis (IE). The collection date of the first positive blood culture was used as reference point for determining time to onset of clinical symptoms, microbiological findings, imaging results compatible with focal infection, and occurrence of additional infective foci.

Results We included 266 patients with first-time SAB. Among patients with CVC-related SAB, clinical onset, collection of the first positive blood culture, and microbiological confirmation almost coincided. In contrast, among patients with VO or IE, the onset of clinical symptoms most often preceded the collection of the first positive blood culture, and imaging and microbiological confirmation were most frequently obtained subsequent to the SAB diagnosis. CVC-related SAB was infrequently associated with further foci ($n = 15/15.5\%$). Conversely, more than one infective focus was observed in 44 (56.4%) patient with VO and 68 (64.8%) patients with IE.

Conclusions The sequence of clinical symptoms, diagnostic confirmation, and occurrence of multiple infective foci varied considerably with different infective foci in SAB. Based on these results, we propose a pragmatic and evidence-based terminology for the clinical course of SAB and suggest the terms “portal of entry”, “infective focus”, “multiple infective foci”, and “dominant infective focus”.

Keywords *Staphylococcus aureus* bloodstream infection · Infective focus · Clinical course · Terminology

Introduction

Staphylococcus aureus bloodstream infection (SAB) is a serious disease associated with osteoarticular infection, infective endocarditis, and a 30-day mortality of 20–30%

in the Western world [1, 2]. Early identification and control of the infective focus remain the mainstays of clinical management in patients with SAB [3, 4]. Indeed, the prognosis of SAB has been demonstrated to vary considerably according to the infective focus, viz respiratory focus, endocarditis and an unidentified focus are associated with high mortality, whereas SAB due to the infection of intravascular access devices is associated with a better outcome [2, 5, 6]. Nevertheless, rather different and inconsistent definitions of the infective focus have been employed in prior studies of SAB and terms such as source of infection, portal of entry, primary and secondary infective foci and primary

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and secondary SAB have been used interchangeably [7–16]. Consequently, several aspects of the systemic dissemination of *S. aureus* infection remain unclear and there is a lack of detailed data elucidating the onset of clinical symptoms, blood culture draw, microbiological confirmation, imaging results, occurrence of multiple infective foci, and whether the chronology of these events differs according to the infective focus.

Such data are important to extend our knowledge of the clinical course of patients with SAB and might help to reduce the interval from onset of infection to initiation of appropriate antimicrobial treatment, thereby potentially contributing to improved clinical outcomes. Therefore, using a prospective cohort of patients with SAB, we elucidated the clinical course of SAB with special attention to the timing and order of events concerning onset of clinical symptoms, diagnostic confirmation, and the presence of multiple infective foci in relation to the infective focus. Furthermore, we briefly introduce the terms used to describe the clinical course of SAB and discuss their usefulness in clinical settings.

Patients and methods

Setting

The present study uses prospectively collected patient data from the Invasive *S. aureus* Infection Cohort (INSTINCT) which was conducted in two German tertiary care university hospitals in Cologne and Freiburg between 1 January 2006 and 31 December 2011. Details of the INSTINCT study have been described previously [17, 18]. Clinical variables were prospectively recorded by a study group led by infectious diseases physicians and clinical microbiologists during the patients' hospital stay.

Patients with *S. aureus* bloodstream infection

Eligible cases were defined as patients ≥ 18 years of age with at least one blood culture positive for *S. aureus* and accompanying clinical symptoms and signs of infection. We restricted the study population to patients with first-time SAB. Furthermore, patients were excluded if an additional clinically significant bacterial pathogen was isolated from the blood culture. We classified all SAB patients as either community-acquired SAB (CA-SAB) or hospital-acquired SAB (HA-SAB) based on the interval between time of admission and sampling of the first positive blood culture (≤ 2 vs. > 2 days, respectively) [19]. The subset of patients with CA-SAB and recent healthcare contacts predating the current hospitalization were further classified as healthcare-associated SAB (HCA-SAB) if one or more of the following

criteria were met: (1) intravenous therapy, wound care, or specialized nursing care in the 30 days before SAB onset, (2) contact to a hospital or hemodialysis clinic or intravenous chemotherapy within 30 days of the onset of SAB, (3) > 2 days of hospitalization during the three months before the onset of SAB, or (4) admission from a nursing home [19].

Demographics and comorbidity

We noted the patients' age at the time of blood culture draw and obtained information on gender. Next, information of all preexisting comorbidities included in the Charlson Comorbidity Index (CCI) was collected. The CCI is a validated comorbidity scoring system assigning between 1 and 6 points to a range of major disease categories [20]. The aggregate score was computed for each patient and three levels of comorbidity were defined: low (score = 0), intermediate (score = 1–2), or high (score > 2). In addition, we collected information on a history of chronic alcohol abuse and active intravenous drug use which are not included in the CCI.

Onset of clinical symptoms, microbiological confirmation, and imaging results

For each patient, we obtained a detailed medical history to gain information on the time of onset of clinical symptoms, defined as systemic signs of infection (fever and/or chills) with or without accompanying local signs of infection. We collected data on all available non-blood culture microbiological findings serving as diagnostic confirmation of *S. aureus* infection, e.g., cultures of catheter tips, bone biopsies, and heart valve biopsies. Furthermore, data on reports from ultrasonography, magnetic resonance imaging, computed tomography scans, and echocardiographic investigations were obtained.

Portal of entry and infective focus

Information on the portal of entry and the infective focus was individually reviewed post-hoc taking into account the patient history, clinical signs, microbiological findings, and imaging results. We defined the portal of entry as the site where the infection had most likely been initiated, i.e., where *S. aureus* due to either infection or procedure had initially breached the physical barrier and entered the bloodstream. Accordingly, the portals of entry were categorized into (1) skin (a) skin and soft tissue infections, (b) intravenous drug abuse, or (c) other injections, (2) vascular device, (3) other, and (4) unknown. The infective focus was defined as the site of infection considered most likely to be responsible for seeding *S. aureus* into the bloodstream. To elucidate a

wide and still clearly defined clinical spectrum of SAB, we chose to restrict the study population to patients with the presence of one (or more) of the following three infective foci: (1) central venous catheter (CVC)-related infection, (2) vertebral osteomyelitis (VO), and (3) infective endocarditis (IE). Within these three groups, we further obtained data on any additional infective foci identified during the course of infection.

Statistical analysis

First, the study population was characterized in a contingency table according to the three different infective foci; CVC-related infection, VO, and IE. Next, using the date the first positive blood culture was drawn as reference point, we computed the median time with interquartile ranges (IQRs) to onset of clinical symptoms, microbiological findings, imaging results, and diagnosis of additional infective foci for each patient, and graphically displayed the results stratified by the infective focus. The time of diagnosis of any additional infective foci was established by clinical signs, microbiological findings, or imaging results, whichever came first. To examine whether the chronology of clinical and diagnostic events differed in subsets of SAB patients, we repeated the analyses stratifying by (1) mode of acquisition (CA-SAB, HA-SAB, and HCA-SAB) and (2) oxacillin susceptibility (MSSA and MRSA). All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna Austria) and STATA software version 11.2 (STATA, College Station, TX, USA).

Results

Descriptive data

During the study period, we identified 266 patients with first-time SAB and one of the three predefined infective foci. A CVC was an infective focus in 97 (36.5%) of patients, 78 (29.3%) patients were diagnosed with VO and 105 (39.5%) patients had IE. A total of 14 (5.3%) patients had overlapping infective foci (a brief description of these patients' clinical course and infective foci is given in Online Resource 1).

The proportion of male patients did not differ notably across the three groups. However, patients with a CVC as an infective focus were slightly younger than patients with VO and patients with IE (Table 1). All patients with a CVC as an infective focus were either classified as HA-SAB (96.9%) or HCA-SAB (3.1%), whereas 43.6% of patients with VO and 48.6% of patients with IE were classified as CA-SAB, respectively (Table 1). A substantial difference between the three groups was neither found with MRSA nor with the median CCI scores. As expected, the vascular device was

considered the most likely portal of entry among all patients with a CVC as the infective focus. The portal of entry was microbiologically confirmed in 74 (76.3%) of these patients and determined based on clinical signs of infection alone in 23 (23.7%) cases. Among patients with VO, the skin was the most likely portal of entry in 27 (34.6%) of patients [microbiologically confirmed in 9 (11.5%) cases], whereas no portal of entry was identified in 45 (57.7%) of patients. Among patients with IE, the most frequent portals of entry were the skin [34 (32.3%) patients, microbiologically confirmed in 10 (9.5%) cases], vascular devices [27 (25.7%) patients, microbiologically confirmed in 18 (17.1%) cases], and in 43 (41.0%) of patients the portal of entry remained unknown (Table 1).

Sequence of clinical and diagnostic events according to the infective focus

Among patients with CVC-related SAB, the time the first positive blood culture was drawn, onset of clinical symptoms, and microbiological confirmation (cultures of catheter tips positive for *S. aureus*) were close (Fig. 1a). In contrast, among patients with IE, the onset of clinical symptoms most often preceded the time of blood culture draw (median time = -1.5 days, interquartile range (IQR) -4; 0), and imaging confirmation was most frequently obtained subsequent to the SAB diagnosis [median time = 3 days (IQR 1; 8)]. Among patients with VO, the median time from onset of clinical symptoms to the time the first positive blood culture was drawn was -4 days (IQR -11; -1), and median time to microbiological and imaging confirmation was 2 days (IQR 0; 7.5) and 1 day (-1; 8.5), respectively.

CVC-related infection was infrequently associated with further foci ($n = 15/15.5\%$). Conversely, in 68 (64.8%) patients with IE and 44 (56.4%) patient with VO more than one infective focus was observed within a median of 0 days (IQR -4; 0) and 0 days (IQR -2; 2), respectively (Fig. 1b). We observed no consistent pattern or major differences in analyses stratified according to the mode of acquisition (hospital-acquired SAB versus community-acquired SAB) or according to oxacillin resistance (MSSA and MRSA) (shown in Online Resource 2).

Discussion

In this prospective cohort study, we observed notable variation in the clinical course of patients with SAB. In patients with CVC-related SAB, the time the first blood culture was drawn, onset of clinical symptoms, and microbiological confirmation were close. In contrast, among patients with IE and VO, the onset of clinical symptoms most often preceded the time the first positive blood culture was drawn and imaging

Table 1 Characteristics of 266 patients with first-time *Staphylococcus aureus* bloodstream infection from the INSTINCT cohort (Cologne and Freiburg, Germany), 2006–2011

Focus	Central venous catheter	Vertebral osteomyelitis	Infective endocarditis
Numbers (%)	97 (36.5)	78 (29.3)	105 (39.5)
Gender			
Male	65 (67.0)	48 (61.5)	72 (68.6)
Age, median (IQR)	59 (44–70)	68 (55–74)	65 (48–73)
≥ 18–39 years	18 (18.6)	3 (3.8)	17 (16.2)
40–59 years	31 (32.0)	22 (28.2)	24 (22.9)
60–79 years	44 (45.4)	43 (55.1)	55 (52.4)
≥ 80 years	4 (4.1)	10 (12.8)	9 (8.6)
<i>S. aureus</i> bloodstream infection			
Community-acquired	0 (0)	34 (43.6)	51 (48.6)
Healthcare-associated	3 (3.1)	31 (39.7)	29 (27.6)
Hospital-acquired	94 (96.9)	13 (16.7)	25 (23.8)
MRSA	12 (12.4)	7 (9.0)	9 (8.6)
Charlson comorbidity Index (CCI) score			
CCI score, median (IQR)	3 (2–4)	2 (0–4)	3 (1–5)
Low (0)	8 (8.2)	20 (25.6)	10 (9.5)
Intermediate (1–2)	38 (39.2)	28 (35.9)	32 (30.5)
High (> 2)	51 (52.6)	30 (38.5)	63 (60.0)
Portal of entry			
Skin	0 (0)	27 (34.6)	34 (32.3)
SSTI	0 (0)	17 (21.8)	19 (18.1)
IV drug use	0 (0)	3 (3.9)	14 (13.3)
Other injections ^a	0 (0)	7 (9.0)	1 (1.0)
Vascular device	97 (100)	2 (2.6)	27 (25.7)
Other ^b	0 (0)	4 (5.1)	1 (1.0)
Unknown	0 (0)	45 (57.7)	43 (41.0)

Patients were selected based on the presence of three different infective foci (central venous catheter, vertebral osteomyelitis, or infective endocarditis). Fourteen patients had overlapping foci and are thus represented in several columns

IQR interquartile range, *MRSA* methicillin-resistant *S. aureus*

^aIntramuscular injection ($n=5$), intraarticular injection ($n=2$), transcatheter arterial chemoembolization ($n=1$)

^bEpidural catheter ($n=2$), ureteral double-J stent ($n=1$), infected vaginal pessary ($n=1$), respiratory tract ($n=1$)

confirmation was most frequently obtained subsequent to the SAB diagnosis. Patients with CVC-related infection rarely developed further infective foci, whereas this was observed in more than half of patients with IE and VO, respectively.

The time from blood culture positivity to final diagnostic confirmation of the infective focus was considerably shorter for patients with CVC-related infection, as compared with patients with VO and IE. Moreover, while additional infective foci were frequently observed in patients with VO and patients with IE, this was rarely seen in patients with CVC-related infection. Early identification and control of the portal of entry and/or infective focus are strongly associated with decreased risk of developing further infective foci in patients with SAB [2, 5, 6]. As focus

identification and control most frequently is more accessible and straightforward among patients with manifest CVC-related infection, this most likely explains part of our findings. In contrast, the portal of entry was only identified in roughly half of the patients with IE and patients with VO in our study population. This may be due to unsuccessful identification despite extensive clinical efforts or, in some cases, it could be that the portal of entry had resolved spontaneously or due to antibiotic treatment at the time of the SAB diagnosis. In addition, it cannot be precluded that in some cases of SAB the portal of entry does not always constitute an actual infective focus (e.g., intravenous drug abuse without local infection leading to IE or hemodialysis and subsequent VO).

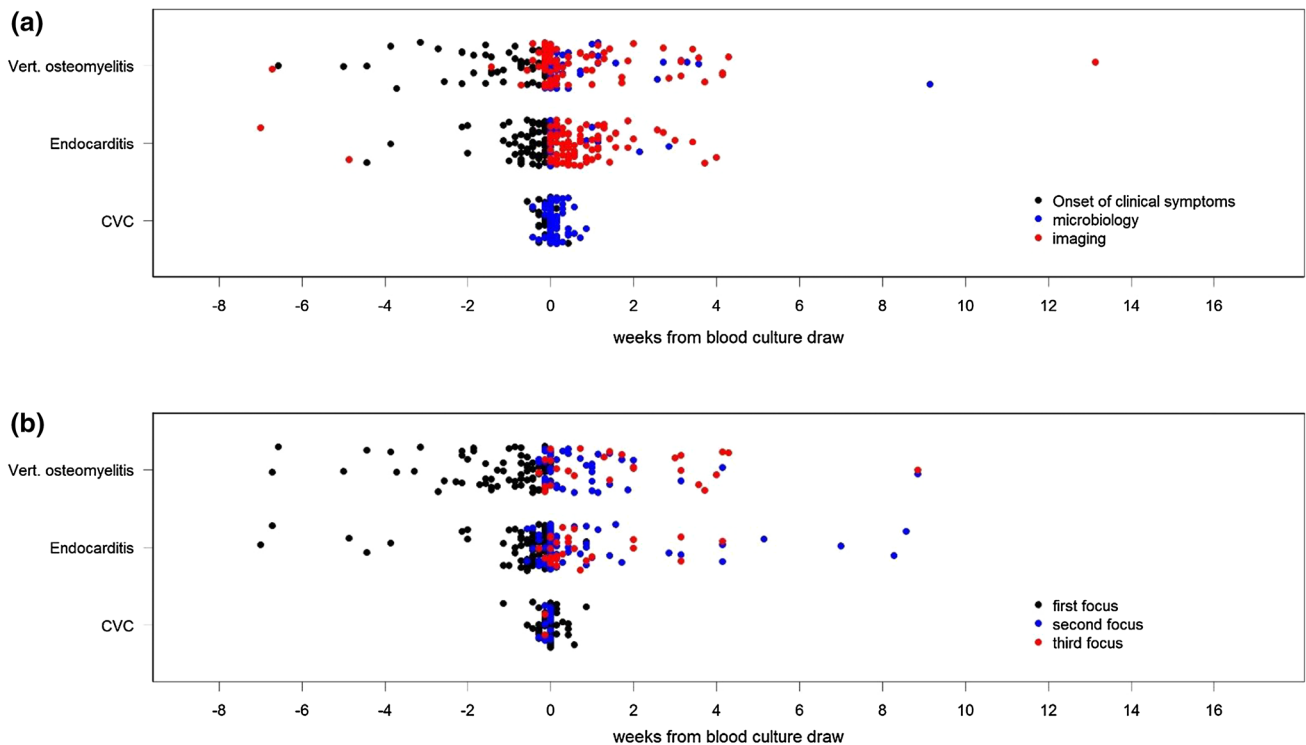


Fig. 1 Time to onset of clinical signs of infection, microbiological findings, and imaging results according to each of the three foci (a) and occurrence of additional infective foci (b)

In previous studies of SAB, the terms used in the description of the clinical course have been defined with considerable inconsistency [7–16]. In SAB, the bacteria access the blood by breaching the body's protective barriers at a specific site, which has most frequently been described as the *portal of entry* [7–10]. Nevertheless, the same and other studies have employed different terms for the portal of entry, including the *primary site of infection* [7], the *initial staphylococcal lesion* [8], the *source of infection* [13–15], and the *primary infective focus* [9]. Furthermore, assuming that the portal of entry always constitutes an infective focus, the term the *primary infective focus* has also been used in a number of previous studies to denote the initial staphylococcal infection leading to bacteraemia while any additional foci were thought to be the result of the SAB and designated *secondary infective foci* [7, 9, 13, 14]. In contrast, other prior studies have used the prefixes primary and secondary only to discern between *primary SAB* where no portal of entry or associated infection site was identified and *secondary SAB* in which the bacteraemia is assumed to stem from an identified portal of entry and/or infective focus [8, 11, 12, 16]. Finally, the occurrence of infective foci in multiple organ systems has often been referred to as *metastatic infection*. However, the concept remains inconsistently defined [10, 11, 21–23] and other terms such as *metastatic complications* [24],

complicating infective foci [10], and *complicated SAB* [13, 14, 25] have been used interchangeably.

As suggested by our data, the full extent of *S. aureus* infection may not be obvious at the time of the SAB diagnosis. Thus, several infective foci may be present and the sequence of occurrence is not always clear. Indeed, as the pathophysiological events are most frequently putative and unobserved, distinguishing between the aforementioned primary and secondary infective foci or primary or secondary SAB may prove very difficult in everyday clinical practice. Although the time elapsed from onset of clinical symptoms to the diagnosis of SAB was less than 2 weeks in the majority of cases it should, nevertheless, be noted that some patients demonstrated a notably insidious clinical course with onset of clinical symptoms as early as 7 weeks before the SAB diagnosis. Furthermore, additional infective foci were frequently observed in patients with VO and IE and occurred as late as 9 weeks after the first positive blood culture was drawn, which emphasizes the importance of continuous monitoring for additional infective foci to attain optimal focus control and adequate treatment duration. Therefore, it may possibly prove more clinically useful to describe the clinical course of SAB simply in terms of (1) *the portal of entry* and (2) *the infective focus/foci* and omit theoretical assumptions of sequence. In patients with multiple infective foci, the clinical presentation and the existing

Table 2 A suggested updated terminology for the clinical course of *Staphylococcus aureus* bloodstream infection

Term	Definition
Portal of entry	The site where the infection has most likely been initiated, i.e., where <i>S. aureus</i> due to either infection or procedure has initially breached the physical barrier and entered the bloodstream. Although the portal of entry often constitutes an actual infective focus, this may not always be the case
Infective focus	The site of infection considered most likely to be responsible for seeding <i>S. aureus</i> into the bloodstream based on clinical signs, microbiological findings, and imaging results
Multiple infective foci	The presence of more than one infective focus. As the order of occurrence is often unclear at the time of the SAB diagnosis, theoretical assumptions of sequence may not be clinically useful
Dominant infective focus	In patients with multiple infective foci, the clinical presentation and the existing evidence on the ranked prognostic impact of different infective foci (i.e., infective endocarditis > vertebral osteomyelitis > CVC-related infection) may help the clinician determine a dominant infective focus guiding clinical management including therapy duration

evidence on the ranked prognostic impact of the different infective foci (e.g., IE > VO > CVC-related infection) [1, 3, 5, 6] could possibly help the clinician determine a so-called *dominant infective focus*¹ which could guide clinical management including adequate treatment duration (Table 2).

The main strengths of our study include the restriction of the study population to patients with first-time, monomicrobial SAB and the use of comprehensive prospectively recorded data. Nevertheless, some potential limitations of the study should be addressed. We only included patients from tertiary care medical centers, thus our results may not be directly applicable to other settings. Even so, it seems reasonable to assume that these results may apply to other settings and countries with similar demographics and equal access to healthcare. In addition, information on the onset of clinical symptoms were obtained subsequent to the SAB diagnosis, therefore, we cannot rule out that these particular data have been affected by some degree of recall bias and thus inaccuracy. Still, the clinical data were meticulously obtained by infectious diseases physicians and clinical microbiologists during the hospitalization, and we consider it unlikely that misclassification of onset of clinical symptoms has influenced our results notably. We chose only to include SAB patients with CVC-related infection, IE, or VO. However, we cannot entirely rule out that some patients may have died before an infective focus was identified or that some patients with one of the three predefined foci were falsely classified as another or unknown infective focus. If such misclassification was particularly pronounced for one type of the three predefined foci, it might have influenced our findings.

In conclusion, the order of events concerning onset of clinical symptoms, diagnostic confirmation, and presence of multiple infective foci varied considerably with different infective foci in patients with SAB. In patients with VO and IE, additional foci were diagnosed as late as 9 weeks after the SAB diagnosis which underlines the importance of continuous search for additional infective foci to attain optimal focus control and adequate treatment duration. To ensure a

consistent, pragmatic, and evidence-based terminology for the clinical course of SAB, we suggest the terms *portal of entry*, *the infective focus*, *multiple infective foci*, and *dominant infective focus*, as defined above, yet further clinical studies addressing this important issue are indeed warranted.

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Authors' contributions JS: study design, data management, analysis and interpretation, and manuscript preparation. AJK: data collection, study concept and design, data management, analysis and interpretation, and manuscript review. SRR, WVK, HS, AFW: data collection, study design, interpretation of the data, manuscript review. HCS: study design, interpretation of the data, manuscript review. All the authors have read and approved the final draft submitted.

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Compliance with ethical standards

Ethical approval The study and data collection were approved by the institutional review boards of the University Medical Centers Freiburg and Cologne. We followed the ethical standards set by the Helsinki Declaration of 1975, as revised in 2004, and the research guidelines of the Universities of Freiburg and Cologne. Written informed consent was obtained from the patients at the University Medical Center Cologne. The institutional review board of the University Medical Center Freiburg considered the investigation as evaluation of service within a quality assurance program and waived the need for written informed consent. The study is registered in the German Clinical Trials Registry (DRKS00005045).

Conflict of interest A.J.K. has received payments for lectures from BD Biosciences, bioMérieux, MSD Sharp & Dohme, Limbach Gruppe

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