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ORIGINAL PAPER

Clinical significance of coagulase-negative staphylococci other than *S. epidermidis* blood stream isolates at a tertiary care hospital

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Abstract
Purpose We retrospectively evaluated blood culture (BC) isolates of coagulase-negative staphylococci other than *Staphylococcus epidermidis* (NonSe-CoNS) for clinical relevance at a tertiary care hospital in Germany from January 2011 to September 2015.
Methods Clinical data were correlated to microbiological results based on medical records. Infection was considered likely if (1) no other infection and (2) two or more isolates of the same species were present and (3) symptoms ameliorated after therapy. Infection was considered possible if a foreign body was present and (1) and (3) were fulfilled. All the other cases were considered contaminations.
Results 313 patients with blood cultures positive for NonSe-CoNS were identified. 61 patients were excluded, either because of missing data or multiple pathogens in the same blood culture. Of the remaining 252 patients, 58 (23 %) were classified as possible ($n = 32$) or likely ($n = 26$) infections. *S. haemolyticus* was the most frequent isolate (infection: $n = 28$), followed by *S. hominis* ($n = 13$), *S. capitis* ($n = 12$), and *S. lugdunensis* ($n = 3$). One patient died from NonSe-CoNS infection. The source of infection in the majority of patients was foreign bodies ($n = 43$), and endocarditis was present in six cases. Staphylococci always considered contaminations were: *S. auricularis, S. caprae, S. schleiferi*, *S. pettenkoferi*, *S. saccharolyticus*, and *S. simulans*. The growth of NonSe-CoNS in the anaerobic BC bottle only and a time to positivity >36 h were associated with contaminations.
Conclusions One out of four NonSe-CoNS isolates was clinically relevant in our cohort, where *S. haemolyticus*, *S. capitis*, *S. hominis,* and *S. lugdunensis* contributed to 96.6 % of all relevant infections.

Keywords Coagulase-negative Staphylococci · Bacteremia · *S. haemolyticus* · *S. lugdunensis* · Blood culture · Contamination

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Introduction

Coagulase-negative staphylococci (CoNS) are frequent findings in blood cultures. Since CoNS are common inhabitants of skin and mucous membranes, the possibility of a contamination has to be considered. However, these isolates may as well represent clinically relevant (eventually nosocomial) infections. CoNS are also the most common cause of foreign body infections, such as central venous catheters (CVC), pace makers, prosthetic joints, and others [1, 2]. Clinically, these infections present often less severe than other blood-stream-related pathogens, such as *Staphylococcus aureus* or *Candida* spp. A specific treatment of these infections is nevertheless complicated due to widespread multiple drug resistances especially to oral antibiotics [2, 3].

The most common CoNS blood culture (BC) isolate is *S. epidermidis*, but several other species (coagulase-negative staphylococci other than *S. epidermidis*, NonSe-CoNS), such as *S. haemolyticus*, *S. hominis*, *S. capitis,* and *S.*

lugdunensis, may be found in a human environment albeit less frequently. Species distribution in clinical samples varies: taken together *S. epidermidis* accounts for more than 50 % of all CoNS isolates [4]. Gatterman et al. report that NonSe-CoNS are responsible for 33 % (n = 161/494) of CoNS blood-stream infections in a German population (whereas *S. epidermidis* accounts for 67 %) [5]. Species distribution is also influenced by the examined clinical specimen, since different staphylococci species show niche preferences, e.g., *S. capitis* is found on the human head, *S. saprophyticus* is mainly isolated in bladder urine (cystitis in young females), *S. cohnii* is isolated from human feet, and *S. auricularis* is isolated from the external auditory meatus [2, 4]. Only little information is available on the clinical relevance of NonSe-CoNS, although evidence suggests that virulence varies among different CoNS species. *S. lugdunensis*, for example, is considered to be more virulent than other CoNS species by some [6–8], but not all authors [9]. In general mortality due to CoNS, central-line-associated blood-stream infections seem to be less severe compared to other pathogens [10].

It is a recurrent challenge to discriminate between clinically relevant infections and possible contaminations in CoNS BC isolates. With regard to intravascular catheter-related infections, there is broad consensus that the growth of the same organism in paired blood culture samples drawn from a peripheral vein and the suspected source indicates true or relevant infection [11]. There is, however, evidence that even one positive BC isolate might reflect clinically relevant infection [12, 13]. Another tool in discriminating between contamination and infection is differential time to positivity (TTP): TTP > 16 h [14, 15] or TTP > 36 h [13] has been associated with contamination in CoNS.

We conducted a retrospective study, where all positive blood culture isolates for NonSe-CoNS were evaluated for clinical relevance at a tertiary care academic hospital in Germany.

Patients and methods

Hospital characteristics

The Regensburg University Hospital is an 833-bed tertiary care academic teaching hospital in the south-eastern part of Germany. All major clinical departments are present, including a stem-cell transplantation unit, a level 1 trauma center, and kidney, liver, and heart transplantation centers.

Microbiology

BC sets were obtained according to local standard protocols. BCs were then processed in the microbiology laboratory using a BD Bactec FX system (Becton & Dickinson, Heidelberg, Germany). A BC set consists of an anaerobic and an aerobic bottle. A set was considered positive when bacteria (NonSe-CoNS in our case) grew in one of the bottles. In addition, TTP was registered according to laboratory standards. Bacterial species were identified by matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI TOF MS) using a Microflex mass spectrometer (Bruker Daltonik, Bremen, Germany). The retrieved spectra were analyzed with the BioTyper software (Bruker). Antibiotic susceptibility was tested using the BD Phoenix 100 system (Becton & Dickinson, Heidelberg, Germany).

All BCs positive for NonSe-CoNS isolates between January 1st 2011 and September 15th 2015 were retrieved from the laboratory database and evaluated retrospectively.

Likelihood of infection

All positive BC results identified were correlated to clinical characteristics retrieved from electronically available discharge letters. Infection was considered to be likely when all the following criteria were fulfilled: (1) no other infection was more likely at the time, the BC was drawn (e.g., patient admitted with pneumonia); (2) two or more positive BCs of the same species were present (or detection of the same species in another clinically relevant sample); and (3) decrease of clinical symptoms or markers of inflammation (e.g., fever, symptoms, C-reactive protein, and procalcitonin) after pathogen-directed therapy (either antibiotic therapy and/or removal of the foreign body in the setting of a foreign body-associated infection).

Infection was considered to be possible if a foreign body was present and only criteria 1 and 3 were fulfilled. Several studies could demonstrate the relevance of a single positive BC in CoNS infection [13, 16–18].

Positive BCs were considered to be contamination (a) if NonSe-CoNS positive blood cultures were not mentioned in the discharge letter; (b) if NonSe-CoNS were rated as not clinically relevant by the attending doctors; or (c) if the above-mentioned criteria for likely or possible infection were not met.

If no information or discharge letter of a patient with positive BCs was available, these cases were excluded from our study. Cases were also excluded if another pathogen apart from NonSe-CoNS was isolated in the same BC set. Other relevant data collected for review included: age, gender, malignancies (solid or hematological), immunosuppression, antibiotic therapy, and duration of therapy. In addition, the laboratory data TTP of BC and the resistance profile of the pathogen isolated were obtained. Data were initially retrieved from discharge letters and analyzed using a standardized protocol by one of the authors (FHi). If likelihood of infection was not evident in one of the patient

cases, another author (FHa) evaluated the same case using the same protocol ($n = 8$). In the case of any disagreement, a third infectious disease specialist (BS) made the final decision ($n = 1$).

Statistical analysis

Description and analytic statistics were calculated using the IBM Statistical Package for the Social Sciences 21 (IBM, USA). TTP between different groups was analyzed using non-parametric test (Kruskal–Wallis) and using 2 × 2 squares for cutoffs. Chi-squared tests were used to compare frequencies observed between categorical variables.

The study was approved by the research ethics committee of the University of Regensburg.

Results

The review of microbiological laboratory records yielded BC sets from 313 patient cases positive for NonSe-CoNS to be potentially included in our study. 30 patients had to be excluded due to insufficient data available. Another 31 cases were excluded due to more than one bacterial species present in the BC, leaving 252 patient cases available for evaluation (Fig. 1).

Median age in our cohort was 62 years (range from 2 to 94 years), and median age of patients with NonSe-CoNS infection was 60 years (range from 5 to 87 years). 70.7 % ($n = 41$) of the patients with likely or possible infection due to NonSe-CoNS were male, and were 68.3 % ($n = 132$) of all patient cases with contamination.

Likely infection or possible infection was diagnosed in 58/252 cases (23.0 %; likely: $n = 26$, possible: $n = 32$), and contamination was assumed in 194 cases (77.0 %). Nearly, half of all possible and likely infections were caused by *S. haemolyticus* ($n = 28$), more than 20 % each were caused by either *S. hominis* ($n = 13$) or *S. capitis* ($n = 12$), and only few were caused by *S. lugdunensis* (n = 3), *S. warneri* ($n = 1$), and *S. cohnii* ($n = 1$). Not associated with likely or possible infections and, therefore, always considered as contaminants were: *S. pettenkoferi* ($n = 7$), *S. caprae* ($n = 2$), *S. saccharolyticus* ($n = 3$), *S. auricularis* ($n = 1$), *S. simulans* ($n = 1$), and *S. schleiferi* ($n = 1$) (Fig. 2). There was no significant difference between the different species regarding rates of contaminants vs. possible/likely infection (Chi-Square, $p = 0.23$).

The majority ($n = 42$, 72.4 %) of likely or possible infections due to NonSe-CoNS was associated with foreign bodies (CVC: $n = 19$, port: $n = 14$, tunneled hemodialysis catheter: $n = 2$, Hickman line: $n = 2$, cerebral shunt: $n = 2$, others: $n = 3$). Two patients had prosthetic valve endocarditis (PVE, one caused by S. *haemolyticus* and the other caused by *S. capitis*), and four patients had native valve endocarditis (NVE, one caused by *S. haemolyticus* and three caused by *S. capitis*). The source of infection was unknown in nine cases (in all these patients, however, foreign bodies were at least present and likely the source of infection—although this was not specifically mentioned in the discharge letter: *S. haemolyticus*: $n = 1$, *S. capitis*: $n = 2$, *S. hominis*: $n = 6$). In one case of septic arthritis, *S. haemolyticus* was isolated. No NonSe-CoNS species was significantly associated with the frequent comorbidities malignancy or immunosuppression (Chi-square test in

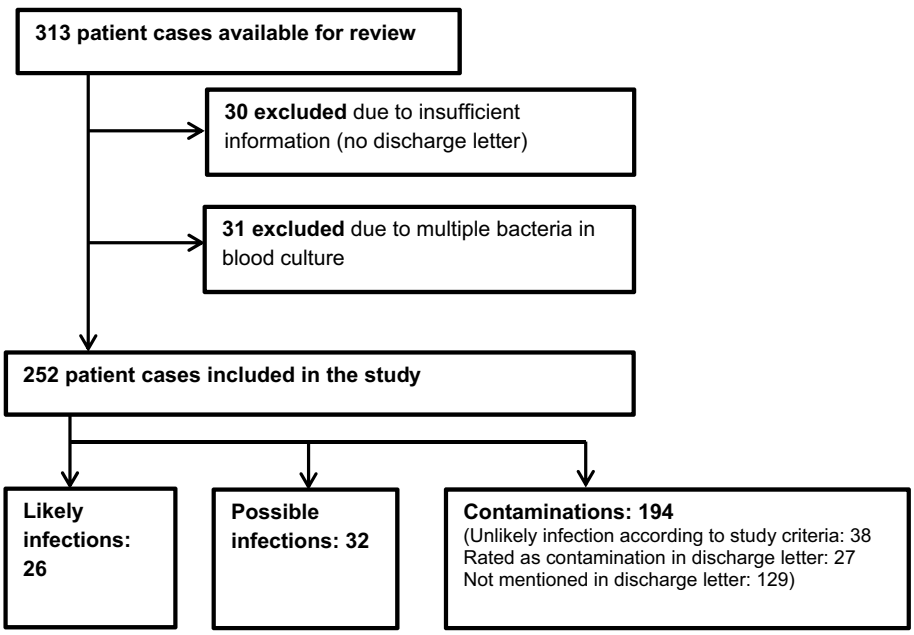

Fig. 1 Enrollment and analysis of patients with at least one positive blood culture for NonSe-CoNS

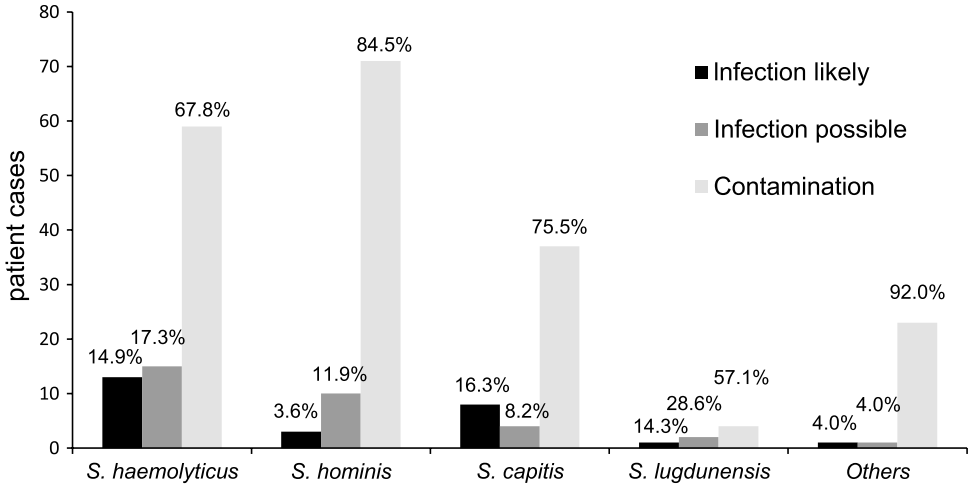

Fig. 2 Patient cases of infection (likely or possible) vs. contamination in all 252 NonSe-CoNS isolates which were include in our study, responsible for infection in "others", were *S. warneri* und *S. cohnii*

patient cases with *S. haemolyticus*, *S. hominis,* and *S. capitis* not significant).

Most patients recovered from NonSe-CoNS infection (84.5 %), eight patients died due to other causes (other infections, multi-organ failure, and malignancy), and one death was associated with *S. haemolyticus* endocarditis (the patient also had end-stage esophageal cancer; death in this case might also be partly attributable to the underlying malignant disease). Most patients with NonSe-CoNS infection were treated with either vancomycin (55.2 %) or linezolid, daptomycin, or teicoplanin (10.3 %) (Table 1). The majority of isolates from patients with likely or possible infection were resistant to methicillin (75.7 %) (Table 2). No resistance against vancomycin, daptomycin, or linezolid was detected in any NonSe-CoNS isolate (either infection or contamination). Interestingly, the antibiotic therapy was not adequate in four cases with possible or likely infection: one of them had a port infection and the catheter was removed and the second one was discharged home with no further information available. The two remaining patients died due to other causes before the final microbiological identification of NonSe-CoNS could be established.

Median TTP for the first positive BC bottle in a given set (either aerobic or anaerobic) was 14 h in patients with likely, 16 h in patients with possible infection, and 20 h in patients with contaminations. There was a significant difference in TTP in patients with likely or possible infection vs. patients with contamination (Kruskal–Wallis test: $p = 0.01$).

We examined different cutoffs for TTP in our setting: These cutoffs of 16 and 36 h, respectively, had sensitivity and specificity for contamination vs. infection of 66 %/67 % (16 h cutoff) and 15 %/95 % (36 h cutoff) in our study (Fig. 3). The positive predictive value (PPV) for an isolate becoming positive after 16 h to be an infection rather than contaminant was 25 %, the negative predictive value (NPV) was 75 %, PPV for 36 h was 25, and NPV for 36 h was 91 % (Fig. 3).

In all the cases, where NonSe-CoNS isolates were considered possible or likely infection, the aerobic BC bottle was positive for growth (and in the 19 cases, both aerobic and anaerobic were positive). The growth of NonSe-CoNS in the anaerobic bottle only was always associated with contamination in our cohort ($n = 22$).

Discussion

To our knowledge, this is the largest study to date on the clinical relevance of NonSe-CoNS. CoNS play an important role in hospital-acquired infections and are frequently associated with foreign bodies. The discrimination between infection and contamination on the other hand is far more difficult.

The detection of NonSe-CoNS isolates was of clinical relevance in nearly every fourth patient in our cohort. *S. haemolyticus*, *S. capitis,* and *S. hominis* together accounted for more than 90 % of all relevant NonSe-CoNS BC isolates. *S. haemolyticus* accounted for nearly 50 % of all infections and two out of six endocarditis cases. In all the cases, modified Duke criteria [19] for the diagnosis of endocarditis were fulfilled (one major criterium and at least three minor criteria positive). In the other patients, NVE ($n = 3$) and PVE ($n = 1$) were caused by *S. capitis*. Chu et al. [20] reported that 6.6 % of all the cases with NVE were caused by CoNS and 85 % of these by *S. epidermidis,* while only very few were caused by *S. hominis* ($n = 4$), *S. lugdunensis* ($n = 3$), *S. capitis* ($n = 1$), *S. capris* ($n = 1$), and *S. simulans* ($n = 1$) (and none by *S. haemolyticus*). Other authors reported on the cases of NVE being caused by *S. haemolyticus* as well [21]. NonSe-CoNS endocarditis is a rare but potentially serious event and should be

Table 1 Characteristics of patients with likely or possible infection with NonSe-CoNS positive blood cultures ($n = 58/252$)

Characteristics of patients with CoNS infection	All species Number of patient cases (%)
Gender	
Male	41 (70.7)
Department	
Hematology	18 (31.0)
Gastroenterology	14 (24.1)
Cardiology/Pulmonology	8 (13.8)
Nephrology	2 (3.4)
Surgery	3 (5.2)
Neurosurgery	3 (5.2)
Cardiac surgery	4 (6.9)
Traumatology	3 (5.2)
Pediatrics	3 (5.2)
ICU patients	20 (34.5)
Immunosuppression	27 (46.6)
Malignancy	31 (53.4)
Comorbidities	
Bone marrow transplantation	8 (13.8)
Leukemia	17 (29.3)
Lymphoma	6 (10.3)
Solid tumor	8 (13.8)
Solid organ transplantation	4 (6.9)
Coronary artery disease	8 (13.8)
Renal insufficiency	12 (20.7)
Trauma	3 (5.2)
Outcome	
Recovered	49 (84.5)
Died due to other causes	8 (13.8)
Died due to CoNS infection	1 (1.7)
Antibiotic therapy	
Vancomycin	32 (55.2)
Linezolid	3 (5.2)
Daptomycin	2 (3.4)
Teicoplanin	1 (1.7)
Cephalosporins	3 (5.2)
Fluoroquinolons	2 (3.4)
Flucloxacillin	3 (5.2)
Others	5 (8.6)
Unknown	7 (12.1)
Source of infection	
Foreign body	42 (72.4)
Endocarditis (native valve)	4 (7.0)
Endocarditis (prosthetic valve)	2 (3.4)
Others	1 (1.7)
Unknown	9 (15.5)

included in the differential diagnosis if bacteremia without obvious focus is observed.

Staphylococcus haemolyticus has been reported previously, as the most frequently isolated CoNS in clinical samples besides *S. epidermidis* [22]. In a recent study from India, *S. haemolyticus* was the second most frequently found NonSe-CoNS (after *S. saprophyticus* mainly found in urine samples) [23]. The species distribution among isolates from infections with NonSe-CoNS may depend on the study setting. Ruhe et al. [13] investigated the relevance of NonSe-CoNS in BC isolates in a US-American hospital. From 160 patient cases with NonSe-CoNS positive BCs, 32 of them fulfilled study criteria for true infection. In their study, *S. hominis* was the major pathogen responsible for 50 % ($n = 16$) of all CoNS infections, and another 41 % were caused by *S. haemolyticus* ($n = 13$). Other NonSe-CoNS associated with clinically relevant bacteremia in their cohort were *S. warneri* ($n = 1$) and *S. lugdunensis* ($n = 2$)—similar to the observation in our study.

Staphylococcus lugdunensis has been described as a pathogenic staphylococcal species in several reports. Vandenesch et al. reported the 11 cases of *S. lugdunensis* endocarditis, where only three patients survived despite adequate therapy [7]. The mortality rate of *S. lugdunensis* endocarditis in a study from Switzerland was 23 % (three patients of 11 died) [24]. In a recent US-American study, 15 cases of *S. lugdunensis* endocarditis (ten of them NVE) were evaluated, two of these patients died, and six underwent surgical intervention. Interestingly, marked valvular destruction similar to endocarditis with *S. aureus* was noted [25]. In our study, the isolation of *S. lugdunensis* reflected a likely or possible infection in only three of seven isolates, and all these patients recovered from their infection without any complications. Of note, all these were associated with foreign bodies and no endocarditis case was found. *S. lugdunensis* bacteremia is a rare event in our setting with only seven *S. lugdunensis* isolates. The isolation of *S. lugdunensis* was judged clinically relevant in nearly half of all the cases though. Ebright et al. also reported a small number of relevant blood-stream infections with *S. lugdunensis* ($n = 6$), none of them with fatal outcome [9]. In children, *S. lugdunensis* bacteremia is a similarly rare event: only ten of 277 BC CoNS isolates yielded *S. lugdunensis* in a study of Sato et al. nine of these patients were considered to have a clinically relevant infection, all of whom had a favorable outcome, and none had endocarditis [26]. In summary, the relevance of *S. lugdunensis* has yet to be established, and geographical differences may apply.

There was no significant correlation between underlying diseases (such as malignancy) and NonSe-CoNS species:

Table 2 Microbiology characteristics of NonSe-CoNS isolates with likely or possible infection

	S. haemolyticus	*S. hominis*	*S. capitis*	*S. lugdunensis*	*S. warneri* and *S. cohnii*	All species
Isolates resistant to… *n* (%)						
Oxacillin/cefazolin	26 (92.9)	11 (91.7)	3 (25)	2 (66.7)	2 (50)	44 (75.9)
Rifampicin	1 (3.6)	0 (0)				1 (1.7)
Moxifloxacin	15 (53.6)	2 (16.7)	0 (0)			17 (29.3)
Vancomycin/daptomycin/linezolid/teicoplanin	0 (0)					0 (0)
Number of positive BC pairs						
1	17 (60.7)	10 (76.9)	5 (41.7)	2 (66.7)	1 (50)	35 (60.3)
2	7 (25)	3 (23.1)	4 (33.3)	0 (0)	1 (50)	15 (25.9)
≥3	4 (14.3)	0 (0)	3 (25)	1 (33.3)	0 (0)	8 (13.8)

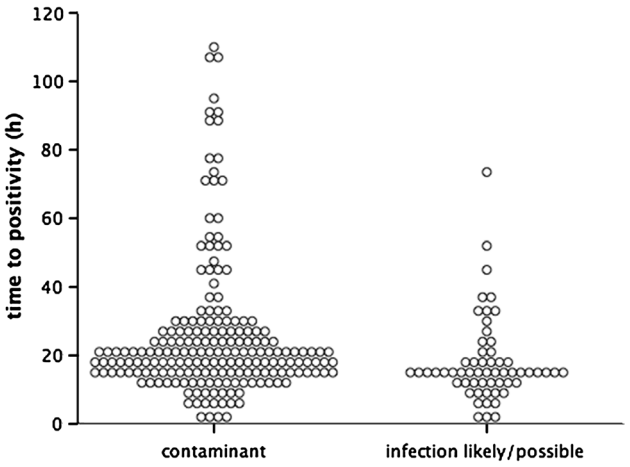

Fig. 3 TTP of the first positive BK bottle (aerobic or anaerobic) in the cases with contamination vs. cases with infection (likely and possible)

CoNS are often found in patients with malignancies (either hematological or solid tumors) or immunosuppression, but these patients do also tend to receive CVCs or other indwelling catheters.

Interestingly, 22 NonSe-CoNS isolates that were considered contaminations grew in the anaerobic BC bottle only, whereas all isolates representing possible or likely infections grew in the aerobic BC bottle (and in some cases in the anaerobic bottle as well). This finding might provide an additional aid to discriminate between infection and contamination. Due to the limited sample size, however, this observation has to be interpreted carefully and further studies are warranted.

As in the previous studies, there was a significant difference in TTP of likely and possible infection vs. contaminations. In our study, TTP >36 h had an NPV of 91 % for contamination which might be helpful in discriminating between infection and contamination in NonSe-CoNS. Ruhe et al. could also demonstrate an association between the clinical relevance of NonSe-CoNS BC isolates and PTT <36 h [13]. Similar findings are reported by Zhang and colleagues, where in an analysis of 386 episodes of bloodstream infections, a TTP >24 h was associated with Gram-positive bacteria (e.g., CoNS), and 98 % of all blood cultures were positive within 36 h [27].

In general, infections caused by NonSe-CoNS were of comparably low virulence: most patients recovered from infection after antibiotic therapy and/or removal of the foreign-body-associated infection. However, Lim and colleagues could show that in an ICU setting, nearly 20 % of blood-stream-infection-related mortality occurred in central-line-associated infections (but in this study, only 2/39 central-line-associated infections were due to NonSE-CoNS, whereas the major pathogens isolated were *S. aureus* and *Candida* species) [28]. Several deaths in our cohort were due to other causes (other infections, malignancy, and multi-organ failure unrelated to staphylococcal infection). This is in accordance with the previous reports on the generally subacute and less fulminant course of infections with CoNS [2]. Interestingly, CoNS-related blood-stream infections seem to be associated with lower procalcitonin levels than bacteremia caused by other pathogens, as Aimoto et al. could demonstrate in patients with febrile neutropenia [29].

Resistance against the usual anti-staphylococcal beta-lactam antibiotics (oxacillin or 1st Gen. cephalosporins) was high in our study (*S. haemolyticus* 92.9 %, *S. hominis* 84.6 %; the exception being *S. capitis* with only 25 %). Agents active against MRSA/MRSE (such as vancomycin) must, therefore, be considered the best empirical choice in suspected infections with NonSe-CoNS.

Our study is first limited by its retrospective nature. The classification into true infection (likely or possible) or contamination was based on the retrospective evaluation of electronic records which might have been not entirely comprehensive in some cases. It is possible that the classification of infection vs. contamination might be inaccurate in some cases, as other investigators speculated previously [13, 30]. We chose to apply strict classification criteria as

mentioned above. There is a possibility that the rate of clinically relevant infections might either have been underestimated (NonSe-CoNS were considered a contamination if not mentioned in the discharge letter which might not always be correct) or overestimated (in only ~40 % isolates judged as infection were found in more than one BC pair).

Third, several NonSe-CoNS species were observed in small numbers (e.g., *S. lugdunesis, S. schleiferi,* and *S. warneri*). Especially for *S. lugdunensis,* there is conflicting evidence on its significance and pathogenicity. Similarly, NonSe-CoNS species not associated with infections were generally found in small numbers only (such as *S. pettenkoferi*, *S. caprae*, *S. saccharolyticus*, *S. auricularis*, *S. simulans,* and *S. schleiferi).*

Conclusions

Infections with NonSe-CoNS are of comparably low virulence in general. Almost one in four NonSe-CoNS isolates from BC isolates was of clinical relevance though. Patients should, therefore, be evaluated carefully, especially if *S. haemolyticus, S. hominis*, *S. capitis,* or *S. lugdunensis* are found. These four species contributed to more than 96 % of infections in our cohort with *S. haemolyticus* being the most frequent-isolated species. Susceptibility to oxacillin/cefazolin was low. Drugs with activity against MRSA (such as vancomycin) should, therefore, be recommended as first line therapy in pending antibiotic susceptibility testing.

The growth of NonSe-CoNS in the anaerobic BC bottle only was associated with contaminations in our cohort, and a TTP >36 h had NPV of 91 % for contamination in NonSe-CoNS which might be helpful in the interpretation of BC findings.

Compliance with ethical standards

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

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