Epidemiology and significance of coagulase-negative staphylococci isolated in blood cultures from critically ill adult patients

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ABSTRACT

Background: Little published data are available on the epidemiology and significance of coagulase-negative staphylococci (CoNS) in blood culture isolates among critically ill adult patients.

Objectives: To describe the epidemiology and frequency of CoNS blood culture isolates in critically ill adults, and investigate the association between time to positivity (TTP) of blood cultures and number of culture-positive bottles with organ dysfunction and mortality.

Design, setting and participants: A retrospective chart audit in the intensive care unit of a tertiary hospital comprising all patients who had positive blood cultures for CoNS in 2009.

Main outcome measures: TTP, number of culture-positive bottles, Sequential Organ Failure Assessment (SOFA) scores, resolution of fever and white cell response and inotrope requirement, length of stay in ICU and mortality.

Results: In 2009, there were 1514 and 109 positive blood culture sets for the hospital and ICU patients, respectively. Of these, 515 sets from patients outside the ICU (34% of all hospital positive blood cultures) and 54 from the ICU (49.5% of all ICU positive blood cultures) were positive for CoNS. Patients with TTP $\leqslant$ 24 hours had higher organ failure scores by 0.9 (95% CI, 0–3.4; $P = 0.052$). There was a trend towards an association between increased 28-day mortality and TTP $\leqslant$ 24 hours (7/22 v 3/32; $P = 0.071$). There was no significant correlation between number of bottles positive for culture and mortality, length of stay, SOFA score, resolution of fever, white cell response, and inotrope requirement.

Conclusions: Early TTP of blood cultures with CoNS may be associated with poorer outcome and may be a marker of true infection. Given the relatively high frequency of this microbiological problem, larger prospective observational studies are required to more clearly define the significance of a CoNS blood culture isolates in critically ill adult patients.

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Coagulase-negative staphylococci (CoNS) are frequently isolated from blood cultures in intensive care units and are ranked as the third most common cause of bacteraemia in hospitalised patients.[1] As they are part of the normal flora of the skin, they are often deemed contaminants arising from the blood culture collection process and typically represent 70%–80% of all contaminated blood cultures;[2,3] however, these organisms are also known to cause prosthetic valve endocarditis, infections of vascular devices and ventriculoperitoneal shunts, urinary tract infections and sepsis, more so in immunocompromised hosts.[4] Given the potential for these organisms to cause serious infections, it is important to distinguish between contamination and true infection, particularly in blood samples taken from critically ill patients. Few studies have explored the clinical significance of CoNS blood culture isolates among critically ill adults. Despite a high probability that CoNS isolation in blood is frequently a contaminant, determining the likelihood that it represents a true infection is a significant challenge for the clinician.

Several methods have been used to attempt the differentiation of contamination from infection — time to positivity (TTP) of blood cultures, number of blood culture bottles positive within a set, number of positive sets, absence of a mixture of species, and the presence of clinical features of sepsis syndrome.[5] Moreover, it is unclear whether treatment should be initiated on receipt of a report of CoNS bacteraemia. Treatment practices vary and are largely empirical.

Several reports have been published pertaining to the epidemiology of coagulase-negative bacteraemia among non-critically ill patients.[6-11] Most published data on CoNS bacteraemia relate to neonatal and paediatric critically ill patients,[12,13] and reports from adult ICUs are sparse.[6,14]

The purpose of this retrospective study was to examine the frequency of blood cultures positive for CoNS among critically ill adult patients, examine the pattern of antibiotic use, and investigate the association between markers of true infection (such as TTP and number of positive bottles) with CoNS and outcome in the critically ill population.

Methods

This study was conducted in the tertiary referral 28-bed adult ICU of Princess Alexandra Hospital from 1 January to

Table 1. Demographic data of intensive care unit patients with blood cultures positive for coagulase-negative streptococci, Princess Alexandra Hospital, 2009

Characteristic	
Total no. of patients	54
Men/women	39/15
Mean age in years (SD)	54 (16)
Mean APACHE II score (SD)	17 (7)
Mean ICU length of stay in days (SD)	11 (13)
Mean hospital length of stay in days (SD)	48 (54)
Admission diagnosis, no. (%)	
Sepsis*	16 (30%)
Postoperative	9 (17%)
Trauma	11 (20%)
Cardiovascular	9 (17%)
Neurological	9 (17%)
Risk factors, no. (%)	
Central venous cannula	49 (91%)
Arterial cannula	52 (96%)
PICC	3 (6%)
Dialysis catheter	3 (6%)
Pulmonary artery catheter	2 (4%)
Intra-aortic balloon pump	2 (4%)
Total parenteral nutrition	4 (7%)
Propofol administration	37 (69%)
Immunocompromised†	7 (13%)

APACHE = Acute Physiology and Chronic Health Evaluation.
PICC = peripherally inserted central catheter.
* Central nervous system (2); respiratory (4); gastrointestinal (4); unsourced (4); neutropenic (2). † Lymphoma (2); post renal transplant (1); acute myeloid leukaemia with neutropenic sepsis (3); chronic steroid therapy for asthma (1).

31 December 2009. Ethics approval was obtained from the hospital's human research ethics committee before the start of the study.

Data were retrospectively collected through chart review of all the patients who had positive blood cultures for CoNS while they were in the ICU. These patients were identified from the hospital's microbiology database. The following data were collected for each ICU patient: demographic and clinical data, risk factors, antibiotic use, number of bottles positive and TTP. The risk factors studied were presence of vascular devices like central venous lines, arterial lines, peripherally inserted central catheters (PICCs), immunosuppression, total parenteral nutrition, recent surgery and intravenous propofol administration. The major outcome measures examined were changes in the Sequential Organ Failure Assessment (SOFA) scores, resolution of fever and white cell response and inotrope requirement, length of stay in ICU and 28-day mortality.

Laboratory methods

Blood samples were collected using aseptic technique. Twenty millilitres of blood were collected and inoculated in two equal aliquots of 10 mL each into a BacT/ALERT (bioMérieux Australia, NSW) aerobic bottle and an anaerobic bottle and incubated at 37° C. Organisms isolated from blood culture bottles were identified by the automated BacT/ALERT system.[15] On recognition of a positive culture, fluid was taken from these bottles, Gram stained and subcultured on agar plates. Direct tube coagulase and the slide coagulase test were used to identify the presence of coagulase-producing staphylococci. Staphylococcal isolates that tested negative for the coagulase enzyme were then further speciated using the VITEK (bioMérieux Australia) identification system.[16]

Statistical analysis

Analysis was performed using SAS, version 9.1 for Windows (SAS Institute, Cary, NC, USA). Categorical variables were compared using Fisher's exact test. We used linear mixed models with unstructured correlation to investigate association of prespecified potential explanatory variables with the outcome: daily SOFA scores recorded for 5 days after suspected CoNS infection. The explanatory variables were number of positive bottles (one or two), TTP ($\leq$ 24 v > 24 hours), antibiotic therapy changed, line changed, and whether vancomycin was administered after suspected infection.

Unless specified, results are presented as mean (SD).

Results

In 2009, 12 876 blood cultures were collected from all patients presenting or admitted to the Princess Alexandra Hospital. Of these, 1300 blood cultures were collected from ICU patients. There were 1514 positive blood culture sets (13.1%) among hospital patients and 109 (8.4%) among ICU patients. There were 515 culture sets positive for CoNS among patients outside the ICU (overall positivity rate, 4.4%) and 54 (overall positivity rate, 4.2%) among ICU patients. The CoNS positivity rate as a proportion of positive blood cultures was 34.0% for hospital and 49.5% for ICU patients.

Demographic details

The mean age of the 54 ICU patients (39 men, 15 women) was 54 years (SD, 16 years). The indications for blood cultures were new-onset pyrexia (33); septic shock (2); leukocytosis (3); new-onset systemic inflammatory response

Table 2. Comparison of characteristics of 54 patients who had one and two bottles blood culture positive for coagulase-negative staphylococci*

	One bottle positive	Two bottles positive	*P*
No.	32	22	
Men/women	22/10	17/10	0.49
Mean age in years (SD)	52 (16)	57 (17)	0.49
Central venous cannula	28	20	0.69
Arterial cannula	30	22	0.23
Propofol use	23	14	0.52
Immunosuppression	0	7	0.006
Hospital mortality	6	4	0.95

* Data are no. of patients unless otherwise stated.

syndrome (1); infected-looking central venous cannula exit site (1); new-onset radiological infiltrates (1); unspecified (13). The mean lengths of ICU and hospital stays were 11 days (SD, 13 days) and 48 days (SD, 54 days), respectively. Seven patients were immunocompromised. The demographic data are summarised in Table 1.

Microbiological data

Twenty-two of the 54 patients (41%) had two bottles that tested positive for CoNS, and the remaining 32 grew the organism in only one bottle. There was no significant correlation between number of bottles positive for culture and mortality ($P = 1.00$), length of stay ($P = 0.91$), resolution of fever ($P = 0.93$), white cell response ($P = 0.92$), and inotrope requirement ($P = 0.53$). A comparison of characteristics of patients who had one and two bottles positive is provided in Table 2.

The mean TTP was 32 hours (SD, 17 hours). Twenty-two patients (41%) returned positive cultures for CoNS in 24 hours or less of sample collection. There was a trend towards an association between increased 28-day mortality and TTP $\leq$ 24 hours (7/22 v 3/32; $P = 0.07$). A comparison of characteristics of patients who had early and delayed blood culture positivity is provided in Table 3. Patients with TTP $\leq$ 24 hours had a higher mean SOFA score by 0.9 (95% CI, 0–3.4, $P = 0.05$). The absolute daily SOFA scores for the two groups are provided in Table 4. There was no association between TTP $\leq$ 24 hours and length of stay ($P = 0.16$), resolution of fever ($P = 0.52$), white cell response ($P = 0.22$) and inotrope requirement ($P = 0.93$).

Effect of prior antibiotic therapy and antibiotic change after culture positivity

Nine patients were taking vancomycin before blood samples were drawn. Following positive culture reports, vancomycin therapy was continued for eight of these patients and initiated for another 16 patients. No change was made for the remaining 29 patients. Continuation or initiation of vancomycin therapy was not associated with reduced mortality ($P = 0.31$), resolution of fever ($P = 0.46$), white cell response ($P = 0.56$) or inotrope requirement ($P = 0.72$).

Discussion

To the best of our knowledge, this is the first investigation of the epidemiology and significance of CoNS bacteraemia in critically ill adult patients. Our cardinal findings were the high proportion of blood culture isolates positive for CoNS and a trend towards an association between early TTP of the culture and adverse outcomes. Immunocompromised patients were more likely to have two bottles positive for culture.

The frequency of CoNS positive blood cultures (as a proportion of all positive blood cultures) was 50% in critically ill patients in our ICU. The corresponding CoNS positivity proportion for the hospital was 34%. Published CoNS positivity rates range from 24% in a tertiary centre in Sydney,[6] 42% in North America[11] to nearly 85% in Taiwan.[17]

Although CoNS isolation from blood culture is frequently a contaminant, determining whether it represents a true infection is a significant challenge for clinicians. As noted, few studies have explored the clinical significance of CoNS bacteraemia in critically ill patients.

A short TTP has often been suggested as a marker of true bacteraemia. This is based on the notion that in a true infection, the bacterial load is higher and therefore is likely to result in a more rapid growth. One study suggested that a TTP greater than 3 days is far more likely to represent contamination.[18] In the paediatric population, a TTP less than 15 hours had a high positive predictive value for true infection.[19] We chose 24 hours as that had been shown to

Table 3. Comparison of characteristics of 54 patients with early and delayed blood culture positivity for coagulase-negative staphylococci*

	TTP $\leq$ 24 hours	TTP > 24 hours	*P*
No.	22	32	
Men/women	19/3	20/12	0.05
Mean age in years (SD)	59 (18)	50 (15)	0.21
Central venous cannula	19	30	0.35
Arterial cannula	21	31	0.78
Propofol use	13	24	0.21
Immunosuppression	5	2	0.11
Hospital mortality	7	3	0.07

TTP = time to positivity. * Data are no. of patients unless otherwise stated.

Table 4. Comparison of serial absolute daily SOFA scores of patients with early and delayed blood culture positivity for coagulase-negative staphylococci

Day	TTP	No. observed	No.*	Mean SOFA score (SD); range
1	> 24 hours	32	32	8.71 (3.41); 4.0–17.0
	⩽ 24 hours	22	22	9.81 (3.97); 3.0–18.0
2	> 24 hours	32	32	7.90 (3.41); 1.0–16.0
	⩽ 24 hours	22	21	8.57 (3.84); 1.0–15.0
3	> 24 hours	32	31	7.00 (3.35); 1.0–16.0
	⩽ 24 hours	22	21	8.14 (3.97); 1.0–16.0
4	> 24 hours	32	30	6.13 (2.73); 1.0–12.0
	⩽ 24 hours	22	19	7.21 (3.90); 1.0–15.0
5	> 24 hours	32	30	5.96 (2.69); 1.0–12.0
	⩽ 24 hours	22	19	7.00 (3.80); 1.0–15.0

SOFA = Sequential Organ Failure Assessment. TTP = time to positivity.
* There were some missing SOFA scores for five patients due to patient deaths (13 missing observations). These represent less than 5% of the total potential data, and no assumptions were made about these missing data in our analysis.

be a relevant cut-off in non-critically ill adults.[5] In our study, patients with a TTP of 24 hours or less had statistically significant higher SOFA scores and a trend towards increased mortality. Moreover, all immunocompromised patients had a TTP of 24 hours or less. Taken together, this would suggest that a TTP of 24 hours or less could be suggestive of a true infection in critically ill patients.

The other frequently used variable to distinguish a true infection from contamination is the number of bottles positive within a given culture set — the greater the number of bottles positive, the more likely it is to represent a true infection. In our study, there was no correlation between number of bottles positive and SOFA scores or mortality. However, all immunocompromised patients grew positive cultures in two bottles. The lack of a strong correlation between number of bottles positive and outcome in our study is in accord with data of Mirrett and colleagues, who concluded that number of positive bottles was not a reliable predictor of infection.[20]

Antibiotic administration after culture positivity was not associated with any differences in outcome with respect to fever resolution, leukocytosis or inotrope requirement in the group as a whole or even within the subgroups of early or delayed TTP. Based on our findings that a TTP of 24 hours or less may be a marker of true bacteraemia, one would expect that antibiotic change following culture positivity would result in improved outcomes. Possible reasons for the discrepancy include small patient numbers in the subgroups, the use of non-specific clinical indices of infection, such as fever and leukocytosis, or the likelihood that CoNS infections more often resolve with removal of intravascular devices than with antibiotic therapy.

Clinical significance

CoNS bacteraemia is a frequent problem among hospitalised and ICU patients. The importance of this is highlighted by the fact that the clinical significance is often unclear and that antibiotic initiation policies for CoNS bloodstream isolates vary between centres. Furthermore, other therapeutic strategies are triggered, including removals and changes of cannulae. All of these have significant health and economic implications.

Limitations of the study

This study is limited by its retrospective design and the small sample size. Moreover, owing to the retrospective design we could not test for reliable biomarkers of infection such as procalcitonin.[21,22] Whether quantitative cultures would have added any further value is unclear. Although this method is of benefit in confirming infection in sputum and urine samples, it does not have the same reliability in blood cultures.[23] As this is a hypothesis-generating study with no a-priori outcome assessment, the *P* values should only be interpreted as a probability and not dichotomised into significant or non-significant at the 0.05 threshold.

Conclusion

In conclusion, CoNS isolates from blood cultures are frequently seen in critically ill adults. Although they are often deemed to be contaminants, we suggest that early TTP of blood cultures of these organisms may be associated with poorer outcome and may be a marker of true bacteraemia. Given the relatively high frequency of this microbiological problem, its potential consequences, and the lack of guidelines on when antibiotic therapy should be instituted, larger prospective observational studies are required to more clearly define the significance of CoNS bloodstream isolates in critically ill adults.

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