

# Coagulase-negative *Staphylococcus*, catheter-related, bloodstream infections and their association with acute phase markers of inflammation in the intensive care unit: An observational study

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**OBJECTIVE:** To examine the relationship between the isolation of coagulase-negative *Staphylococcus* in blood cultures and acute phase markers of inflammation.

**METHODS:** The present study was a prospective observational analysis conducted at three medical/surgical intensive care units (ICUs) involving adult patients with an expected ICU stay of more than 24 h duration.

**RESULTS:** Of the 598 patients enrolled, 573 developed suspected bloodstream infection and 434 (72.6%) had blood cultures sent 24 h after ICU admission; 142 were excluded due to positive cultures from other sites. Of the remaining 292 patients, 31 (10.7%) grew coagulase-negative *Staphylococcus*, 59 (20.2%) grew known pathogenic organisms and 202 (69.2%) did not grow any organisms in their blood cultures. Twenty-five patients without suspicion of infection served as the control group. Interleukin (IL)-6, procalcitonin (PCT) and C-reactive protein (CRP) levels were highest among the known pathogen group (IL-6 271.8 U/L, PCT 4.6 U/L and CRP 164 mg/L), were similar between the coagulase-negative *Staphylococcus* and negative culture groups (IL-6 67.0 U/L versus 61.4 U/L [P=1.00]; PCT 1.0 U/L versus 0.9 U/L [P=0.80]; and CRP 110 mg/L versus 103 mg/L [P=0.75]), and were lowest in the control group (IL-6 31.0 U/L, PCT 0.2 U/L and CRP 41.0 mg/L). In the coagulase-negative *Staphylococcus* group, patients who died by day 28 had increased inflammatory biomarker levels compared with survivors, although the differences were not statistically significant.

**CONCLUSIONS:** Coagulase-negative *Staphylococcus* isolated from blood cultures were associated with lower levels of inflammation compared with bloodstream infections due to known pathogens and were comparable with levels in patients with negative cultures.

**Key Words:** Catheter-related bloodstream infection; Coagulase-negative *Staphylococcus*; C-reactive protein; Interleukin-6; Procalcitonin

Catheter-related, bloodstream infections (CRBSIs) are a major source of morbidity and mortality in the intensive care unit (ICU). Coagulase-negative *Staphylococcus* (CoNS) is the most commonly encountered organism in CRBSIs, causing between 11% and 45% of infections with an incidence of 15.8 per 10,000 hospital admissions (1,2), at an associated cost of US\$33,000 to US\$71,000 per

Les infections du sang par le staphylocoque à coagulase négative, les infections du sang liées au cathéter et leur association avec les marqueurs d'inflammation en phase aiguë à l'unité de soins intensifs : une étude d'observation

**OBJECTIF :** Examiner la relation entre l'isolement de staphylocoque à coagulase négative dans les hémocultures et les marqueurs d'inflammation en phase aiguë.

**MÉTHODOLOGIE :** Étude d'observation prospective

**LIEU :** Trois unités de soins intensifs (USI) médicaux et chirurgicaux

**PATIENTS :** Tous les patients dont le séjour prévu à l'USI pour adultes dépassait 24 heures

**RÉSULTATS :** Sur les 598 patients participants, 573 ont présenté une présomption d'infection du sang, et une hémoculture a été envoyée en laboratoire 24 heures après l'admission à l'USI de 434 (72,6 %) d'entre eux; 142 ont été exclus en raison de cultures positives d'autres foyers. Sur les 292 patients restants, 31 (10,7 %) ont développé un staphylocoque à coagulase négative, 59 (20,2 %) des organismes pathogènes connus et 202 (69,2 %) ne présentaient aucun organisme dans le sang. Vingt-cinq patients sans présomption d'infection ont servi de groupe témoin. Les taux d'interleukine (IL)-6, de procalcitonine (PCT) et de protéine C réactive (CRP) étaient les plus élevés dans le groupe infecté par des pathogènes connus (IL-6 271,8 U/L, PCT 4,6 U/L et CRP 164 mg/L), étaient similaires dans les groupes de staphylocoque à coagulase négative et aux cultures négatives (IL-6 67,0 U/L par rapport à 61,4 U/L [P=1,00]; PCT 1,0 U/L par rapport à 0,9 U/L [P=0,80] et CRP 110 mg/L par rapport à 103 mg/L [P=0,75]) et étaient les plus faibles dans le groupe témoin (IL-6 31,0 U/L, PCT 0,2 U/L et CRP 41,0 mg/L). Dans le groupe ayant un staphylocoque à coagulase négative, les patients qui étaient décédés le 28<sup>e</sup> jour présentaient des taux de biomarqueurs inflammatoires plus élevés que les survivants, même si les différences n'étaient pas statistiquement significatives.

**CONCLUSIONS :** Le staphylocoque à coagulase négative isolé dans les hémocultures s'associait à des taux plus faibles d'inflammation que les infections du sang causées par des pathogènes connus et était comparable aux taux observés chez les patients dont les cultures étaient négatives.

episode (3). The incidence of CoNS CRBSIs is increasing with the increased use of implanted devices, such as central venous catheters and temporary dialysis catheters (4), which are especially common in the ICU, secondary to the frequent requirement for one or more of these catheters, and the repeated requirements for access to these devices due to the severity of underlying patient disease (5).

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When blood cultures performed for suspected infection are positive for CoNS, it is often difficult to determine whether the presence of this organism in the blood is a pathogen or a contaminant. There have been several strategies proposed to enhance the diagnosis of CoNS CRBSIs (6), but these methods remain imperfect and often involve the removal of the catheter in question for diagnosis. Most commonly, the diagnosis of CoNS CRBSI remains a clinical diagnosis and one of exclusion, where no other potential source of infection or infectious organism is identified.

Systemic inflammation in the ICU, as manifested by systemic inflammatory response syndrome (SIRS), is very common (7). Distinguishing between SIRS caused by infection and SIRS secondary to other causes is very challenging clinically, and there is an increasing amount of literature evaluating the utility of biomarkers for this indication (8). These biomarkers include interleukin (IL)-6 and the acute phase markers of inflammation procalcitonin (PCT) and C-reactive protein (CRP), among others. These new biomarkers have been used in enhancing the diagnosis of infection and predicting patient outcome (9-11) but have not yet been applied to predicting patient outcome and guiding clinical decision making regarding CRBSIs caused by CoNS.

The purpose of the present study was to determine whether patients with blood cultures positive for CoNS had associated elevations of inflammatory biomarkers. We hypothesized that CoNS-positive blood cultures generally do not cause elevations in acute phase markers of inflammation, as seen in bacteremias with known pathogens, but that increased levels of acute phase markers of inflammation within CoNS-positive blood culture populations may be predictive of poorer clinical outcomes. If our hypothesis is correct, then acute phase markers of inflammation may be useful in guiding management and predicting clinical outcomes.

## METHODS

A prospective, multicentre, observational study in three general medical/surgical tertiary care ICUs for the primary purpose of evaluating a novel diagnostic marker for sepsis, was conducted (12). A secondary analysis examining the relationship between bloodstream infections and inflammatory mediators is also described. All patients admitted to the ICU and expected to stay more than 24 h were included. Individuals admitted for routine cardiac monitoring (ie, elective surgery), overdoses and pediatric patients (<18 years of age), were excluded. Because the overall goal was to compare the levels of inflammatory markers associated with isolated CoNS in blood cultures with other known pathogen levels in the blood, patients with infections at other sites were excluded. Blood cultures were ordered as per clinical suspicion of infection and at the discretion of the clinical team. Two researchers reviewed patient charts independently to ensure appropriate group allocation. Study patients were divided into the following four groups according to the organisms grown in the blood cultures: patients who grew known pathogens in their blood (eg, *Acinetobacter* species, *Aeromonas* species, *Burkholderia cepacia*, *Citrobacter* species, *Escherichia coli*, *Enterobacter* species, *Enterococcus* species, *Haemophilus influenzae*, *Klebsiella* species, *Moraxella catarrhalis*, *Morganella* species, *Neisseria meningitidis*, *Pasteurella* species, *Proteus* species, *Pseudomonas aeruginosa*, *Serratia* species, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, beta-hemolytic *Streptococcus* and *Streptococcus pneumoniae*); patients who grew CoNS in their blood with no other organisms in the blood or at other sites within 72 h of their culture draw date; patients who did not grow any microorganisms in their blood cultures or at any other site within 72 h of their culture draw date; and patients without any suspicion of infection, as indicated by the fact that they never had any blood cultures drawn or antibiotics prescribed. These patients served as the control group. This selective grouping of patients was established in an attempt to provide a 'pure' group of patients admitted to the ICU to enable answering of the study question. For patients with drawn-blood cultures, the levels of acute phase markers of inflammation were obtained within 24 h of the blood culture being drawn.

To determine the levels of acute phase markers of inflammation for the control group, blood was drawn on day 3 of ICU admission. To be considered noninfected, day 3 of ICU admission was chosen to allow sufficient time in the ICU without suspicion of infection.

## Clinical management

Because the present study was observational in nature, the clinical team was responsible for making all management decisions. Decisions pertaining to culturing blood and initiating antibiotic therapy were left to the discretion of the clinical teams.

## Clinical data collection

Baseline demographics, medical history and reasons for ICU admission were obtained from patients or their charts. Necessary variables were recorded to calculate Acute Physiology and Chronic Health Evaluation II (APACHE II) (13), on admission, and Sequential Organ Failure Assessment (SOFA) scores (14) daily until day 28, death or discharge from the ICU.

## Laboratory tests

Blood samples were collected in the morning following enrollment and each subsequent day until discharge from the ICU, death or a maximum of 10 days. Plasma was analyzed for inflammatory markers using the following assays: CRP (high-sensitivity cardiac C-reactive protein reagent used in conjunction with the UniCel DxC 600/800 system, Beckman Coulter Inc, USA), procalcitonin (B-R-A-H-M-S PCT LIA, Thermo Fisher Scientific, Germany); IL-6 (ELISA kit, Cat BMS-213, Bender Med Systems Inc, USA). Blood cultures were drawn throughout the ICU admission as indicated based on a clinical suspicion of infection.

## Outcome measures

The clinical outcomes for the present study included 28-day mortality, ICU-free days and ventilator-free days in the first 28 days, and maximum and delta SOFA scores. The delta SOFA score was calculated by subtracting the maximal SOFA score from the baseline SOFA score (14).

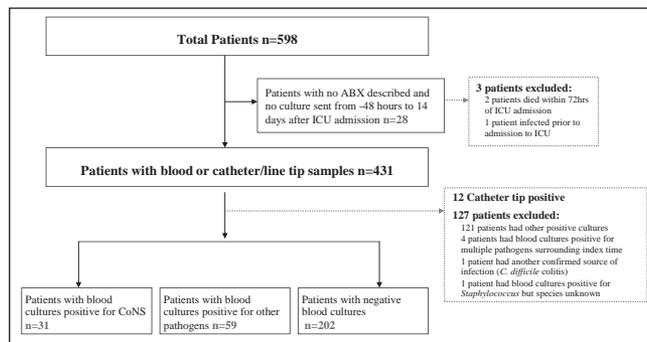
## Statistical analysis

Patient characteristics, clinical outcomes and biomarkers within  $\pm 24$  h of the index date were compared among four patient groups with different organisms grown in blood cultures. Categorical variables were described as counts and percentages and were compared using the  $\chi^2$  test. Normally distributed variables were described as means  $\pm$  SDs and compared using the ANOVA test, whereas other continuous variables were described as medians with quartiles, and differences were tested using the Kruskal-Wallis test (15). Box-and-whisker plots were used to depict the inflammatory biomarker levels among the four patient groups and between 28-day survivors and nonsurvivors.

## RESULTS

A total of 598 patients were enrolled in the present study. Twenty-eight patients had no antibiotics prescribed and no cultures sent from 48 h before to 14 days after ICU admission. Three of these patients were excluded (one patient had a diagnosed infection the week before and two patients died within 72 h of ICU admission), and the remaining 25 patients served as the control group. Of the remaining 570 patients, 434 (72.6%) had at least one blood culture drawn 48 h after ICU admission. Of these, 142 were excluded because they had another site with a positive culture (ie, sputum) (n=130) or because only the line tip was positive (n=12) with no associated positive blood culture. Of the remaining 292 patients, 31 (10.6%) had blood cultures positive only for CoNS, 59 (20.2%) were positive for other previously described pathogens and 202 (69.2%) had negative blood cultures (Figure 1).

Baseline patient characteristics (Table 1) were similar among the CoNS, known pathogen-positive and culture-negative groups, but differed significantly from the control group. The control-group patients were younger and had lower APACHE II and SOFA scores. Moreover,



**Figure 1**) Flowchart depicting the patient breakdown and allocation for the study population. Patients with catheter tip-positive cultures were excluded from the final analysis. ABX Antibiotics; CoNS Coagulase-negative Staphylococcus; ICU Intensive care unit

the primary admission diagnosis differed significantly among groups with a predominance of sepsis in the known pathogen-positive group.

Levels of IL-6, PCT and CRP were highest in the group with blood cultures positive for known pathogens, lower in the CoNS and negative-culture groups, and lowest in the control group (P<0.05, Table 2). Acute phase markers of inflammation levels were most similar between the CoNS and negative culture groups (IL-6 67.0 IU/L versus 61.4 IU/L [P=1.00]; PCT 1.0 IU/L versus 0.9 IU/L [P=0.80]; and CRP 110 mg/L versus 103 mg/L [P=0.75]), and values were lowest in the control group for each of IL-6, PCT and CRP (31.0 IU/L, 0.2 IU/L and 41.0 mg/L, respectively) (Table 2).

The overall mortality rate in the study population was 25.6% at 28 days. The mortality rate was highest among the known pathogen group and lowest in the control group (37.3% versus 0%; P=0.005). The mortality rate was similar between the CoNS and culture-negative groups at 28 days (22.6% versus 25.7%; P=0.71) (Table 3).

In the CoNS group, seven (22.6%) patients died. There were no statistically significant differences in inflammatory cytokines levels at 24 h between survivors and nonsurvivors (Table 4). However, in absolute

**TABLE 1**  
**Baseline patient characteristics**

	Other pathogens (n=59)	CoNS (n=31)	Negative culture (n=202)	Control (n=25)	P*
Age, years	63.4±15.1	63.5±15.4	60.4±15.5	51.6±19.7	<b>0.01</b>
Sex, male, n (%)	30 (50.8)	17 (54.8)	116 (57.4)	12 (48.0)	0.71
APACHE II score	25.6±7.7	23.5±7.9	22.4±7.0	12.3±6.4	<b>&lt;0.001</b>
Baseline SOFA score	6.3±2.8	5.3±3.0	4.9±2.8	1.3±1.6	<b>&lt;0.001</b>
Comorbidities, n	3.0±1.4	3.3±1.4	3.0±1.3	3.1±1.4	0.79
Admission, n (%)					0.27
Medical	50 (84.7)	25 (80.6)	147 (72.8)	18 (72.0)	
Surgical	9 (15.3)	6 (19.4)	54 (26.7)	7 (28.0)	
Primary admission diagnosis, n (%)					<b>&lt;0.001</b>
Cardiovascular/vascular	6 (10.2)	4 (12.9)	19 (9.4)	3 (12.0)	
Respiratory	17 (28.8)	12 (38.7)	72 (35.6)	2 (8.0)	
Gastrointestinal	8 (13.6)	4 (12.9)	32 (15.8)	3 (12.0)	
Neurological	2 (3.4)	3 (9.7)	12 (5.9)	2 (8.0)	
Sepsis	14 (23.7)	1 (3.2)	12 (5.9)	0 (0.0)	
Trauma	5 (8.5)	3 (9.7)	16 (7.9)	4 (16.0)	
Metabolic	4 (6.8)	1 (3.2)	12 (5.9)	7 (28.0)	
Postoperative conditions	2 (3.4)	1 (3.2)	17 (8.4)	4 (16.0)	
Renal	0 (0.0)	2 (6.5)	4 (2.0)	0 (0.0)	
Orthopedic	1 (1.7)	0 (0.0)	5 (2.5)	0 (0.0)	
Heart rate, beats/min	120.1±22.5	110.5±23.7	110.1±21.4	102.7±19.6	<b>0.01</b>
Temperature, °C	38.3±1.4	37.7±1.5	38.2±1.3	37.9±0.5	0.24
Respiratory rate, breaths/min	28.5±9.4	29.0±12.9	26.0±8.3	28.1±6.7	0.20
White blood cell count, ×10 <sup>9</sup> /L	13.7±10.2	12.4±6.7	13.3±6.3	8.7±2.7	0.10

Data presented as mean ± SD unless otherwise indicated. \*P represents comparisons between control group, other pathogens, coagulase-negative Staphylococcus (CoNS) and negative culture groups. Statistically significant P values are highlighted in bold. APACHE II Acute Physiology and Chronic Health Evaluation II; SOFA Sequential Organ Failure Assessment

terms, nonsurvivors had much higher levels of IL-6, PCT and CRP compared with survivors (102.7 IU/L versus 65.4 IU/L, 1.5 IU/L versus 0.6 IU/L and 136.5 mg/L versus 103 mg/L, respectively) (Table 4).

**DISCUSSION**

In the present study, we examined the relationship between acute phase markers of inflammation and the isolation of CoNS in blood cultures from patients with suspected bloodstream infection. While exhibiting higher levels of inflammation than patients without suspected infection, patients with blood cultures positive for CoNS did not have acute phase markers of inflammation that were significantly elevated over patients with negative blood cultures. Furthermore, they had lower levels of acute phase markers of inflammation when compared with other pathogenic organisms (Table 3). Thus, overall, isolated CoNS-positive blood cultures do not indicate an increased inflammatory response above those found in other ICU patients when infection is suspected.

The pathogenicity of CoNS has been widely debated. Current molecular techniques suggest CoNS, of which *Staphylococcus epidermidis* is the most important pathogenic species, do not share any of the major virulence factors or toxins with *S aureus* (16). Other studies examining the proinflammatory and immunogenic potential of *S epidermidis* have shown in animal models that intradermal injections of *S epidermidis* do not cause local inflammatory reactions (17). Furthermore, *S epidermidis* does not cause an immunoglobulin G response and, in fact, *S epidermidis* injection is associated with the release of IL-10, an anti-inflammatory cytokine (17). It has been postulated that because of its low virulence, *S epidermidis* is only able to persist in the bloodstream by evading host defenses through biofilm formation, rather than attacking the host through toxin production (17-19). Strain-specific production of exotoxin has been reported within the *S epidermidis* family (20), but the vast majority of *S epidermidis* strains are not exotoxin producing, and this may explain the lack of increased markers of inflammation associated with *S epidermidis* bacteremia compared with patients who grew known pathogenic organisms on blood culture (Table 3). It is possible that

**TABLE 2**  
**Inflammatory biomarker levels according to group**

	Other pathogen (n=59)	CoNS (n=31)	Negative culture (n=202)	Control (n=25)	P*
Procalcitonin, U/L (n)	4.6 (24)	1.0 (13)	0.9 (113)	0.2 (18)	<0.05
C-reactive protein, mg/L (n)	164.0 (34)	110.0 (19)	103.0 (132)	41.0 (23)	<0.01
Interleukin-6, U/L (n)	271.8 (24)	67.0 (13)	61.4 (113)	31.0 (17)	<0.02

Data presented as median values of inflammatory biomarkers drawn within 24 h of the index date, unless otherwise indicated. \*P values are representative of comparisons made between other pathogens and coagulase-negative *Staphylococcus* (CoNS), negative culture and control groups

**TABLE 3**  
**Clinical outcomes according to group**

	Other pathogens (n=59)	CoNS (n=31)	Negative culture (n=202)	Control (n=25)	P
Maximum SOFA	11.1±3.8	8.3±3.6	8.8±4.0	3.2±2.0	0.001*†
Delta SOFA	4.9±3.1	3.2±2.5	4.1±3.0	2.3±2.2	0.01†
Days on mechanical ventilation	8.0±8.4	5.6±4.5	5.9±5.8	0.6±0.8	<0.001*
Days in intensive care unit	12.6 ±17.0	8.8±6.2	10.5±13.5	3.1±1.2	0.02*
Mortality at day 28, n (%)	22 (37.3)	7 (22.6)	52 (25.7)	0 (0.0)	0.005*

Data presented as mean ± SD unless otherwise indicated. \*P between control group and other pathogen, coagulase-negative *Staphylococcus* (CoNS) and negative culture groups; †P between other pathogen and CoNS group. SOFA Sequential Organ Failure Assessment

exotoxin-producing strains may be associated with higher levels of acute phase markers of inflammation and increased mortality. However, exotoxin levels were not quantified in collected blood, and additional studies examining the presence of exotoxin in the blood of patients infected with *S. epidermidis* and other CoNS need to be performed to investigate this hypothesis.

Another possible explanation for CoNS not being associated with increased levels of inflammatory biomarkers may stem from CoNS being a contaminant in the blood cultures. If this were the case, patients would not truly be infected and it may be inferred that inflammatory biomarker level would not be elevated. The study population may itself include two different subpopulations: one that had true blood culture positivity with CoNS and another in which CoNS was as a contaminant. Contamination of blood cultures by CoNS is most likely to occur at the time of collection due to breaks in aseptic culture collection technique. Biomarkers may be useful to differentiate between these two populations. Currently, there are no validated or well-studied methods to accomplish this, and the number of blood cultures that return positive for CoNS is what is most commonly used at present to provide this differentiation. Unfortunately, we did not quantify the percentage of blood cultures that were positive for CoNS, so it is not possible to solidify this conclusion. Additional work quantifying and adjudicating true CoNS CRBSIs versus CoNS contamination is necessary to determine whether biomarkers may be used to aid in this differentiation.

Absolute bacterial load may have contributed to the levels of inflammation biomarkers and patient outcomes. According to this hypothesis, higher organism load in the blood may cause increased inflammation and lead to poorer patient outcome. The present study was not structured to answer this question, and more work will need to be performed to test this hypothesis. Finally, CoNS bacteremia may not necessarily be the cause of inflammation but may be an epiphenomena in patients who have systemic inflammation caused by SIRS. If this hypothesis was correct, then treatment of the underlying cause of SIRS would be all that is required, rather than treatment for the CoNS.

While the mortality rate of patients with blood cultures positive for CoNS was similar to those with negative cultures, there was a wide range of inflammatory profiles in these patients. Recently, there has been much work focused on uncovering novel markers of inflammation. The most important and promising of these in bacterial infections include IL-6, CRP and PCT (21,22). IL-6 has been previously demonstrated to be closely related to the severity of the physiological response to infection and systemic inflammation, and PCT has been shown to be related to the systemic inflammatory response, especially when associated with bacterial infections (23). CRP is an acute phase protein that is released by the liver as a consequence of inflammation but is less specific than both IL-6 and PCT for inflammation secondary

**TABLE 4**  
**Coagulase-negative *Staphylococcus* biomarkers and outcomes**

	Patients		P
	Deceased by day 28 (n=7)	Alive at day 28 (n=24)	
Procalcitonin, U/L (n)	1.5 (3)	0.6 (11)	0.31
C-reactive protein, mg/L (n)	136.5 (6)	103.0 (17)	0.42
Interleukin-6, U/L (n)	102.7 (3)	65.4 (11)	0.70

Data presented as median values unless otherwise indicated

to infection (24-26). Previous studies have demonstrated that while IL-6, PCT and CRP levels are all elevated in septic patients, IL-6 and PCT levels correlate with SOFA scores and may be predictive of clinical outcome (10,25). In the present study, when compared with survivors, patients with blood cultures positive for CoNS and who died by 28 days had elevated levels of IL-6, PCT and CRP within 24 h of their positive blood cultures (Figure 3). These findings were not statistically significant because of the small sample size, but the differences were clinically important. Statistically significant differences, however, may have emerged between these two groups had a larger sample size been available; this would be necessary to sufficiently power an investigation of this finding.

A limitation of the present study was the small sample size. Our measurements of IL-6, PCT and CRP levels showed great variability, and given the small sample size and large variability, the present study was underpowered to show statistically significant differences in acute phase markers of inflammation. Ultimately, these observations are hypothesis generating and require additional studies to examine the role of CoNS in the systemically inflamed patient. An additional limitation was that we could not determine overall bacterial burden. Unfortunately, while we collected culture results, we did not keep track of how many sets of blood cultures were sent to the laboratory and, thus, we cannot comment on the proportion of positive cultures in each patient. This prevents us from attempting to establish bacterial load and likely contaminants versus true bacteremias, and from making any concrete conclusions regarding the CoNS-bloodstream load and its relationship to systemic inflammation. Additional work will need to be performed to investigate these theories.

## CONCLUSION

The levels of acute phase markers of inflammation are elevated in critically ill patients. CoNS isolated in blood cultures are associated with lower levels of inflammation compared with bloodstream infections due to known pathogens and are comparable with patients who

have negative cultures. In the subset of patients with CoNS-positive blood cultures, higher levels of IL-6, PCT and CRP were associated with increased mortality. Additional studies are needed to determine whether inflammatory biomarker levels may be used to guide antibiotic therapy in patients with CoNS.

**DISCLOSURES:** The authors have no financial disclosures or conflicts of interest to declare.

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