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The ConMan Trial: Coagulase Negative Staphylococcal Infections: To Treat or Not to Treat

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Abstract

Background: Coagulase negative *Staphylococci* (CoNS) positive blood cultures represent a complex and common challenge in clinical medicine. CoNS are common in skin flora and are often mistaken as contamination. Conversely, CoNS can also be implicated in severe and life-threatening bacteremia requiring prompt treatment. A gray area in terms of treatment approach exists for health care providers. The primary aim of this study was to examine predictive factors in patients who have positive CoNS blood cultures that met the CDC case definition of a laboratory confirmed bloodstream infection (LCBI-II) that were subsequently found to have clinically significant true bacteremia. **Methods:** A retrospective cohort of 288 patients that had at least two separate blood cultures positive for a coagulase negative *Staphylococci* between November 1st, 2017, and November 1st, 2018, were examined to determine if there were any patient specific factors that would indicate a true bacteremia with CoNS. **Results:** Retrospective regression analysis demonstrated that those subjected to antibiotics for two days or more (OR = 3.01), those subjected to antibiotics for seven days or more (OR = 2.86), and patients with central access (OR = 4.06) were more likely to have a true infection. Although not statistically significant, an association was also found in immunosuppressed patients (OR = 1.65), and in patients with implanted hardware (OR = 1.16). **Conclusion:** Patients receiving antibiotics for greater than two days and patients with a central

line were more likely to have a true bloodstream infection with coagulase negative *Staphylococci*.

Keywords

Coagulase Negative Staphylococci (CoNS), Positive Blood Culture, True Bacterium, Central Access, Immunosuppressed, Infectious Disease

1. Introduction

There has been a growing interest over the last decade in expanding our knowledge of clinical decision making in the presence of coagulase negative *Staphylococci* (CoNS) [1]-[3]. While it is understood that CoNS can result in severe and even life-threatening infections, there is little consensus as to when patients with positive CoNS cultures should be treated aggressively [4]. Earlier studies have shown possible predictive factors such as central venous catheters, but additional evidence-based research is needed to assist in decision making [5]-[8]. The most common microorganisms in blood cultures are CoNS, as blood cultures are commonly contaminated by coagulase negative *Staphylococci* which are ubiquitous in the skin flora, and can be a consequence of contamination from another source [9] [10].

The Centers for Disease Control and Prevention (CDC) definition of a primary laboratory confirmed bloodstream infection (LCBI) excludes the use of common commensals, such as CoNS, but there is an alternate definition of an LCBI that is specifically designed to capture bloodstream infections (BSIs) that are caused by common commensals. An LCBI-II is defined as a laboratory confirmed bloodstream infection that requires that the patient have at least one clinical symptom that includes: fever, chills, or hypotension, and the same common commensal is identified in at least two separate blood cultures, and the infection is not related to an infection at another site [1]. Unfortunately, the broadness of this criteria in the current guideline has been shown to be suboptimal in distinguishing between contamination and true bacteremia, in which the patient had viable bacteria in the bloodstream and symptoms of active infection [11]-[13]. In a sample of 162 patients with at least one positive blood culture, 24 qualified as true infections per CDC criteria while only 20 were considered to have true infections when using clinical assessments [11]. The study concluded that neither LCBI criteria nor clinical assessment were sufficient on their own. A similar study reviewed a total of 471 cases of CoNS positive blood cultures [12]. They found that cases were typically overtreated with antibiotics when compared to the CDC criteria and the decision about the significance of positive blood culture findings were often not evidence based.

A tertiary care center that examined blood cultures positive for CoNS other than *Staphylococcus epidermidis* analyzed 252 patients who met inclusion criteria

[13]. They found 23% of these cases would be classified as possible or likely true bacteremia. The presence of foreign bodies was found in a majority of those cases. Four species (*Staphylococcus haemolyticus*, *S. capitis*, *S. hominis*, and *S. lugdunensis*) accounted for the majority of clinically significant pathogens. A similar prospective study looked at 296 cases with at least 2 blood cultures positive for a CoNS [6]. The authors did not investigate the species of CoNS but followed patient outcomes to determine when the cultures represented true bacteremia. They found that 97 (33%) of these infections were clinically significant and found that a shorter time to positivity of cultures, presence of a central line, and multiple positive cultures from different site were positively correlated with true bacteremia. A tertiary care center reviewed the records of 960 patients with positive blood cultures and examined the 405 that contained CoNS [14]. It was found that 22% of these cases were considered to be clinically significant. They determined the best algorithm was defined as either at least 2 positive blood cultures for CoNS within 5 days, or one positive blood culture with clinical evidence of infection. In this study, the criteria had a sensitivity of 62% and specificity of 91%. Accurate identification and susceptibility testing of CoNS isolates that meet the criteria for a laboratory confirmed bloodstream infection II (LCBI-II) are crucial to minimize excessive antibiotic use [15]. There are clear opportunities for improvement in the knowledge and practices regarding blood culture contamination [16].

The purpose of this study was to determine which predictive factors (e.g., age, presence of implanted hardware, central venous catheters, etc.) in patients with CoNS positive blood cultures were indicative of a true laboratory confirmed bloodstream infection (LCBI-II). Based on previous literature, it was speculated that recent implantation and/or the presence of foreign bodies would have a positive correlation with a LCBI-II in addition to indwelling vascular access catheters [7] [17]. As body mass index (BMI) is categorized for the patient population, those who are overweight or obese with a positive CoNS culture were expected to have higher LCBI-II correlation in comparison to patients with a normal BMI.

2. Materials and Methods

The study design was a retrospective analysis of patients admitted to a teaching hospital with blood cultures collected from November 1, 2017 - November 1, 2018. All patients had at least 2 positive blood cultures from on separate occasions within 24 hours. Data was extracted using their electronic health records and true CoNS was defined as an LCBI-II. Variables collected for examination included patient age, body mass index, venous access status, urinary catheter status, immunosuppression as defined by having an ANC of less than 1000, presence of any hardware, and antibiotic usage. Inclusion criteria consisted of age ≥18 years, and at least two blood cultures positive for CoNS more than 48 hours after hospital admission. Exclusion criteria included patients transferred from outside hospitals with diagnosis of CoNS, and patients with incomplete medical records. Ethics board approval was sought and obtained from the University of Tennessee College

of Medicine (IRB #19009).

Statistical Analysis

Continuous variables were described as mean (Standard deviation SD) or median (Interquartile range IQR), appropriately according to whether or not they are normally distributed. Categorical variables were described as frequency counts and percentages (n, %). In the analysis of risk factors associated with true CoNS bacteremia (LCBI-II), univariate logistic regression was used to initially screen possible predictive factors. All variables significant in univariate analysis will be included in multivariate logistic or Cox regression models to analyze independent risk factors. Odds ratio (OR) and 95% confident Intervals, and p-value were reported from logistic and Cox regression models. All statistical analysis were performed using the statistical package R3.6.0 and all results used a 2-tailed analysis with an alpha level of significance set at 0.05.

3. Results

The review of hospital records revealed 353 potential patients for inclusion into the study, 65 patients had to be excluded due to various reasons, including: transfers from another facility (2), and incomplete medical records such as antibiotic duration, culture locations, or location of access (63), leaving 288 patients to be examined. The mean age for the sample was 62.08 years (SD ± 15.99 years). The sample was almost evenly divided amongst gender, with males (n = 146) accounting for 50.69% of study participants. White persons accounted for the majority of the population, with 81.3% (n = 234) of the study population identifying as such. The average BMI of the patients was 29.98 (SD ± 10.60 points), which would be considered overweight.

The median length of stay (LOS) for study participants was 8.48 days (SD ± 12.9 days), which is slightly longer than the hospital's average LOS. Over 95.5% (n = 275) of patients received antibiotics during the admission of interest, with 60.4% (n = 174) of patients receiving more than two days of antibiotics, and 11.1% (n = 32) of patients receiving more than seven days of antibiotics. A full characterization of the study population can be found in Table 1.

3.1. Univariate Analysis of True Predictors of CoNS

Univariate logistic regression was performed and showed the patients receiving antibiotics for greater than two days (OR = 3.01, $p = 0.005$) or patients receiving antibiotics for greater than seven days (OR = 2.86, $p = 0.013$) were up to three times more likely to have a true CoNS bloodstream infection. Patients with vascular access through a central venous catheter (OR = 4.06, $p < 0.0001$) were four times more likely to have a defined LCBI-2 bloodstream infection with CoNS. Patients over the age of 65 were less likely to have a true CoNS BSI (OR = 0.48, $p = 0.033$). Table 2 reports the full results of the univariate analysis.

Table 1. Baseline demographics and characteristics.

Variable	Patients (N = 288)
Age, years (Mean, sd)	62.08 ± 15.99
BMI Mean	29.98 ± 10.60
WBC Mean	13.12 ± 7.04
Hospital LOS Median (IQR)	8.48 ± 12.9
Race (N, %)	
White	234 (81.3%)
African American/Black	43 (14.9%)
Hispanic/Latino	4 (0.01%)
Unknown	7 (0.02%)
Gender (Male)	146 (50.69%)
Mortality	31 (10.7%)
No Antibiotics	13 (4.51%)
One Day or More	275 (95.5%)
Abx 2 days or above	174 (60.4%)
Abx 7 days or above	32 (11.1%)
Foley	69 (23.9%)
Immunosuppressed	150 (52.1%)
Hardware Implanted	46 (15.9%)

SD = Standard Deviation, Abx = Antibiotics, IQR = Interquartile Range, LOS = Length of Stay, Foley = Foley Catheter.

3.2. Multivariate Analysis of True Predictors of CoNS

A Pearson's chi-squared test was performed between the variables for patients receiving antibiotics greater than two days and patients receiving antibiotics greater than seven days. The analysis revealed a high proportion of patients receiving antibiotics for greater than two days were associated with a high proportion ($p < 0.0001$) of patients receiving antibiotics for greater than seven days. Therefore, for the multiple logistic regression analysis, only patients receiving antibiotics greater than two days was used to avoid a multicollinearity error. Multiple logistic regression was then performed on the variables who had significant results in the univariate analysis. The analysis showed that the two variables, patients receiving antibiotics greater than two days (OR = 2.61, $p = 0.018$) and central venous assess (OR = 3.69, $p < 0.0001$) continued to be associated with a significantly higher likelihood of true LCBI-2 CoNS bloodstream infections. Table 3 reports the results of the multiple logistic regression analysis.

Table 2. Univariate analysis of predictors of true CoNS (LCBI-II).

	No CoNS (N = 243)	True CoNS (N = 45)	OR	95% CI	P-Value
Abx 2 days or above n (%)	138 (56.8%)	36 (80.0%)	3.01	(1.45, 6.92)	0.005*
Abx 7 days or above	22 (9.1%)	10 (22.2%)	2.86	(1.21, 6.42)	0.013*
Foley	59 (24.3%)	10 (22.2%)	0.89	(0.4, 1.84)	0.755
Immunosuppressed	122 (50.2%)	28 (62.2%)	1.65	(0.86, 3.22)	0.134
Hardware	38 (15.6%)	8 (17.8%)	1.16	(0.47, 2.58)	0.727
Access:					
Central	61 (25.1%)	26 (57.8%)	4.06	(2.11, 7.94)	<0.0001*
Peripheral	182 (74.9%)	19 (42.2%)			
Age:					
65 or above	124 (51.0%)	15 (33.3%)	0.48	(0.24, 0.93)	0.033
Sex:					
Male	121 (49.8%)	25 (55.6%)	1.25	1.25	0.494
BMI:					
Normal	76 (32.6%)	12 (27.3%)			
Over-weight	61 (26.2%)	12 (27.3%)	1.27	(0.53, 3.05)	0.593
Obese	63 (27.0%)	15 (34.1%)	1.51	(0.66, 3.51)	0.331
Morbid Obese	33 (14.2%)	5 (11.4%)	0.96	(0.29, 2.82)	0.942
Mortality	25 (10.3%)	6 (13.3%)	1.34	(0.47, 3.28)	0.552
Hospital LOS (IQR)	5.0 (3.0, 9.0)	6.0 (5.0, 10.5)	1.01	(0.99, 1.03)	0.206

* = significant at $p < 0.05$. Abx = Antibiotics, IQR = Interquartile Range, LOS = Length of Stay, OR = Odds Ratio.

Table 3. Multivariate analysis of predictors of True CoNS (LCBI-II).

	OR	95% CI	P-value
Abx 2 days and above	2.61	(1.23, 6.08)	0.018*
Central Access	3.69	(1.90, 7.28)	0.000*

4. Discussion

The findings of this study provide additional insight into the incidence of true bloodstream infections caused by CoNS, by examining the individual variables that may place a patient at higher risk of having a true CoNS bloodstream infection. The study showed that receiving antibiotics for greater than two days and the presence of a central venous catheter were associated with a higher likelihood of having a true LCBI-2 CoNS bloodstream infection through multiple logistic regression.

4.1. Antibiotic Usage

The results of this study provide further insight into the risks that antibiotic duration and the use of potentially unnecessary antibiotics may have for patients. Inappropriate antibiotic usage can lead to a variety of negative effects for patients including the potential disruption of the gut microbiome, higher risk of opportunistic infections such as *Clostridioides difficile*, and development of antimicrobial resistance [18]. Patients that received antibiotics for at least two days were 2.6 times more likely (p = 0.0176) to have a true CoNS bloodstream infection than patients who did not receive antibiotics or received antibiotics for less than two days. The utilization of antibiotic stewardship practices, which are now required in the acute care setting, could help address this [18]. The implementation of a variety of methods to improve antibiotic utilization, including antibiotic timeouts at 72 hours post admission, have been successful, but this results in the patient usually receiving at least 72 hours of antibiotics. As seen in the findings of this study, this could result in an increased risk for the patient to develop a CoNS bloodstream infection. One option could be to implement a 24-hour antibiotic timeout post admission, which could potentially provide another touchpoint for the antibiotic use evaluation and potential discontinuation. However, this may prove not to be practical in implementation as most microbiologic cultures can take a minimum of 48 hours to provide results.

4.2. Central Venous Catheters

The presence of a central venous catheters has been well shown in prior literature to increase the risk of a variety of infections for patients, most commonly an infection of the catheter itself [8] [13]. Dwell time of the central venous catheter is an important aspect to consider as well, as prior evidence shows that the risk of bloodstream infection increases as catheter dwell time increases, regardless of the catheter placement [19]. Central venous catheter utilization is another important variable for consideration. Historically, the majority of central line utilization has occurred in the ICU setting. However, new evidence shows that over 70% of central line utilization occurs in non-ICU settings, which allows for ample opportunity of potential bacterial contamination of the venous catheter, as infection rates in non-ICU settings are much higher compared to ICU settings [20] [21]. It would be interesting to look at the location of the culture collection in future analyses to see if there is a difference in true CoNS BSI events by setting.

4.3. Age

Age is a known factor that increases risk for a variety of healthcare associated events, particularly in catheter-associated urinary tract infections. But in regard to CLABSI and age, the evidence is inconclusive. Stevens and colleagues found that there was no statistically significant difference in median age between a group of patients who developed a CLABSI vs. those who did not (58 vs. 59, p = 0.30) [22]. In a two-year prospective study looking at MDRO infections in central lines

in three body sites, Pitiriga and colleagues found that no differences in age were observed in CLABSIs among the three sites ($p = 0.14$) [23]. In this study, age was associated with a 52% decreased risk of having a true CoNS bloodstream infection. The reasons for this are unclear, and further investigation is needed.

4.4. BMI

The researchers theorized that having a BMI in the overweight or obese category would increase the patient's risk of having a true CoNS BSI. Interestingly, the results showed that while patients having a Body Mass Index in the overweight or obese category had a slightly increased risk (OR = 1.27, 1.51) of having a true CoNS bloodstream infection, these results were not statistically significant ($p = 0.5938, 0.3317$).

4.5. Limitations

Limitations of the study include the retrospective nature of the study, and the use of existing electronic medical records, which left the research team unable to verify the accuracy of all records, which limits the generalizability of the findings. The researchers also did not track the timing of the administration of the antibiotic in regard to the positive blood culture, so temporality was unable to be determined, and if the antibiotics were started in response to the positive culture or if the patient was already on the antibiotics when the culture was taken. This variable could be helpful in future analysis to determine the potential causal relationship between antibiotic administration and positive blood culture for CoNS.

Central venous catheter type was also not collected. Certain central venous catheters, either by placement or line type, are associated with higher infection rates [23]. Categorizing this variable in the future may allow for additional analysis that may specify line types that may increase the risk of a true CoNS bloodstream infection. The duration of catheter dwell was also not collected, which has been shown in prior literature to increase the risk of a bloodstream infection [24]. Examining this variable could provide further insight for clinicians to the types of bacteria that may be more likely to be cultured from shorter or longer dwelling central venous catheters and may guide interventions considered when confronted with a blood culture containing a coagulase negative *Staphylococci* organism.

Antibiotic usage greater than two days and the presence of a central venous catheter were associated with an increased risk of having a true LCBI-2 bloodstream infection with a coagulase negative *Staphylococci* through multiple logistic regression. Univariate analysis showed that antibiotic use for greater than 7 days was also associated with a higher risk of a true CoNS BSI. Advanced age over 65 years was associated with a decreased risk of an LCBI-2 CoNS infection. Further research is needed to corroborate and expand the findings of this study.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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