

# Coagulase-negative Staphylococci – A True Pathogen in Bloodstream Infections and their Resistance Patterns in a Tertiary Care Hospital

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## Abstract

Coagulase-negative staphylococci (CoNS) are primary skin commensals that have long been considered contaminants even when grown in blood cultures. This group of organisms has been recently recognized as a potential causative pathogen of septicemia. This increase has been attributed to the increased use of intravascular and prosthetic devices. Hence, we aimed to estimate the prevalence of CoNS as a true pathogen in adult and pediatric blood cultures along with their antibiotic susceptibility patterns. A total of 1076 adult and 611 pediatric blood cultures were subjected to an automated BacT/ALERT continuous monitoring system. Isolated CoNS were considered true pathogens if they met the diagnostic, clinical, and laboratory criteria. Antimicrobial susceptibility testing for pathogenic CoNS was carried out using the Kirby-Bauer disk diffusion method and interpreted as per CLSI 2021. CoNS were considered true pathogens in 23 (42.5%) of 54 adults and 12 (41.3%) of 29 pediatric CoNS isolated from blood cultures. Methicillin-resistant CoNS was detected in 66% and 70% of adult and pediatric cultures, respectively. All the CoNS isolates were sensitive to vancomycin and linezolid. Coagulase-negative staphylococci (CoNS) can either be a contaminant or a true pathogen, whose discrimination based on clinical and laboratory indices plays a pivotal role in the management of patients with sepsis.

**Keywords:** Coagulase-negative Staphylococci (CoNS), Blood Culture, True Pathogen

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## INTRODUCTION

Bloodstream infections are serious clinical conditions characterized by the presence of either viable bacteria or fungi in the blood, as evidenced by positive blood cultures. This may be a primary infection or secondary to localized infections such as urinary tract infection, endocarditis, meningitis, and pneumonia.<sup>1</sup> Bloodstream infections are of serious concern as they initiate a cascade of host inflammatory responses leading to sepsis, which is life-threatening. Sepsis leads to significant morbidity and mortality when not treated with the appropriate antimicrobial drugs at the right time.

According to the World Health Organization global report on sepsis (2020), sepsis is responsible for the deaths of approximately 1 million people worldwide, including 2.9 million children.<sup>2</sup> Even patients who survive the critical phase of sepsis are still at risk. Half of the survivors either die or succumb to long-term detrimental illnesses. Effective antimicrobial therapy within the first hour of septic shock significantly decreases the mortality rate in these individuals.<sup>3</sup>

Blood culture is the gold standard for the diagnosis of bloodstream infections.<sup>4</sup> Positive blood culture is a defining factor in the diagnosis of bloodstream infection (BSI). A BSI is defined as a positive blood culture result in an individual with systemic signs of infection that can be either primary or secondary to any identified source of infection.<sup>5</sup> A positive blood culture is considered significant only after ruling out contamination to avoid inappropriate antibiotic usage, leading to selection pressure on multidrug-resistant organisms. This further increases infection rates, leading to prolonged hospitalization and a higher healthcare economic burden.<sup>6</sup>

Adequate treatment of BSI requires the in vitro susceptibility of isolated organisms to the given antimicrobials administered at the earliest, at the right dose through the proper route.<sup>7</sup> Multidrug-resistant gram-negative organisms are common etiological agents, accounting for approximately 30% of hospital-acquired BSI. However, there has been a recent rise in gram-positive organisms, such as *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and Enterococci.<sup>8</sup>

CoNS are the primary commensals of the skin that play key roles in cutaneous homeostasis.<sup>9</sup> They have long been considered as contaminants even when grown in blood cultures. Recently this group of organisms has been recognized as a potential nosocomial pathogen that causes septicemia, attributing this recent rise to the increased use of intravascular and prosthetic devices.<sup>10</sup>

Hence, it is necessary to determine the prevalence of CoNS as a true pathogen and determine its antimicrobial susceptibility patterns for effective clinical management

This study aimed to estimate the prevalence and establish the significance of CoNS as a true pathogen isolated from blood cultures using the following objectives:

1. To estimate the prevalence of CoNS in blood culture samples
2. To determine whether the isolate is a true pathogen or contaminant
3. To know the antibiotic susceptibility pattern of those significant pathogens
4. To detect methicillin resistance and inducible clindamycin resistance among the CoNS isolates

## MATERIALS AND METHODS

### Study design

This was a hospital-based descriptive cross-sectional study conducted at Meenakshi Medical College and Research Institute, Kanchipuram over a period of one year, from January 2021 to December 2021. The study population included individuals of both sexes and all age groups.

The inclusion criteria for this study were as follows:

1. Blood samples received for culture and sensitivity in the Microbiology laboratory from suspected cases of adult and pediatric sepsis.
2. Blood cultures flagged positive within 24 hours with pure growth of CoNS.

The exclusion criteria were as follows:

1. Blood cultures flagged positive after 24 hours.
2. Blood cultures positive for organisms other than CoNS.

**Ethical approval and informed consent**

This study was approved by the Institutional Ethics Committee and the written informed consent was obtained from all the study participants.

**Sample size and sampling method**

Two sets of samples sent for blood culture and sensitivity testing from adult and pediatric patients who met the sampling criteria were included in the study using a random sampling method. A total of 1076 adult and 611 pediatric eligible blood cultures were included in the study.

**Study tool and data collection method**

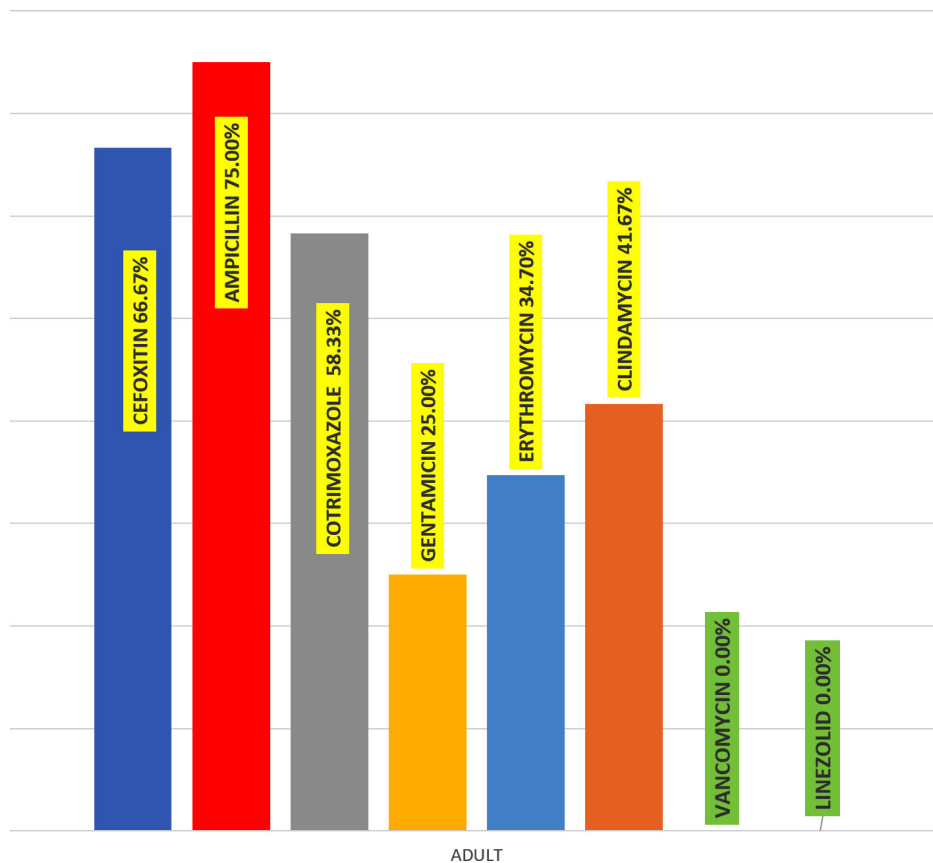
A predetermined protocol was used to collect the demographic and clinical details of patients.

Adult and pediatric BacT/ALERT blood culture bottles were used. A blood culture set included two bottles with 8–10ml blood/bottle for adults and 3–5ml blood/ bottle for pediatric

patients. Blood for culture was collected under strict aseptic precautions from two different venipuncture sites before the initiation of antibiotic treatment. All samples were incubated using an automated BacT/ALERT continuous monitoring system. When growth was indicated by the system, the samples were further subcultured and identified according to standard conventional bacteriological culture methods.

Blood cultures showing pure growth of CoNS were analyzed. Details on other relevant clinical parameters and investigations were collected to determine the pathogenic significance of CoNS.

CoNS isolates were considered true pathogens if they met the following criteria: Laboratory indices include pure growth of CoNS in both blood culture samples of a set, differential time to positivity was less than 24 h and



**Figure 1.** Resistance pattern of CoNS isolates in adults

presence of three or more of the following clinical indices such as fever >100°C, total leukocyte count >12000/mm<sup>3</sup>, septic clinical appearance, systolic blood pressure <90mmHg, >48 hours of hospital admission, and the presence of any risk factors (long-term intravascular catheterization, immunosuppressed patients with central lines, peritoneal dialysis or hemodialysis patients, and patients with extensive postsurgical infections with CoNS.

Antimicrobial susceptibility testing for pathogenic CoNS was carried out using the Kirby Bauer disk diffusion method for erythromycin, clindamycin, ampicillin, cotrimoxazole, linezolid, and minimum inhibitory concentration (MIC) by E strip for vancomycin, as per the CLSI 2021 guidelines.

## RESULTS

A total of 1076 adult and 611 pediatric blood cultures were collected during the study period. Of the 1076 adult and 611 pediatric blood cultures, 128 (11.8%) and 67 (10.96%) were flagged positive within 24 hours, respectively. Of these, 54 (42.18%) adult and 29 (43.28%) pediatric culture isolates CoNS as shown in Tables 1 and 2.

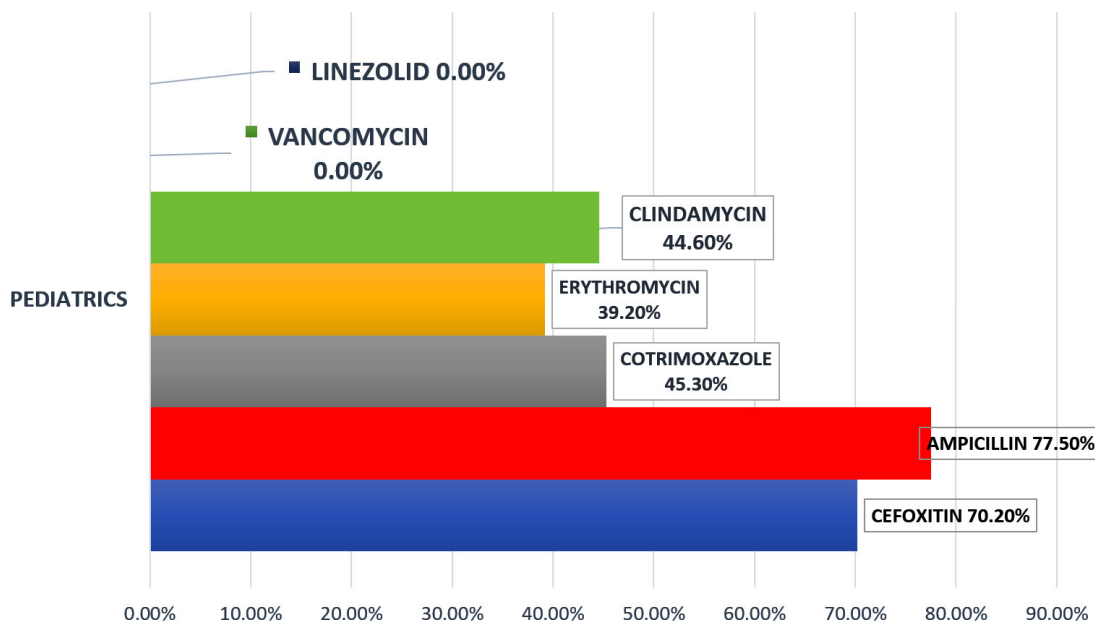
Antibiograms of CoNS isolated from adults showed resistance to ampicillin (75%), trimethoprim-sulfamethoxazole (58.33%), gentamycin (25%), erythromycin (34.70%), and clindamycin (41.76%), as shown in Figure 1. Methicillin-resistant CoNS was detected in approximately two-thirds (66.6%) of adult isolates, indicating an increasing prevalence of MR-CoNS

**Table 1.** Culture positivity among blood cultures from the adult population

Blood Culture	Adult
Total	1076
Positive	128 (11.8%)
CoNS isolated	54 (42.18%)
Pathogenic CoNS	23 (42.5%)

**Table 2.** Culture positivity among blood cultures from the pediatric population

Blood Culture	Pediatrics
Total	611
Positive	67 (10.96%)
CoNS isolated	29 (43.28%)
Pathogenic CoNS	12 (41.3%)



**Figure 2.** Resistance pattern of CoNS isolates in the pediatric population

The antibiogram of CoNS isolated from the pediatric population showed resistance to ampicillin (77.50%), trimethoprim-sulfamethoxazole (45.30%), erythromycin (39.20%), and clindamycin (44.60%) as shown in Figure 2. Methicillin-resistant CoNS were detected in 70.20% of pediatric isolates.

## DISCUSSION

BSI is defined as a positive blood culture retrieved from an individual with systemic signs of infection that can be either primary BSI or secondary to any identified source of infection. A positive blood culture is considered significant only after ruling out contamination to avoid inappropriate antibiotic usage leading to selection pressure on multidrug-resistant organisms. This further increases the infection rates, leading to prolonged hospitalization and a higher healthcare economic burden.<sup>6</sup>

CoNS are the most frequently considered contaminants and are low-virulence pathogens capable of causing bloodstream infections, especially in the presence of intravascular/prosthetic devices. This poses a challenge in determining the significance of CoNS as a true pathogen. The results of this study conducted in a tertiary care hospital are discussed below.

In this study, CoNS were isolated from 42.18% (54 of 128) of adult blood cultures. This was much higher than that reported by Khan *et al.*, whose CoNS isolation rate was 8.76%, thus proving the rise of the once-thought-normal commensal CoNS as a true pathogen.<sup>11</sup>

According to the diagnostic criteria described above, 42.5% (23 of 54) of adult CoNS isolates were true pathogens in the present study. This is increased compared to Khan *et al.*<sup>11</sup> and Sidhu *et al.*<sup>12</sup> showing that 34.78% and 24% of CoNS isolates were true pathogens, respectively. This may be attributed to automated identification systems in recent times, which have made the identification of microorganisms much easier than before. The second reason may be the well-established diagnostic criteria, which makes it easy to emphasize the causal association between CoNS and bloodstream infections.

In the pediatric age group, 41.3% of isolates were true pathogens in this study, which is higher (32.7% and 22%) than the studies by Asifa Nazir *et al.*<sup>13</sup> and Al Haqan *et al.*, respectively.<sup>14</sup> The latter study divided the study population into sepsis and non-sepsis groups based on diagnostic criteria that included similar parameters to the present study such as clinical presentation, CRP, differential time to positivity, and presence of a single organism.

The significance of CoNS isolation in pediatric blood cultures has always remained enigmatic, which is attributed to patient factors, such as difficulty in collecting samples, especially in convulsive and non-cooperative infants. However, with two positive blood cultures, clinical criteria, and markers of infection, early initiation of appropriate therapy is helpful in reducing mortality in this population.<sup>15</sup>

The increasing rates of CoNS isolation in the pediatric population are also attributed to preterm birth, low birth weight babies, prolonged hospital stays, frequent use of invasive devices, and poor infection control practices.<sup>15</sup>

Methicillin resistance was observed in approximately 66.7% of the adult CoNS isolates in the present study, which was higher than that reported by Singh *et al.* where 57.6% were MR-CoNS.<sup>16</sup> In a retrospective study conducted by Cui *et al.* in China where Oxacillin was used as a marker of methicillin resistance, 93.6% of the isolates were found to be MR-CoNS.<sup>17</sup> In contrast, in the pediatric population, methicillin resistance was found to be 70% in the present study, which is very similar (70%) to that reported by Ansari *et al.*, ranging from 40% to 100% among various CoNS species.<sup>18</sup>

None of the isolates in the present study showed resistance to vancomycin and linezolid which was similar to previous studies,<sup>19,20</sup> where vancomycin-resistant CoNS detection was performed on various clinical isolates and nasal samples respectively.

Detection of inducible clindamycin resistance by the D zone test revealed that 17.39% of the isolates were erythromycin-resistant and clindamycin-susceptible. This is higher than that reported by Khan *et al.* but lower than that

reported by Manandar *et al.*, who showed 11% and 23.2% of inducible clindamycin resistance, respectively.<sup>21,22</sup> All clinical isolates were included in these two studies, unlike the present study, where the sample matrix was only blood from patients with bacteremia.

## CONCLUSION

Blood culture is crucial in case of suspected sepsis and determines the course of clinical management, especially in the first 48 hours. Blood culture-positive patients have increased early mortality compared to culture-negative patients. Hence, it is important to distinguish between a true pathogen and a contaminant before issuing blood culture reports. CoNS are organisms that can either be a contaminant or a true pathogen, whose discrimination using clinical and laboratory indices plays a pivotal role in the management of sepsis patients. This study shows that there has been a significant increase in the prevalence of CoNS as a true pathogen. Most isolates were multidrug-resistant, minimizing the available treatment options. The timely reporting of CoNS and a proper antibiotic policy in place prevent inappropriate usage of antibiotics, thereby preventing the emergence of another potential MDR pathogen.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

None.

## DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

## ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee, Meenakshi Medical College and Research Institute, Kanchipuram, with reference number 85/MICRO/IEC/2021.

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

## REFERENCES

1. Viscoli C. Bloodstream Infections: The peak of the iceberg. *Virulence*. 2016;7(3):248-251. doi: 10.1080/21505594.2016.1152440
2. WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide. <https://www.who.int/news/item/08-09-2020-who-calls-for-global-action-on-sepsis---cause-of-1-in-5-deaths-worldwide>. Accessed January 7, 2023.
3. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589. doi: 10.1097/01.CCM.0000217961.75225.E9
4. Lamy B, Dargere S, Arendrup MC, Parienti JJ, Tattevin P. How to Optimize the Use of Blood Cultures for the Diagnosis of Bloodstream Infections? A State-of-the Art. *Front Microbiol*. 2016;7:697. doi: 10.3389/fmicb.2016.00697
5. Timsit JF, Ruppe E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. *Intensive Care Med*. 2020;46(2):266-284. doi: 10.1007/s00134-020-05950-6
6. Dargere S, Cormier H, Verdon R. Contaminants in blood cultures: importance, implications, interpretation and prevention. *Clin Microbiol Infect*. 2018;24(9):964-969. doi: 10.1016/j.cmi.2018.03.030
7. Timsit JF, Soubirou JF, Voiriot G, et al. Treatment of bloodstream infections in ICUs. *BMC Infect Dis*. 2014;14(1):489. doi: 10.1186/1471-2334-14-489
8. Deng S, Feng S, Wang W, Zhu H, Gong Y. Bacterial Distribution and Risk Factors of Nosocomial Blood Stream Infection in Neurologic Patients in the Intensive Care Unit. *Surg Infect (Larchmt)*. 2019;20(1):25-30. doi: 10.1089/sur.2018.085
9. Argemi X, Hansmann Y, Prola K, Prevost G. Coagulase-Negative Staphylococci Pathogenomics. *Int J Mol Sci*. 2019;20(5):1215. doi: 10.3390/ijms20051215
10. Asaad AM, Qureshi MA, Hasan SM. Clinical significance of coagulase-negative staphylococci isolates from nosocomial bloodstream infections. *Infect Dis*. 2016;48(5):356-360. doi: 10.3109/23744235.2015.1122833

11. Khan F, Kirmani S, Siddiqui N, et al. CONS in blood culture: contaminants or pathogens? 2015;(1):88-94.
12. Sidhu SK, Malhotra S, Devi P, Tuli AK. Significance of coagulase negative Staphylococcus from blood cultures: persisting problems and partial progress in resource constrained settings. *Iran J Microbiol.* 2016;8(6):366-371.
13. Nazir A. Neonatal sepsis due to coagulase-negative Staphylococci: a study from Kashmir valley, India. *Int J Contemp Pediatr.* 2019;6(2):650-655. doi: 10.18203/2349-3291.ijcp20190705
14. Al-Haqan A, Boswihi SS, Pathan S, Udo EE. Antimicrobial resistance and virulence determinants in coagulase-negative staphylococci isolated mainly from preterm neonates. *PLOS ONE.* 2020;15(8):e0236713. doi: 10.1371/journal.pone.0236713
15. A Grace JU, Obaro SK. A Systematic Review of Coagulase-Negative Staphylococci in Neonatal Sepsis. *Clin Microbiol.* 2019;8(2):1000326. doi: 10.4172/2327-5073.1000326
16. Singh S, Dhawan B, Kapil A, et al. Coagulase-negative staphylococci causing blood stream infection at an Indian tertiary care hospital: Prevalence, antimicrobial resistance and molecular characterisation. *Indian J Med Microbiol.* 2016;34(4):500-505. doi: 10.4103/0255-0857.195374
17. Cui J, Liang Z, Mo Z, Zhang J. The species distribution, antimicrobial resistance and risk factors for poor outcome of coagulase-negative staphylococci bacteraemia in China. *Antimicrob Resist Infect Control.* 2019;8(1):65. doi: 10.1186/s13756-019-0523-5
18. Ansari F, Banerjee T, Kumar A, Anupurba S. Coagulase-Negative Staphylococci in Neonatal Blood: How Concerning? *J Lab Physicians.* 2023;15(01):126-130. doi: 10.1055/s-0042-1757411
19. Ashagrie D, Genet C, Abera B. Vancomycin-resistant enterococci and coagulase-negative staphylococci prevalence among patients attending at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar, Ethiopia. *PLoS One.* 2021;16(4):e0249823. doi: 10.1371/journal.pone.0249823
20. Al-Tamimi M, Abu-Raideh J, Himsawi N, Khasawneh A, Hawamdeh H. Methicillin and vancomycin resistance in coagulase-negative Staphylococci isolated from the nostrils of hospitalized patients. *J Infect Dev Ctries.* 2020;14(1):28-35. doi: 10.3855/jidc.11025
21. Khan AA, Farooq J, Abid M, Zahra R. Assessment of inducible clindamycin resistance and Hyper Variable Region (HVR) of *mecA* gene in clinical *staphylococci*. *Pak J Med Sci.* 2020;36(2):136-140. doi:10.12669/pjms.36.2.665
22. Manandhar S, Shrestha R, Tuladhar RS, Lekhak S. Inducible Clindamycin Resistance and Biofilm Production among Staphylococci Isolated from Tertiary Care Hospitals in Nepal. *Infectious Disease Reports.* 2021;13(4):1043-1052. doi:10.3390/idr13040095