

# Coagulase Negative Staphylococcus Species Isolated from Blood Culture: A Pathogen or a Contaminant?

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## ABSTRACT

**Introduction:** Coagulase negative staphylococci (CoNS) are the most frequent blood culture isolates and an important cause of nosocomial blood stream infections especially in catheterised patients. CoNS are also the most common contaminants of blood cultures and are proven to be especially problematic. These uncertainties may result in over diagnosis and indirect overuse of antimicrobials especially vancomycin.

**Aim:** To determine the clinical significance of CoNS isolated from blood culture of patients admitted in a tertiary care hospital.

**Materials and Methods:** A prospective cross-sectional study was conducted in Bharati Hospital Research Center, Pune, Maharashtra, India, from August 2019 to July 2020 (One year). Patients whose paired/multiple blood culture samples showed pure growth of CoNS were included in the study. CoNS were identified by Vitek 2 system and antimicrobial susceptibility was reported. Clinical history of all patients was taken who showed pure growth of CoNS in either one or multiple sites of the automated blood culture bottles. Isolated CoNS were considered

as pathogen only if clinical and laboratory parameters are fulfilled. Chi-square test was used to find out statistical significance of isolated pathogenic CoNS.

**Results:** A total 147 CoNS isolated from blood cultures of suspected patients of sepsis were included in study. About 23 (15.6%) CoNS were isolated from both the sites. Remaining 124 (84.4%) CoNS were isolated from single site. CoNS were considered as pathogen in all 23 cases based on clinical and laboratory criteria. The most frequent isolated CoNS was *S. haemolyticus* 7 (30.4%), followed by *S. epidermidis* 5 (21.7%), *S. hominis* 3 (13.1%), *S. lugdunensis* 3 (13.1%), *S. scuri* 2 (8.7%), *S. xylosus* 1 (4.3%), *S. caprae* 1 (4.3%), *S. capitis* 1 (4.3%). Methicillin resistance was observed in 15 (65.2%) CoNS strains.

**Conclusion:** Patients suffering from CoNS from their blood stream should be carefully evaluated clinically. Proper blood collection techniques need to be followed to avoid contamination of blood culture samples and to avoid diagnostic dilemma.

**Keywords:** Methicillin resistance, Nosocomial bloodstream infection, *Staphylococcus haemolyticus*

## INTRODUCTION

Blood stream infections (bacteremia, fungemia and sepsis) are the most life-threatening infections which requires urgent antimicrobial treatment. Blood cultures are one of the most important specimens managed by the clinical microbiology laboratory. Blood cultures are needed to establish the diagnosis of blood stream infections and are useful in directing appropriate antimicrobial therapy [1]. CoNS are among the most frequently isolated pathogens in blood cultures and an important cause of nosocomial blood stream infections [2]. The infection caused by CoNS is increasing as the number of artificial devices and catheters being inserted through skin become higher [3].

CoNS are also the most common contaminants of blood cultures and are proven to be especially problematic [4]. In order to be clinically significant, repeated isolation of same strain of CoNS is needed and also it should be confirmed by genotyping methods. These uncertainties may result in over diagnosis and indirect overuse of antimicrobials especially vancomycin. This may contribute to the development of resistance that will amplify the likelihood of morbidity, mortality and total hospital costs [5,6].

The clinical relevance of a single blood culture positive for CoNS is difficult to assess, mainly because of lack of a diagnostic reference standard for nosocomial blood stream infection. Contamination is generally presumed if only one of at least two sets of blood cultures is positive for CoNS, whereas true blood stream infection is assumed if at least two blood cultures yield same CoNS spp. [2,7]. The clinical criteria which is essential for

the true bacteremia includes whether the patient has fever or body temperature below 36°C, blood pressure <90 mmHg. Also, other predisposing factors like intravenous catheter or indwelling foreign devices, immunosuppressed patients, postsurgical infections, patients undergoing haemodialysis/peritoneal dialysis, prolonged duration of hospitalisation and other laboratory infections are also included [3,8-10].

If these criteria are taken into consideration, then it can be concluded that CoNS species isolated from blood is a pathogen and not a contaminant. There are various studies regarding clinical significance of CoNS from blood culture, but due inappropriate blood culture specimen collection practices CoNS are frequently isolated and reported by various laboratories without considering the clinical parameters [3,8-10]. This leads to overuse of antimicrobials. So, to emphasise the importance of appropriate sample collection and infection control practices, the study was undertaken to determine the clinical significance of CoNS isolated from blood culture of patients admitted in a tertiary care hospital and also to study their antimicrobial susceptibility pattern.

## MATERIALS AND METHODS

A prospective cross-sectional study was performed for one year from August 2019 to July 2020 in Bharati Hospital, Pune which is a tertiary care hospital in Maharashtra, India. The study was approved by Institutional Ethical Committee (IEC) (IEC Number- BVDUMC/IEC/80). Informed consent from patient was not needed as study

included isolated CoNS species and clinical details were taken by communicating with clinicians only.

**Inclusion criteria:** Patients who have given paired/multiple blood culture samples yielding pure growth of CoNS were included in the study.

**Exclusion criteria:** Patients who have sent only one blood culture bottle were excluded. Blood cultures yielding other organisms or giving mixed growth were not considered.

**Sample size:** Sample size estimation was based upon published results of Khan F et al., [1]. Their result shows 34.7% prevalence of significant CoNS, using prevalence of 34.7%, allowable absolute error of 8 and 5% level of significance, minimum sample size obtained was 136. However, actual sample size collected for study was 147.

N=Sample size

Z=Statistic corresponding to level of confidence

P= expected prevalence from studies

D= precision (corresponding to effect size 8)

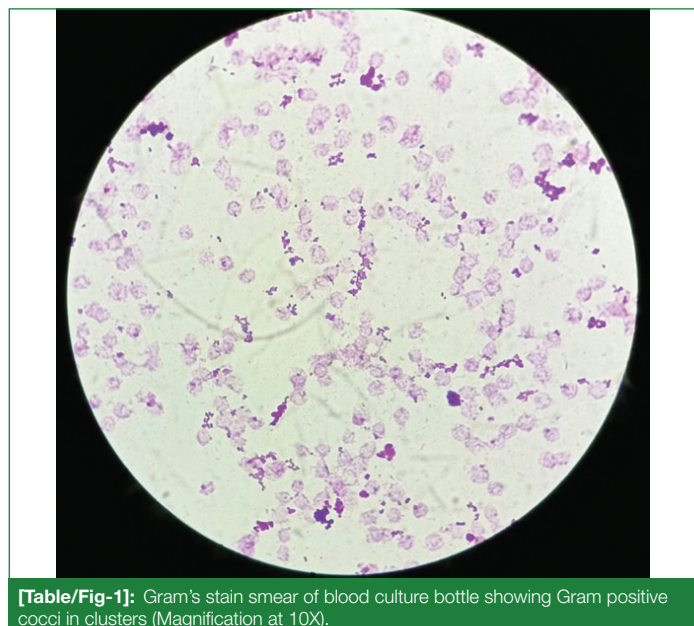
Sample size formula-  $N = \frac{Z^2 * P[100-P]}{(d)^2}$

$$N (136) = \frac{(1.96)^2 * 34.7 * 65.3}{(8)^2}$$

## Procedure

**Sample collection:** Blood culture samples were collected by dedicated phlebotomy team/clinician with all aseptic precaution. Minimum two samples were taken by venipuncture from right and left peripheral veins (median cubital or cephalic veins). Sometimes samples were collected from right and left artery (if veins are not accessible) or rarely from pre-existing Central venous/HD catheter. Automated blood culture bottles from patients of suspected sepsis were received and incubated in the BD BACTEC machine for five days. Gram's stain [Table/Fig-1] was performed from all flagged bottles. Time duration of Bactec beep was noted as less than 48 hours or more than 48 hours. Subcultures were done on Blood agar and MacConkey's agar. CoNS were identified by Vitek 2 system and antimicrobial susceptibility was reported. Clinical history of all patients was taken who showed pure growth of CoNS in either one or multiple sites (mentioned above) of the BACTEC bottles.

A clinical significance of isolated CoNS from blood culture was determined as per following clinical and laboratory parameters [1,3].



[Table/Fig-1]: Gram's stain smear of blood culture bottle showing Gram positive cocci in clusters (Magnification at 10X).

**Clinical criteria:** Presence of one or more of the following clinical factors will be determined based on patient's history. 1. Persistent fever >38°C or body temperature <36°C 2. Total leucocytes count >12000/ $\mu$ L or <4000/ $\mu$ L 3. Hypotension -systolic blood pressure < 90 mmHg. 4. Signs of sepsis. 5. Presence of IV catheter. 6. Invasive devices. 7. Procedures or surgery. 8. Immunocompromised state. 9. Long term stay in intensive care unit. 10. Dialysis.

**Laboratory criteria:** 1. Time duration of BACTEC beep (within 48 hours). 2. Same isolates from two or more blood BACTEC bottles.

## STATISTICAL ANALYSIS

Statistical analysis was done by using Chi-square test and Statistical Package for the Social Sciences (SPSS) software version 28.0.

## RESULTS

As per inclusion criteria, 147 adult patients were included as their blood culture samples yielded pure growth of CoNS from one or both sites. Out of 147 pure CoNS isolates, only 23 (15.6%) CoNS were isolated from both right and left sites. Remaining 124 (84.4%) CoNS were isolated from single site and were considered as contaminants.

All 23 CoNS isolated from both sites were considered pathogenic based on their above clinical criteria. Out of these 23 cases, 20 (87%) patients had fever. Raised Total leucocyte count was seen in 10 (43.5%) patients. Intravascular catheter was present in 9 (39.1%) patients. Invasive procedures and surgical site infections were not seen in any of the patients. One (4.3%) patient was having underlying immunosuppression due to uncontrolled diabetes mellitus. About 16 (69.6%) patients were admitted in ICU for prolonged period, 20 (86.5%) patients fulfilled both the laboratory criteria that is raised TLC and BACTEC positivity before 48 hours of incubation. In 3 patients, BACTEC beep was received late (72 hours), so they could not fulfill one of the laboratory criteria. But they had shown high total leucocyte count and had fever. Two of them were having intravascular catheters and one was having Diabetes Mellitus and Lower respiratory tract infection. So, isolated CoNS were considered pathogenic based on their clinical criteria. We also observed statistically significant association of almost all the clinical criteria with pathogenic CONS except sign of sepsis/ Multiple Organ Dysfunctions (MODS) [Table/Fig-2].

| Criteria                      | Pathogenic CoNS (N=23) (%) | Contaminant CoNS (N=124) | Chi-square value | p-value |
|-------------------------------|----------------------------|--------------------------|------------------|---------|
| <b>Clinical criteria</b>      |                            |                          |                  |         |
| Fever (>38°C)                 | 20 (87)                    | 70 (56.5)                | 7.60             | 0.01    |
| No fever                      | 3 (13)                     | 54 (43.5)                |                  |         |
| Body temperature <36°C        | 0                          | 0                        |                  |         |
| Signs of sepsis, MODS         | 1 (4.3%)                   | 2 (1.6%)                 | 0.72             | 0.40    |
| No signs of sepsis, MODS      | 22 (95.7)                  | 122 (98.4)               |                  |         |
| Staying in ICU                | 16 (69.6)                  | 43 (34.7)                | 9.82             | 0.002   |
| Other than ICU                | 7 (30.4)                   | 81 (65.3)                |                  |         |
| Hypotension (Systolic BP <90) | 7 (30.4)                   | 06 (4.8%)                | 15.76            | 0.001   |
| Normal BP                     | 16 (69.6)                  | 118 (95.2)               |                  |         |
| Intravascular catheter-       |                            |                          |                  |         |
| Yes                           | 9 (39.1)                   | 16 (12.9%)               | 9.45             | 0.002   |
| No                            | 14                         | 108 (87.1)               |                  |         |
| Invasive procedure            | 0                          | 0                        | -                | -       |
| Surgical site infection       | 0                          | 0                        | -                | -       |

|                               |           |            |       |        |
|-------------------------------|-----------|------------|-------|--------|
| Underlying immunosuppression  | 1 (4.3)   | 0          | -     | -      |
| Patient on dialysis           | 0         | 10 (8.06)  | -     | -      |
| <b>Lab criteria</b>           |           |            |       |        |
| Time of positive culture test |           |            |       |        |
| <48 hrs                       | 20 (87)   | 21 (17)    | 47.29 | <0.001 |
| >48 hrs                       | 3 (13)    | 103 (83)   |       |        |
| TLC (>12000 or <4000)         | 10 (43.5) | 26 (21)    | 5.31  | 0.02   |
| Normal TLC                    | 13 (56.5) | 98 (79)    |       |        |
| Raised procalcitonin level    | 20 (86)   | 14 (11.3)  | 62.47 | <0.001 |
| Normal procalcitonin level    | 3 (13)    | 110 (88.7) |       |        |

**[Table/Fig-2]:** Clinical criteria/risk factor among patients infected with significant CoNS (N=23) and CoNS considered as contaminants (N=124).

Out of 23 significantly isolated CoNS from paired blood BACTEC, the most frequent isolated CoNS was *S. haemolyticus* 7 (30.4%), followed by *S. epidermidis* 5 (21.7%) [Table/Fig-3].

| Species                | Number (percentage) |
|------------------------|---------------------|
| <i>S. haemolyticus</i> | 7 (30.4)            |
| <i>S. epidermidis</i>  | 5 (21.7)            |
| <i>S. hominis</i>      | 3 (13.1)            |
| <i>S. lugdunensis</i>  | 3 (13.1)            |
| <i>S. scuri</i>        | 2 (8.7)             |
| <i>S. xylosus</i>      | 1 (4.3)             |
| <i>S. caprae</i>       | 1 (4.3)             |
| <i>S. capitis</i>      | 1 (4.3)             |

**[Table/Fig-3]:** CoNS isolated from both right and left sites (N=23).

Majority of significant CoNS (34.8%) belonged to elderly group [Table/Fig-4]. Fifteen (65.2%) CoNS strains were resistant to Methicillin (MRCONS), while 8 (34.8%) strains were Methicillin sensitive. MRCONS were susceptible to vancomycin, teicoplanin, linezolid and daptomycin [Table/Fig-5].

| Age in years | Male | Female | Total | %    |
|--------------|------|--------|-------|------|
| 20-29        | 1    | 0      | 1     | 4.34 |
| 30-39        | 2    | 4      | 6     | 26.1 |
| 40-49        | 2    | 2      | 4     | 17.4 |
| 50-59        | 2    | 2      | 4     | 17.4 |
| >60          | 8    | 0      | 8     | 34.8 |
| Total        | 15   | 8      | 23    |      |

**[Table/Fig-4]:** Age/Sex wise distribution of patients positive for CoNS isolated from both the sides (n=23).

| Antibiotics                   | Resistance no (%) |
|-------------------------------|-------------------|
| Penicillin                    | 17 (73.91)        |
| Oxacillin                     | 13 (56.52)        |
| Gentamicin                    | 6 (26.08)         |
| Ciprofloxacin                 | 12 (52.17)        |
| Levofloxacin                  | 11 (47.82)        |
| Clindamycin                   | 10 (43.47)        |
| Erythromycin                  | 13 (56.52)        |
| Linezolid                     | -                 |
| Daptomycin                    | -                 |
| Teicoplanin                   | -                 |
| Vancomycin                    | -                 |
| Tetracycline                  | 4 (17)            |
| Rifampicin                    | 4 (17)            |
| Trimethoprim/Sulfamethoxazole | 6 (26)            |

**[Table/Fig-5]:** Antimicrobial resistance pattern of CoNS (N=23).

## DISCUSSION

Blood culture is an important sample processed by clinical laboratory. Positive blood culture can suggest a definitive diagnosis and help in choosing the right antimicrobial therapy. However due to improper sample collection techniques and increased use of intravascular devices, many times coloniser like CoNS, Viridians Streptococci, *Bacillus* sp, Diphtheroids grow in sample [11]. CoNS are frequently considered as contaminants, but they are also among the most frequently isolated pathogens in blood cultures and an important cause of nosocomial bloodstream infections [2]. [Table/Fig-6] shows findings of various studies regarding blood culture contamination rates [1,2,6,11-13]. So, it seems CoNS are gaining more importance as pathogen due to novel therapeutic interventions and increased use of foreign medical devices [1,14].

Various clinical parameters are used in detection of clinical significance of CoNS. Laboratory criteria for true Bacteremia include growth within 48 hours. and isolation of CoNS strains from multiple blood samples taken from different body sites or different time interval. Clinical conditions include predisposing factors like central venous catheter, indwelling foreign devices, age of cases, immunosuppression. CoNS species can only be reported true pathogenic when clinical and laboratory criteria are fulfilled [3,14].

In this present study, after considering the clinical and laboratory criteria, CoNS were considered true pathogens in blood stream infections in only 15.6% of cases, in remaining patients (84.4%) they were reported as contaminants. Sindhu S et al., has done similar study in Amritsar and reported CoNS as true pathogens in 24% cases and in remaining 69% patients it was reported as blood culture contaminant [3]. Majority of significant CoNS species were isolated from age group above 60 years in present study. Similar results were studied by Malik S et al., and Souvenir D et al., [6,15]. It is difficult to collect blood culture sample from paediatric patients. So, in majority of paediatric patients, only one BACTEC bottle were received. As a minimum of two BACTEC blood culture bottles are needed from each patient to differentiate pathogen from contaminant, paediatric cases were not included in present study. The majority of significant CoNS in this present study were isolated from patients admitted in ICU (69.6%). Singh S et al., also found that out of 59 CoNS bloodstream infection, majority (n=12) of patients having CoNS bloodstream infection were admitted to ICU [14]. Sidhu SK et al., found that frequency of CoNS isolates from BSI was higher in pediatric department (38.7%), followed by ICU (31.3%) [3].

The frequently isolated CoNS species in present study was *S. haemolyticus* (30.4%) followed by *S. epidermidis* (21.7%) and *S. hominis* (13.1%). Distasi MA et al., have conducted similar study in Italy [5]. They reported that the commonest CoNS sp causing nosocomial bloodstream infection was (31.2%) *S. epidermidis*, followed by (26.9%) *S. haemolyticus* and (22.2%) *S. hominis*. Different species distribution in developed versus developing countries could be due to the difference in colonisation characteristics of patients and the varying adaptability of different species to selective pressures such as biocides and antimicrobials in the environment.

Considering all the clinical and laboratory criteria, 23 (15.6%) CoNS spp were considered to be true pathogenic. Fever was common in almost (87%) of cases; similar results were reported by Sindhu S et al., in their study (87.8 %), conducted in Amritsar in 2014 [3]. The present study showed presence of intravascular catheter in (39.1%) patients. O' grady NP et al., have also reported that CoNS bacteremia is highly associated with use of intravascular devices representing 30- 60 % of catheter related blood stream infections [16]. In present study, blood culture samples from 87% patients showed growth before 48 hours which was similar to study conducted by Sindhu et al., [3]. The remaining 3 (13%) patients who showed BACTEC beep on or after 72 hours have fulfilled the clinical criteria so were considered pathogenic.

| Author name (Ref No)          | Place of study                                   | Year of publication | Total samples   | CONS isolated  | CONS as pathogen/contaminants   |
|-------------------------------|--|---------------------|---|--|---|
| Yamamoto Kei et al., [12]     | National Center of Global Health Medicine, Japan | 2021                | 56,843 cases  | 2142-contaminants grown<br>CONS from 3126 sets           | 1689 (78%) CoNS as contaminants   |
| Khan F et al., [1]            | JNMCH Aligarh                                    | 2015                | 208 positive blood cultures                                       | 23 (11.1%)   | 8 (34.7%) as pathogen   |
| Chun S et al., [13]           | Korea  | 2019                | Retrospective blood culture records of 13,519 Paediatric patients | 1961- grew pathogens<br>750- possible contaminants grown | 23.8% as pathogen   |
| Elzi L et al., [2]            | University hospital Basel, Switzerland           | 2012                | 3060  | 654 CoNS isolated  | 232 (35%) as pathogen   |
| Malik S and Ravishekhar K [6] | Mumbai   | 2012                | 755 blood cultures<br>136 positive                                | CoNS- 37<br><i>Micrococcus</i> -90<br>Diphtheroids-09    | 123 (16%) were contaminants   |
| Weinstein et al., [11]        | Durham   | 1997                | 1585 episodes of positive blood culture from 1267 patients        | 1844   | 575 (82%) CoNS as contaminants<br>87 (12%) as significant<br>41 (5.8%) unknown significance |
| Present study                 | Pune   | 2022                | 147 patients with pure growth                                     | 23 (15.6%)   | 124 (84.4%) CoNS as contaminants  |

**[Table/Fig-6]:** Various studies regarding blood culture contamination rates.

In this present study, 65.2% isolates showed methicillin resistance. The majority of CoNS isolates (68.6%) were methicillin resistant in a study conducted by Rahman ZA et al., in Malaysia [17]. Jain A et al., have reported similar finding i.e .high prevalence (61.3 %) of methicillin resistance in CoNS in Lucknow in 2011 [18]. In current study, highest resistance (73.9%) was detected to penicillin followed by oxacillin (56.5%) erythromycin (56.5%), ciprofloxacin (52.2%), levofloxacin (47.8%), clindamycin (43.5%), trimethoprim/ sulfamethoxazole ( 26 %), which was similar to the study conducted by Koksai F et al., in Turkey [19]. On the other hand, vancomycin, linezolid, daptomycin and teicoplanin showed no resistance at all which was comparable to various studies [5, 19]. So, present study highlights the importance of clinical association of blood culture reports especially when CoNS are isolated. Only 15.6% of CoNS were considered as actual pathogen. 65.2% strains were MRCONS. All MRCONS isolates were susceptible to vancomycin, teicoplanin, linezolid and daptomycin. Microbiologist and clinician can communicate and decide whether to treat CoNS bloodstream infection or not. This will help to avoid unnecessary use of antibiotics.

### Limitation(s)

Follow-up of patients to see what was the actual treatment given and the response to antimicrobial treatment, morbidity and mortality if any could not be done. Genotyping of isolated CoNS sp was not done. Paediatric patients were not included.

### CONCLUSION(S)

Majority of CoNS isolated from the blood cultures were considered initially as contaminants. But, due to change in therapeutic modalities, there has been an increase in isolation of true pathogenic CoNS from blood cultures. CoNS species are also becoming resistant to commonly used antibiotics. But not all CoNS isolated from blood stream are pathogenic. Therefore, it should be understood that patients suffering from CoNS from their blood stream should be carefully evaluated clinically before starting the antimicrobial therapy to avoid unnecessary use of antibiotics resulting in upsurge of antibiotics resistance in hospitals. Proper blood collection techniques need to be followed to avoid contamination of blood culture samples and to avoid diagnostic dilemma. Training and practice of hand hygiene, strict adherence to infection control practices and good sampling techniques are essential to prevent the contamination rate and development of drug resistance among CoNS species due to unnecessary treatment.

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