Original Research Article

Identification and antibiotic sensitivity pattern of Coagulase negative Staphylococcus causing in bloodstream infection with special reference to linezolid resistance

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Abstract

Introduction: The CoNS species have emerged as the most common cause of healthcare-associated blood stream infection (BSI), partly because of an increase in the number of hospitalized immuno-compromised patients, the increased use of indwelling medical devices.

Material and Methods: It was a retrospective analysis of specimen data for blood culture received in the Department of Microbiology, NHL Municipal Medical College, Ahmedabad over a period of 1 year from March 2019 to February 2020. Positive flagged blood culture bottles were subcultured on nutrient agar, blood agar and MacConkey agar and incubated at 37^0C for 18-24 hours,identification as well as antimicrobial susceptibility testing was performed by Vitek 2 compact system using GP ID and AST cards (P628) as per CLSI 2018.

Result: Out of 643 positive flagged bottles, 305(47.43%) non repeat clinically significant CoNS were obtained. Among the various species of CoNS isolated, Staph. hemolyticus 130(42.62%) was the most frequent followed by Staph. epidermidis 90 (29.5%). The isolates of CoNS showed multiple drug

resistance including very high level of resistance to oxacillin 277(90.81%) followed by Benzylpenicillin 267(87.54%). Lowest resistance was found to vancomycin 15(4.92%). There was emergence of linezolid resistance (LzR) among various CoNS species Overall LzR was seen in 48 (15.73 %) isolates.

Conclusion: Accurate identification of resistant phenotype followed by strict infection control measures are required to prevent nosocomial spread. It is important to keep a close monitoring to track resistance to linezolid particularly when frequent and extended linezolid therapy is prescribed.

Key words

Bloodstream infection, Coagulase-negative Staphylococci, Linezolid resistance, Methicillin resistance.

Introduction

Bloodstream infections (BSI) are infectious diseases defined by the presence of viable bacterial or fungal microorganisms in the bloodstream that elicit or have elicited an inflammatory response characterized by the alteration of clinical, laboratory and hemodynamic parameters [1].

Coagulase-negative Staphylococci (CoNS) are commensal of the skin and mucous membranes and have emerged as the important cause of hospital-acquired infections as well as most common contaminant of blood culture [2].

The CoNS species have emerged as the most common cause of healthcare-associated blood stream infection (BSI) for many years, partly because of an increase in the number of hospitalized immuno-compromised patients, the increased use of indwelling medical devices, such as central venous catheters and other prosthetic implants [4].

Commonly implicated species include S. epidermidis, S. hemolyticus, S. lugdunensis, S. schleiferi, S. warneri, S. hominis, S. simulans, S. capitis, S. cohnii, S. xylosus, and S. saccharolyticus [3].

Clinically significant CoNS should be identified to the species level, because of their increasing importance. Coagulase-negative Staphylococci possess loosely bound exo-polysaccharide layer (slime) in addition to capsule which is known to be associated with infections and reduced antibiotic susceptibility [5].

Currently, there is a paucity of data on the clinically significant CoNS species as conventional identification methods are labor-intensive [6].

So, an automated system which identified them rapidly and accurately up to species level was indeed a need of an hour. Several automated systems are then developed and evaluated. More recently the new VITEK-2 Compact system developed which detects metabolic changes by fluorescence-based methods which facilitate the identification of 6 hours reducing turnaround time for identification**.** The instrument monitors the kinetics of bacterial growth and calculates Minimum Inhibitory Concentrations (MIC) using a unique algorithm [7].

Rising incidence of methicillin-resistant (MR)-CoNS in hospitalized patients is big concern as CoNS are noted for their ability to develop resistance against commonly used antibiotic classes such as beta-lactum, aminoglycoside, macrolides with exceptionally high rate of methicillin resistance is reported [22].

Linezolid (LZD) is a synthetic drug of oxazolidinone class of antibiotics, which is approved for treatment of severe bacterial infections in adults caused by drug-resistant gram-positive bacteria, such as multidrug-resistant S. aureus, coagulase negative staphylococci, penicillin-resistant Streptococcus

pneumonia and vancomycin-resistant Enterococci (VRE) [8].

The bacteriostatic action of antibiotic blocks protein synthesis by interfering with the positioning of A-site tRNA in the peptidyl transferase centre of 23S rRNA in the 50S ribosomal subunit [8].

Resistance to LZD is primarily caused by mutations in the domain V of 23S rRNA gene or the gene cfr (chloramphenicol florfenicol resistance). Co-occurrence of cfr-mediated resistance and mutational resistance has also been documented and pose a therapeutic concern [8].

Aim and objectives

- To identify isolates of CoNS in blood culture.
- To determine their antibiotic susceptibility pattern by fully automated Vitek2 system using Gram positive ID card and p628 AST card as per CLSI 2021 with their clinical significance.

Materials and methods

Inclusion criteria

As per our departmental protocol, we considered significant CoNS bacteremia only if

- 2 or more positive blood culture samples gives the same CoNS species within a 5 days of incubation period
- If only one blood sample available in addition to positive blood culture , the presence of at least two of following clinical parameters according to SIRS criteria body temperature >38°C or < 36°C, heart rate >90 beats /min, respiratory rate >20 breaths/min, total leukocyte count of >12000/mm^3 or <4000/mm^3 or presence of >10% immature neutrophil granulocytes [4].

Identification of CoNS

It was a retrospective analysis of specimen data for blood culture received in the Department of Microbiology, at SVP hospital and NHL Municipal Medical College, Ahmedabad.

Total 305 non repeat clinically significant isolates of CoNS in blood culture were obtained from ICU as well as admitted patients in different wards and tested over a period of 1 year from March 2019 to February 2020.

Positive flagged blood culture bottles were subcultured on nutrient agar, blood agar and MacConkey agar and incubated at 37^0C for 18-24 hours. The Gram staining of smear from isolates were performed, Cocci in cluster showing violet color were provisionally considered as gram-positive cocci.

Further identification was done on the basis of catalase test, slide and tube coagulase test and their identification as well as antimicrobial susceptibility testing was performed by Vitek 2 compact system using GP ID and AST cards (P628) as per CLSI 2018.

Identification cards are inoculated with microorganism suspensions of 0.5 McFarland standards from a plate of pure culture using an integrated vacuum apparatus.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing with Vitek 2 compact system was performed in P628 card using microbroth dilution method according to the manufacturer's instructions as per CLSI 2018.

Antibiotics tested in AST P628 card included Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Levofloxacin, Linezolid, Oxacillin, Rifampicin, Teicoplanin, Tetracycline, Tigecycline, Trimethoprim/ Sulfamethoxazole, Vancomycin.

Results

Out of total 3132 blood culture bottles received at Department of Microbiology, SVP Hospital during period of 1 year from March 2019 to February 2020, 643(20.53%) were flagged as positive by fully automated BacT/Alert 3D machine. Out of total 643 positive flagged blood culture bottles, 305(47.43%) non repeat clinically significant CoNS were obtained. Out of 305 non repeat clinically significant CoNS 154(50.5%) were from Ward followed by 151(49.5%) were from ICU.

There was 193 (63.27%) male predominance and 112(36.73%) female with the male: female: ratio was 1.7:1.

Among the various species of CoNS isolated, Staph. hemolyticus 130(42.62%) was the most frequent followed by Staph. epidermidis 90 (29.5%) and Staph. hominis 60(19.67%). Staph. Arlettae (0.98%), Staph. Auricularis (0.32%), Staph. Capitis (0.32%), Staph. Caprae (1.31%), Staph. cohnii (0.98%), Staph. Equorum (0.32%), Staph. Hyicus (0.32%), Staph. Kloosii (0.65%), Staph. pseudointermed. (1.31%), Staph. Vitulinus (0.32%), Staph. warneri (0.98%), Staph. Xylosus (0.32%) were less frequently isolated from our Hospital (**Table - 1**).

Table - 1: Species identification andLocation-wise distribution of CoNS species (n=305).

Species of CoNS	ICU (n=151)	WARD (n=154)	TOTAL (n=305)
Staph. arlettae	3	0	3
Staph. auricularis	1	0	1
Staph. capitis	0	1	1
Staph. caprae	2	2	4
Staph. cohnii cohnii	0	1	1
Staph. cohnii ureal.	2	0	2
Staph. epidermidis	40	50	90
Staph. equorum	0	1	1
Staph. haemolyticus	68	62	130
Staph. hominis	30	30	60
Staph. hyicus	1	0	1
Staph. kloosii	0	2	2
Staph. pseudintermed.	2	2	4
Staph. vitulinus	0	1	1
Staph. warneri	1	2	3
Staph. xylosus	1	0	1
TOTAL	151	154	305

Staph. Hemolyticus was most commonly isolated from ICU 68(45.03%) as well as ward 62(40.25%)

The clinically significant isolates of CoNS were MDR including very high level of resistance to penicillin.

Similarly, Methicillin resistance (MRCoNS) which is tested by phenotypic oxacillin screen test was also high among the different species 277(90.81%). Lowest resistance was found to vancomycin 15(4.92%) (**Table - 2**).

The sensitive to all antibiotics were found in 9 CoNS isolates.

However, there was emergence of linezolid resistance (LzR) among various CoNS species.

Table - 2: Percentage of antimicrobial resistance seen in different CoNS species.

CoNS species (n=305)	CIP	CM	E	GM	LEV	LNZ	OX	P	RA	SXT	TE	TEC	TGC	VA
S. arlettae (n=3)	66.66 %	0%	66.66 %	0%	66.66 %	0%	66.66%	100 %	0%	33.33 %	0%	0%	0%	0%
S. auricularis (n=1)	0.00%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
S. capitis (n=1)	0.00%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
S. caprae (n=4)	0.00%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
S. cohnii (n=3)	0.00%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
S. epidermidis (n=90)	68.88 %	56.66 %	77.77 %	36.66 %	72.22 %	15.55 %	91.11%	83.33%	44.44 %	46.66 %	24.44%	1.11 %	10%	1.11 %
S. equorum (n=1)	100.%	0%	100%	0%	100%	0%	100 %	100 %	0%	100%	100 %	0%	0%	0%
S. hemolyticus (n=130)	77.69 %	63.07 %	77.69 %	39.23 %	80%	16.92 %	96.15%	93.07%	44.61 %	59.23 %	23.07%	10%	16.15 %	8.46 %
S. hominis (n=60)	79.31 %	51.72 %	84.48 %	32.75 %	79.31 %	15.51 %	93.1 %	93.1 %	50%	55.17 %	22.41%	3.44 %	10.34 %	5.17 %
S. hyicus (n=1)	0.00%	0%	100%	100%	0%	0%	0%	100 %	0%	100%	0%	0%	0%	0%
S. kloosii (n=2)	50.00 %	50%	50%	0%	50%	0%	100 %	50%	50%	0%	0%	0%	0%	0%
S. pseudintermed (n=4)	75.00 %	50%	75%	0%	100%	0%	100 %	100 %	25%	50%	25%	0%	0%	0%
S. vitulinus (n=1)	100%	0%	100%	0%	100%	0%	100 %	100 %	0%	100%	100 %	0%	0%	0%
S. warneri (n=3)	33.33 %	33.33 %	100%	0%	66.66 %	0%	100 %	100 %	0%	33.33 %	33.33%	0%	0%	0%
S. xylosus (n=1)	100%	0%	100%	0%	100%	0%	100 %	100 %	0%	100%	0%	0%	0%	0%
Total (n=305)	220 (72.13 %)	169 (55.41 %)	234 (76.22 %)	104 (34.1 %)	228 (74.75 %)	48 (15.73 %)	277 (90.82%)	267 (87.54%)	130 (42.62 %)	161 (52.79 %)	71 (23.28%)	16 (5.25%)	37 (12.13 %)	15 (4.92%)

CIP - Ciprofloxacin, CM - Clindamycin, DAP - Daptomycin, E - Erythromycin, GM - Gentamicin, LEV - Levofloxacin, LNZ - Linezolid, OX - Oxacillin, P - Benzylpenicillin, RA - Rifampicin, SXT - Trimethoprim/ Sulfamethoxazole, TE - Tetracycline, TEC - Teicoplanin, TGC - Tigecycline, VA – Vancomycin.

Table - 3: Relation between MRCoNS and LzRCoNS.

	Methicillin resistant	Methicillin sensitive	Total
Linezolid resistant	47	1	48(15.73%)
Linezolid sensitive	230	27	257(84.27%)
Total	277(90.82%)	28(9.18%)	305(100%)

Table – 4: Analysis of risk factor and outcome of LzRCoNS patient according to age.

Age	Location			Devices			Outcome			
	ICU	Ward	Total	Central line	No devices	Total	Death	Discharge	LAMA	Total
1 to 10	0	2	2	0	2	2	0	2	0	2
11 to 20	1	0	1	1	0	1	1	0	0	1
21 to 30	3	3	6	2	4	6	2	4	0	6
31 to 40	1	5	6	1	5	6	2	4	0	6
41 to 50	8	2	10	6	4	10	6	2	2	10
51 to 60	2	4	6	1	5	6	1	4	1	6
61 to 70	3	7	10	2	8	10	3	6	1	10
71 to 80	5	2	7	3	4	7	3	3	1	7
TOTAL	23(47.91%)	25(52.09%)	48(100%)	16(33.33%)	32(66.66%)	48(100%)	18(37.5%)	25(52.08%)	5(10.41%)	48(100%)

Overall LzR was seen in 48 (15.73%) isolates. Out of total 48 LzRCoNS, 47(97.91%) were also found MRCoNS (**Table - 3**).

Among 48 patients with LzRCoNS highest incidence is seen in age group of 41 to 50 and 61 to 70 which was 10 each (20.83%). Among 48 patients with Lz resistance, 23(47.91%) were from ICU and 25(52.08%) were from Ward.

16(33.33%) patients were having central line inserted.

Out of 48 patients 18(37.5%) patients passed away, 25(52.085) patients were discharged and 5(10.41%) patients took leave against medical advice (**Table - 4**).

Discussion

Coagulase Negative *Staphylococci* (CoNS) were generally regarded to be the contaminants, having little clinical significance in the past. In the period 1992 to 1998, surveillance conducted in medical-surgical units revealed that CoNS were the most common cause of primary bloodstream infections and the second commonest cause of post-surgical infections [16].

The predisposing risk factors identified for CoNS infections are rheumatic fever with infective endocarditis, intravascular catheters, prosthetic devices, prolonged antibiotics, immunocompromised status, surgery etc. [11].

In the present study, the observed overall rate of true bacteremia with CoNS was higher(47.43%) than reported in previous studies, which found values ranging from 5% to 30%.[22] Recently, Tashiro, et al. [14] found a 39.6% rate of CoNS BSI after investigating patients at a teaching hospital in Japan.

These results indicated the possibility that the incidence of CoNS infection may have increased in recent years compared with the rate in the 1990s. This is not surprising because patient populations and treatment protocols have changed over time and, in particular, the rate of central venous catheterization has increased [15]. Increased device use in ICU increase the risk of acquiring infection may be due to biofilm formation on catheter surface which help microorganism to withstand host defence mechanism as well as prevents entry of antibiotics.

In present study CoNS were isolated from ward 154(50.5%) and ICU 151(49.5%) patients. However, Singh et al isolated majority of CoNS from ICUs [16]. In present study reduced isolation from ICU may be due to adherence to

infection control practices which includes hand hygiene, personal protective equipment, routine environmental cleaning and disinfection, appropiate linen handling, biomedical waste management and safe use and disposal of sharps as well as constant surveillance and monitoring by the Infection Control team in ICU. Strict monitoring by Infection control team may have been overlooked in wards thus emphasizing the need for equal monitoring also in the wards by the ICT team.

There was male predominance 193 (63.27%) and female 112(36.73%)) with the male: female: ratio was 1.7:1. Male predominance was seen in our study may be due to sex dependent genetic factors.

In the present study, the most common CoNS species was Staph. hemolyticus 130(42.62%) was the most frequent followed by Staph. epidermidis 90 (29.05%) and Staph. hom.hominis 60(19.67%). The species distribution of CoNS in our study is in concordance with previous studies from India where *S. haemolyticus* was the most common followed by *S. epidermidis* [16]. In developed countries, *S. epidermidis* is the most frequent CoNS causing BSI followed by *S. haemolyticus* [17]. The difference in colonisation characteristics of patients and the varying adaptability of different species to selective pressures of antimicrobials in the health care setup leads to distribution differentiation in developed versus developing countries.

The isolates of CoNS showed multiple drug resistance including very high level of resistance to oxacillin followed by Benzylpenicillin [18]. Highest MR found in S. hemolyticus.

Lowest resistance found to vancomycin 15(4.92%). Similar findings have been reported. High isolation rates of MRCoNS from our hospital is a matter of concern asthey are resistant to multiple antibiotics leaving very few treatment options. Such strains are becoming the common causes of morbidity and mortality mainly in hospital settings. As well as increases financial burden on health care facility due to prolonged hospital stays and need for investigation and treatment.

Antibiotics like linezolid and vancomycin are the alternative therapeutic agents for these MDR Pathogens and if resistance develops to these drugs we are left with no therapeutic options.

When introduced, it was claimed that LZD has no cross-tolerance against other antibiotics and resistance developed rarely, due to its unique mechanism of action [9].

Overall, emergence of linezolid resistance (LzR) in CoNS ranging from 0% to as high as 16% has been reported from India and abroad [19],We report LzR in 15.73% of our clinical isolates of CoNS which is higher than with data from the global surveillance studies report of 2%.

S. hemolyticus (45.83%) was the most resistant phenotype followed by S. epidermidis (33.33%) Species wise susceptibility to linezolid has been reported by various workers; Kalawat, et al. reported LzR in S. Lugdunensis and S. hominis [9], and recently Matlani, et al. in 2016 [20] reported mucoid strain of S. hemolyticus showing LzR. Such high level of resistance to linezolid is an alarm for the judicious use of this drug.

Emphasizing judicious use of reserve drug like linezolid, vancomycin and tigecycline in routine clinical practice [12]. Due to the ease of oral administration; linezolid has been misused in clinical practice which has gradually led to emergence of resistance against this drug. Linezolid does not display cross resistance with other classes of antimicrobial agents.

Conclusion

Multidrug resistant CoNS is an emerging therapeautic concern and poses a significant

challenge to the treatment of infections caused by these organisms. Accurate identification of resistant phenotype followed by strict infection control measures are required to prevent nosocomial spread. It is important to keep a close monitoring to track resistance to linezolid particularly when frequent and extended linezolid therapy is prescribed. Paucity of newer antimicrobials demands judicious use of linezolid.

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