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RESEARCH ARTICLE

COAGULASE NEGATIVE STAPHYLOCOCCUS: A PREDOMINANT CAUSE OF NEONATAL BACTEREMIA IN A TERTIARY CARE HOSPITAL IN KOLKATA, WEST BENGAL

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ABSTRACT

Coagulase Negative Staphylococcus (CoNS) are emerging as a predominant cause of neonatal septicemia in health care facilities. Blood stream infection due to CoNS are often overlooked as central line colonization or contamination. An attempt was made to find out the prevalence of CoNS bacteremia with their antibiogram in neonatal blood culture samples from NICU of a tertiary care hospital. The study includes 1490 blood culture samples taken from sick neonates over a period of 21 months. Automated culture was done using BACT /ALERT and VITEK -2 machines. Results show that a total of 213(14.3%) samples were positive for gram positive cocci and 154 (10.3%) samples were positive for Gram negative bacilli. Among the gram positive cocci 176(11.8%) were CoNS while only 37(2.4%) was *S.aureus*. Antimicrobial susceptibility revealed that gram positive cocci were highly sensitive to Linezolid, Daptomycin and Vancomycin but were mostly resistant to Benzyl penicillin, Ciprofloxacin, Levofloxacin. Methicillin resistance was seen in 73% Staphylococcus aureus isolates whereas CoNS showed variable resistance. It is imperative to understand the pathogenic potential of CoNS and carry out their antibiogram for proper management of neonatal sepsis rather than mere discarding them as contaminants, otherwise neonatal morbidity will continue to increase.

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INTRODUCTION

Coagulase negative Staphylococcus (CoNS) bacteremia are rampant in hospital setup more so in the neonates. Confusion often arises regarding their pathogenic potential as they are commensals of the skin and mucosa in humans and animals. Studies have shown that they are major cause of neonatal morbidity and mortality (Luiz et al., 2011; Isaacs 2003). A large number of risk factors have been identified for CoNS infections namely immunosuppression, extremes of age, any mucocutaneous breach, previous antibiotic exposure and most importantly presence of indwelling prosthetic devices, catheters (Marra et al., 2007; Mattos et al., 2003; Ruhe et al., 2004). About 38 species of CoNS have been recognized of which 13 are known to colonize humans. The CoNS commonly known to cause infections include *S. epidermidis*, *S.*

saprophyticus, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, *S. schleiferi* and *S. warneri* (Coolen et al., 2013, Mohan et al., 2006). Prior to 1980, most neonatal septicemias were caused by Gram negative bacilli and *Staphylococcus aureus*. Since the last two decades, however, coagulase negative staphylococci (CoNS) has been emerging as the predominant causative organism. (Stoll, Gordon, Korones, et al., 1996, Gaynes, Edwards, Jarvis, et al., 1996, Isaacs, Barfield, Clothier et al. 2000, Gray, Richardson, McCormick et al., 1995, Fanaroff, Korones, Wright et al. 1998, Karlowicz, Buescher and Surka 2000). Several studies done in different areas in USA from 1970 to 1999 showed the predominance of CoNS in neonatal blood cultures. (David et al., 1988, Kumar et al., 1985, Ike Pauli Jr et al., 1999) According to Centre for Disease control and National Health care safety network team CoNS are associated with 30% central line associated blood stream infection (Hidron, Edwards, Patel et al., 2008). Jarvis et al. reported way back in 1987 that CoNS were the most common bacteria in nosocomial setup in both pediatric and neonatal population. (Jarvis, 1987) However in different areas of World

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prevalence of other organisms have also been reported like in Tanzania, Mhada TV *et al.* in 2009-10 found that incidence of *Staphylococcus aureus*, Klebsiella were common. (Mhada *et al.*, 2012) Similar results were reported from Nepal in 2007 by C Shaw while in Libya it was the predominance of gram negative bacilli (Shaw CK, Shaw P, Thapalial A, 2007, Mohamed *et al.*, 2004). In India, studies from different areas between 2003 - 07 showed that Klebsiella was the commonest isolate (Bambala Puthattayil Zakariya *et al.*, 2011, Neelam Kaistha *et al.*, 24). In 2014, one study from eastern India showed the predominance of *S. aureus* while another from western India showed CoNS to be common isolate (Nikhil Kumar Tudu *et al.*, 2014, Dr Sadhvi Parashar 2014). Thus neonatal blood cultures reveal a wide array of causative organisms which varies from one geographic location to another and in different time lines. CoNS isolates have been reported to show multiple antibiotic resistance including Methicillin and sometimes Vancomycin therapy were needed to control these infections (Amita Jain *et al.*, 2004). Our study was designed to evaluate prevalence of CoNS in neonatal bacteremia cases along with their antibiogram and help clinicians in making the proper choice of antibiotic for therapy as well as to take preventive measures to reduce the transmission of organism.

MATERIALS AND METHODS

We have carried out this retrospective study at Quadra Medical Services Pvt. Ltd. a multispeciality diagnostic centre situated in Kolkata, from August 2013 to April 2015. A total of 1490 blood cultures were obtained over a period of 21 months. Blood samples from sick neonates admitted to a neonatal intensive care unit of a tertiary care hospital were collected aseptically in blood culture bottles (BacT/ALERT PF from Biomerieux). It was then incubated in BacT/ALERT machine. The BacT/ALERT Microbial Detection System utilizes a colorimetric sensor and reflected light to monitor the presence and production of carbon dioxide (CO₂) dissolved in the culture medium. If microorganisms are present in the test sample, CO₂ is produced as the organisms metabolize the substrates in the culture medium. When growth of the microorganisms produces CO₂, the colour of the gas-permeable sensor installed in the bottom of each culture bottle changes from blue-green to yellow. The colour change results in an increase of reflectance units monitored by the system. Bottle reflectance is monitored and recorded by the instrument every 10 minutes.

The positive blood culture samples were subcultured in Blood and MacConkey agar respectively. The pure colonies obtained from the subculture were subjected to gram staining. Quantitations of cultures were performed. Only pure growth of gram positive cocci with >50 colony forming units per ml was utilized for identification and susceptibility testing using Biomerieux AST -P628 cards in VITEK 2 machine. This was done according to the theory proposed by Craft and Finer wherein 50cfu/ml was considered to be an indicator of true septicemia. The VITEK® 2 (Biomerieux) compact systems is a fully automated growth based technology that performs bacterial / yeast identification by biochemical analysis using colorimetric method. The gram positive bacteria identification card uses 43 biochemical tests for identification of the

organism. The antibiotics against which susceptibility are checked by MIC are Ciprofloxacin, Clindamycin, Cefoxitin, Daptomycin, Erythromycin, Gentamycin, Levofloxacin, Linezolid, Nitrofurantoin, Oxacillin, Rifampicin, Teicoplanin, Tetracycline, Tigecycline, Trimethoprim / Sulfamethoxazole, Vancomycin.

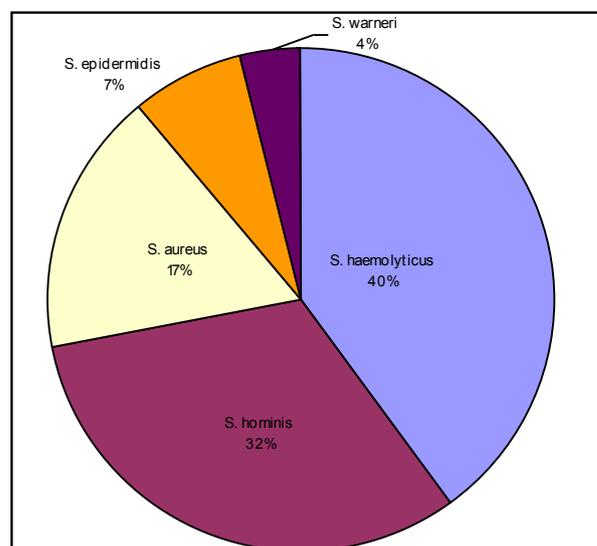
RESULTS

In our study 1490 blood culture samples were collected over a period of 21 months from August 2013 to April 2015 from NICU of a tertiary care hospital. A total of 213(14.3%) samples were positive for gram positive cocci and 154 (10.3%) samples were positive for Gram negative bacilli. *Staphylococcus aureus* was only 17% (37 out of 213) whereas CoNS species were 83% (176 out of 213 samples) among gram positive cocci. The species of CoNS isolated were *S. haemolyticus*, *S. hominis*, *S. epidermidis* and *S. warneri* (vide table and pie chart 1).

Table 1. Percentage distribution of different CoNS and *S. aureus* obtained from neonatal septicemia cases

Sl.No	Organism	Number of cases	Percentage
1	Staphylococcus aureus	37	17%
	CONS		
2	Staphylococcus haemolyticus	85	40%
3	Staphylococcus hominis	69	32%
4	Staphylococcus epidermidis	18	7%
6	Staphylococcus warneri	4	4%
	Total CONS	176	83%
	Total Cases	213	100%

(Table shows high prevalence of CoNS in comparison to *S. aureus*, *S. haemolyticus* among CoNS is the most common isolate)



(*S. haemolyticus* (40%) was the commonest CoNS followed by *S. hominis*)

Figure 1. Pie chart showing distribution of CoNS and *S. aureus* cases from blood culture samples of neonates

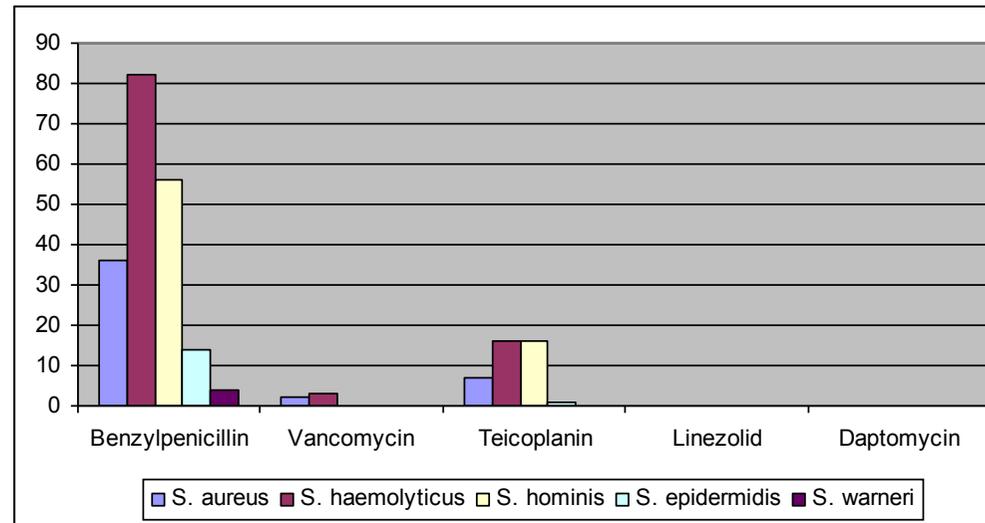
The isolates of Gram positive cocci were found to be highly sensitive to Linezolid, Daptomycin and Vancomycin, but showed variable sensitivity to Teicoplanin and were mostly resistant to Benzyl Penicillin, Ciprofloxacin, Levofloxacin, Erythromycin and Cotrimoxazole. Methicillin resistance was seen in 73% *Staphylococcus aureus* isolates whereas CoNS showed variable resistance with *S. haemolyticus* having resistance in 95 % cases (Table 2).

Table 2. Antibiotic resistance pattern shown by *S. aureus* and different CoNS

Staphylococcus Species	Vancomycin			Linezolid			Daptomycin			Teicoplanin			Oxacillin			Erythromycin		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>S. aureus</i> (37)	28 (76%)	7 (19%)	2 (5%)	37 (100%)	0	0	37 (100%)	0	0	30 (81%)	0	7 (19%)	10 (27%)	0	27 (73%)	10 (27%)	0	27 (73%)
<i>S. haemolyticus</i> (85)	74 (87%)	8 (9%)	3 (4%)	85 (100%)	0	0	85 (100%)	0	0	67 (79%)	2 (2%)	16 (19%)	4 (5%)	0	81 (95%)	1 (1%)	0	84 (99%)
<i>S. hominis</i> (69)	69 (100%)	0	0	69 (100%)	0	0	69 (100%)	0	0	53 (77%)	0	16 (23%)	22 (32%)	0	47 (68%)	12 (17%)	2 (3%)	55 (80%)
<i>S. epidermidis</i> (18)	17 (94%)	1 (6%)	0	18 (100%)	0	0	18 (100%)	0	0	17 (94%)	0	1 (6%)	4 (22%)	0	14 (78%)	5 (28%)	0	13 (72%)
<i>S. warneri</i> (4)	4 (100%)	0	0	4 (100%)	0	0	4 (100%)	0	0	4 (100%)	0	0	2 (50%)	0	2 (50%)	2 (50%)	0	2 (50%)

Staphylococcus Species	Benzylpenicillin			Ciprofloxacin			Levofloxacin			Cotrimoxazole			Tigecycline			Gentamicin		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>S. aureus</i> (37)	1 (3%)	0	36 (97%)	8 (22%)	1 (3%)	28 (76%)	7 (19%)	2 (5%)	28 (76%)	15 (41%)	0	22 (59%)	37 (100%)	0	0	18 (49%)	7 (19%)	12 (32%)
<i>S. haemolyticus</i> (85)	3 (4%)	0	82 (96%)	7 (8%)	2 (2%)	76 (89%)	7 (8%)	1 (1%)	77 (91%)	32 (38%)	0	53 (62%)	85 (100%)	0	0	18 (21%)	7 (8%)	12 (14%)
<i>S. hominis</i> (69)	13 (19%)	0	56 (81%)	29 (42%)	6 (9%)	34 (49%)	30 (43%)	4 (6%)	35 (51%)	25 (36%)	0	44 (64%)	69 (100%)	0	0	66 (96%)	2 (3%)	1 (1%)
<i>S. epidermidis</i> (18)	4 (22%)	0	14 (78%)	10 (56%)	2 (11%)	6 (33%)	9 (50%)	2 (11%)	7 (39%)	11 (61%)	0	7 (39%)	18 (100%)	0	0	15 (83%)	1 (6%)	2 (11%)
<i>S. warneri</i> (4)	0	0	4 (100%)	4 (100%)	0	0	4 (100%)	0	0	4 (100%)	0	0	4 (100%)	0	0	4 (100%)	0	0

(*S. aureus* and CoNS show 100% sensitivity to Linezolis, Daptomycin and Tigecycline and low sensitivity to Benzylpenicillin, Quinolones and Cotrimoxazole)



(Both *S. aureus* and CoNS show low resistance to Vancomycin, Linezolid and Daptomycin and high resistance to Benzylpanecillin)

Figure 2. Histogram showing resistance to commonly used antibiotics by *S. aureus* and different CoNS

DISCUSSION

In the 21st century, CoNS are the most common organism attributing to late onset sepsis in NICU. This is probably more due to advances in neonatal medicine and technology which have increased the survival of low birth weight premature infants having depressed immunity (Collen *et al.*, 2013). Clinical manifestations of CoNS septicemia is often subtle and nonspecific and indistinguishable from sepsis due to other organisms, so it is very difficult for the clinicians to differentiate septicemia from line colonization and contamination. To ameliorate this Craft and Finer had proposed that colony forming units per millilitre (CFU/ml) would be helpful in differentiating between them while according to Haimi-Cohen *et al.* it was the time taken by the cultures to be positive which could be a strong indicator of sepsis (Craft and Finer, 2001, Haimi-Cohen Y *et al.*, 2002). In our study we found that CoNS (176 samples) were much more common than *S.aureus* (37 samples) and also to some extent commoner than gram negative bacilli (154 samples) reflecting the presence of CoNS as the predominant isolate.

Similar results were also obtained in different studies carried out in USA in different decades (Stoll *et al.*, 1996, David *et al.*, 1988). Within India however Bambala *et al.* from South, Neelam kaistha *et al.* from north and Rajlakshmi *et al.* from east found Klebsiella to be the commonest isolate. (Bambala Puthattayil Zakariya *et al.*, 2011, Neelam Kaistha *et al.*, 2010, Rajlakshmi Vishwanathan *et al.*, 2011). In 2014, Dr Tudu from Eastern India found *S. aureus* to be the commonest isolate while Dr Parashar from central India found CoNS to be common. (Nikhil Kumar Tudu *et al.*, 2014, Dr Sadhvi Parashar, 2014). The present study reveals that among all CoNS, *S. haemolyticus* (40%) was the commonest followed by *S. hominis* (32%), *S. epidermidis* (7%) and *S. warneri* (4%) respectively. In most of the studies carried out in both India and outside *S. epidermidis* has been the commonest isolate (Luiz S. *et al.* 2011, D Isaacs, 2003, Collen Nash *et al.*, 2013, Mohan P. Vengkatash *et al.*, 2006, Gray JE, Richardson DK, McCormick MC, *et al.* 1995). Dr Parashar from central India also found *S. epidermidis* (74.1%) to be the commonest isolate. However our study correlates with that of Dr Amita Jain (34%) and Dr Geeta Mehta (36%) who found *S. haemolyticus* to be the commonest CoNS. (Amita Jain *et al.*, 2004, Geeta Mehta *et al.*, 1991)

CoNS isolates have been considered to cause less virulent septicemia than *Staphylococcus aureus* and gram negative bacilli. CoNS infections rarely cause meningitis, and the mortality is low but morbidity is high leading to prolonged hospital stay. (Stoll *et al.*, 1996, Isaacs D, Barfield C, Clothier *et al.*, 2000, Karlowicz *et al.*, 2000). In spite of this drug resistance seems to be on the rise. Methicillin resistance was observed in a high percentage cases of CoNS (95% for *S. haemolyticus* and 68% for *S. hominis*) while it was seen in 73% cases of *Staphylococcus aureus*. This correlates with the study of Dr parashar (69.8%) but not with that of U. Mohan *et al.* (28.3%). (Dr Sadhvi Parashar, 2014; Mohan *et al.*, 2002). Vancomycin resistance was found in 4% cases of *S. haemolyticus* and 5% cases of *S. aureus* which does not correlate with the study of Dr Parashar who found no

resistance to Vancomycin. Linezolid, Daptomycin and Tigecycline were found to be sensitive in all cases. Resistance to Teicoplanin was seen in 19% isolates of both *S. haemolyticus* and *S. aureus*.

Conclusion

CoNS are the predominant causative organisms of neonatal septicemia. It is often very difficult to differentiate between central line colonization, contamination from true bacteremia. Thus it is imperative that efforts should be made to identify CoNS to the species level and perform its antibiotic susceptibility as they have unique resistance pattern. Discarding CoNS isolates as mere contaminants would lead to increased neonatal morbidity and mortality.

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