COAGULASE NEGATIVE STAPHYLOCOCCAL SEPTICEMIA IN NEWBORNS

N.K. Anand
A.K. Gupta
Man Mohan
I.M.S. Lamba
R. Gupta
L. Srivastava

ABSTRACT

The case records of 2177 newborn infants admitted in the Neonatal Intensive Care Unit (NICU) from January, 1989, through July, 1990, with positive blood cultures for coagulase-negative staphylococci (C-NS) were evaluated.

Seventy four (3.4%) neonates yielded C-NS in blood cultures during the study period. Of these, 58 (2.7%) infants had clinical and hematological features compatible with the diagnosis of septicemia. Remaining 16 babies with positive cultures had no evidence of sepsis, and were designated as "C-NS bacteremia".

The age at which positive cultures were obtained differed between the bacteremic and septicemic groups. In bacteremic group, the onset occurred between one to four days of age. In contrast, in septicemic group the range was 6-20 days, with a mean of 10.22 (±3.53) days.

More than two third of total cases of C-NS sepsis were premature and low birth weight (LBW). Prominent clinical features included lethargy, poor feeding and fever. Besides this apneic spells were seen predominantly in babies weighing less than 1500 g. Further, before the diagnosis of C-NS sepsis, more than half of neonates had received prolonged intravenous fluid therapy, a quarter had undergone umbilical catherization and a further quarter needed a ventilator support.

Overall mortality in C-NS sepsis was 17.24%, distinctly higher in neonates with RDS and those requiring mechanical ventilation ($p < 0.05$). Only 1.34% C-NS isolates were resistant to all routinely used antibiotics and sensitivity was maximum with newer cephalosporins, ciproflox and amikacin.

Key words: *Coagulase-negative staphylococci, Neonatal sepsis.*

Coagulase negative staphylococci (C-NS) have generally been dismissed as contaminants when isolated from newborn blood cultures in past(1-2). Recent clinical experience, however, suggests that C-NS should be considered pathogens rather than contaminants in the sick newborn host(3-9). Further, it has now been well established that even low colony counts (cfu) of coagulase negative staphylococci may produce sepsis in babies who are deemed to be at risk(10). This study

From the Departments of Pediatrics and Microbiology, Safdarjang Hospital, New Delhi 110 029 and Institute for Research in Medical Statistics (ICMR), New Delhi 110 029.

Reprint requests: Dr. N.K. Anand, Senior Pediatrician and Head, Department of Pediatrics, Safdarjang Hospital, New Delhi 110 029.

Received for publication October 1, 1990; Accepted March 18, 1991

reports our experience with septicemia caused by coagulase-negative staphylococci during a one and half year period in a newborn intensive care unit.

Material and Methods

The case records of all the newborn infants in the NICU from January, 1989, through July 1990, with positive blood cultures for C-NS were reviewed.

Blood was drawn for culture from a peripheral vein as part of the routine sepsis work-up for suspected infection before antimicrobial therapy was started. Sepsis screen, which also included various hematological parameters such as micro-ESR, TLC, band count to total neutrophil ratio, and morphological changes in neutrophils, was done if infants had meconium aspiration syndrome (MAS) at birth or had come from an infected intrauterine environment (maternal amnionitis), or if they were febrile, or presented with signs such as lethargy, poor feeding, vomitting, diarrhea, temperature instability, unusual jaundice, and recurrent apnea, or if there were suspicious findings on clinical examination. The skin at the site of venepuncture was prepared by careful swabbing with 2% iodine solution and 70% isopropyl alcohol. The blood specimens were collected in glucose and bile broth bottles and after incubation for twenty four hours, samples were subcultured on blood agar and MacConkey agar. Organisms were confirmed as C-NS by Gram stain, typical colony morphology, ability to ferment glucose and negative tube coagulase test(11). Further characterization was not done. Antibiotics sensitivity tests were carried out using disc diffusion method. C-NS isolates were defined as positive when they displayed uniform antibiotic susceptibility from both bottles (glucose broth and bile broth bottles). C-NS isolates that did not meet these criteria were interpreted as culture contaminants. Also, cultures growing multiple bacterial pathogens (including C-NS) were classified as probably contaminated and excluded from further analysis(12).

All cases having C-NS growths on blood cultures were analysed for various characteristics and two groups of neonates were identified: (*i*) Neonates having C-NS as the only growth in blood culture with presence of clinical (such as apnea, bradycardia, fever or temperature instability, hypotension, acidosis, lethargy, irritability, or gastrointestinal disturbances) and hematological evidence (≥2 of the following: band count to total neutrophil ratio >0.2; TLC <5000/mm^3; elevated m-ESR (>6 mm, 1st 3 days; >10 mm thereafter); and morphological changes in neutrophils such as Dohle bodies, toxic granulations and cytoplasmic vacuolization) of sepsis, termed as "C-NS septicemia", and (*ii*) Neonates with C-NS as the only growth in blood culture, but without any other clinical or hematological evidence of sepsis, designated as "C-NS bacteremia".

Statistical methods included calculation of mean, SD, proportion test and multiple logistic regression analysis.

Results

During the 19 months study period, 74 of 2177 (3.39%) neonates yielded C-NS in blood cultures. Of these, 58 (2.66%) infants had clinical and hematological features compatible with the diagnosis of septicemia (C-NS sepsis). Remaining 16 babies with positive blood cultures for C-NS, however, had no evidence of sepsis, and were designated as C-NS bacteremia (probably contaminants).

The age at which the positive blood cultures were obtained differed between

the bacteremic and septicemic group. In bacteremic group, onset occurred between 1-4 days of age, with a mean of 2.66 days. In contrast, in septicemic group, the range was 6-20 days, with a mean of 10.22 (±3.53) days.

As shown in *Table I*, 56.9% of cases of C-NS septicemia were delivered by assisted delivery. The mean gestational age and birth weight (±SD) of these newborns was 35.19 (±3.10) wks and 1751.38 (±415.86) g, respectively. Among the 36 preterms, 14 (38.8%) newborns had the gestation of ≤32 wks. More than two-third of the total cases were low birth weight (LBW), including 15 (25.8%) babies weighing less than 1500 g at birth. In striking contrast, all neonates characterized as having "C-NS bacteremia" were delivered by a normal vaginal delivery and had a mean gestational age and birth weight (±SD) of 38.86 (±1.60) weeks and 2400.44 (±286.76) g, respectively.

Apart from prematurity and LBW, other high risk perinatal factors were present in 40 (68.9%) of the 58 neonates with C-NS sepsis, commonest being birth asphyxia (44.8%), meconium aspiration syndrome (MAS) (41.37%), and prolonged rupture of membranes (PROM) (29.31%). In 23 (39.6%) neonates with C-NS sepsis, however, more than 2 high risk factors were present.

After admission to the NICU, more than half of the neonates with C-NS sepsis had received prolonged intravenous, fluid therapy (>7 days), 24.13% had undergone an exchange transfusion through umbilical catheterization and 25.80% needed a ventilator support. As against this, meconium aspiration syndrome (MAS) (50%) and PROM (50%) were only risk factors in neonates with designation of "C-NS bacteremia".

Over all mortality in C-NS septicemia was 17.24%, distinctly higher in group with neonatal MAS ($p<0.05$), those requiring ventilator support ($p<0.01$), and neonates with respiratory distress syndrome ($p<0.001$). On multiple logistic regression analysis, however, only respiratory distress syndrome (RDS) and mechanical ventilation were found to be significantly correlated to mortality in C-NS septicemia ($p<0.05$). Odd ratio, however, was maximum for hyaline membrane disease (1174.9, $p=0.04$). No significant difference in prognosis according to age of onset of sepsis, or any other high risk factor was observed. In striking contrast, none of the neonates with designation of "C-NS bacteremia" died.

Table II enlists various clinical features seen in C-NS septicemia in order of frequency. As evident lethargy, poor feeding and fever were prominent clinical features being present in >70% cases. Besides this apneic and bradycardic episodes were seen predominantly in babies >1500 g. No obvious septic focus (conjunctivitis, skin infection) was detectable, however, in any of the cases.

Initially all 58 neonates with clinical and hematological evidences of sepsis were treated with a combination of cephaxin and gentamicin. In 34 of them same antibiotics were continued after obtaining the culture sensitivity reports. Remaining cases however, were switched to a combination of amikacin to either ceftriaxone (12 cases) or cloxacillin (12 cases) depending upon the sensitivity pattern (*Table III*). As against this, bacteremic group of neonates received only prophylactic antibiotics (indication being either MAS or PROM) in form of a combination of ampicillin and gentamicin for a period of seven days.

As shown in *Table III*, only 6 isolates

TABLE I–*Perinatal, Postnatal Characteristics and Outcome of Neonates with C-NS Sepsis*

	High risk factors	Total cases (n) (%)	Outcome Survived	Death	p value (Proportion test)
1.	Type of delivery				
	(*i*) normal	25 (43.1)	21	4	>0.05
	(*ii*) assisted	33 (56.9)	27	6	
2.	Gestational age				
	(*i*) Full term	22 (37.9)	20	2	
	(*ii*) Preterm	36 (62.1)	28	8	>0.05
3.	Birth weight				
	(*i*) ≥2200 g	11 (18.7)	11	0	>0.05
	(*ii*) <2200 g	47 (81.3)	37	10	
4.	Birth asphyxia				
	(*i*) No	32 (55.2)	25	7	>0.05
	(*ii*) Yes	26 (44.8)	23	3	
5.	MAS				
	(*i*) No	34 (58.6)	25	1	<0.05*
	(*ii*) Yes	24 (41.4)	23	9	
6	PROM				
	(*i*) No	41 (70.7)	35	6	>0.05
	(*ii*) Yes	17 (29.3)	13	4	
7.	HMD				
	(*i*) No	41 (70.7)	40	1	<0.001*
	(*ii*) Yes	17 (29.3)	8	9	
8.	Prolonged IV therapy (<7 days)				
	(*i*) No	26 (44.8)	24	2	>0.05
	(*ii*) Yes	32 (55.2)	24	8	
9.	Exchange transfusion				
	(*i*) No	44 (75.7)	36	8	>0.05
	(*ii*) Yes	14 (24.2)	12	2	
10.	Ventilator support				
	(*i*) No	43 (74.2)	39	4	<0.01*
	(*ii*) Yes	15 (25.8)	9	6	
11	Age of onset of sepsis (>10 days)				
	(*i*) No	24 (41.4)	21	3	>0.05
	(*ii*) Yes	34 (58.6)	27	7	

were resistant to all routinely used antibiotics. Maximum sensitivity was for newer antibiotics (ceftriaxone, cefuroxime), amikacin and ciproflox followed by cloxacillin, gentamicin and cephaxin.

Discussion

Previous studies have demonstrated that C-NS are significant pathogens in patients with intravascular catheters(13),

TABLE II—*Clinical Features in Neonates with C-NS Septicemia*

Clinical features	Frequency (h)	(%)
Refusal to feed	45	77.5
Lethargy	45	77.5
Temperature change		
Hypothermia	15	25.8
Hyperthermia	36	62.1
Sclerema	27	46.5
Gastric aspirates	22	37.8
Abdominal distention	18	31.3
Apneic spells	12	20.7
Jaundice	12	20.7
Hepatomegaly	8	13.7
Splenomegaly	8	13.7
Bleeding tendency	2	3.4
DIC	1	1.7
Thrombocytopenia	1	1.7
Seizures (pyogenic meningitis)	1	1.7

TABLE III—*Antibiotic Sensitivity Profile of C-NS Isolates*

Antibiotics	No. tested	No. sensitive
1. Penicillin	58	6
2. Chloromycetin	58	25
3. Streptomycin	56	1
4. Cloxacillin	48	40
5. Ampicillin	52	19
6. Kanamycin	56	25
7. Gentamicin	56	36
8. Cephaxin	50	34
9. Ciproflox	56	50
10. Amikacin	56	50
11. Ceftriaxone	12	12
12. Cefuroxime	16	16
13. Multidrug resistant	58	6

cerebrospinal fluid shunts(14), and prosthetic valves(15). C-NS, however, have generally been dismissed as contaminants when isolated from newborn blood cultures in past(1,2). The finding in the present study confirm that C-NS also can be significant nosocomial pathogens in high risk newborn infants(3-9). The incidence of C-NS sepsis in this series of 26.6 cases per 1000 admissions was only next to that estimated for Klebsella species (43.6/1000 admissions) and *E. coli* species (41.3/1000 admissions) during a comparable period.

Since C-NS is a skin commensal, the question is whether to consider them pathogenic when grown from newborn blood culture? Although various methods are available to confirm virulence of a C-NS subtype(16), none is of much practical value(9). Similarly, collection of multiple blood cultures and demonstration of identical growth in them is also not feasible in newborn with relatively small blood volume, and single blood cultures have been considered adequate in this age group(17). In the present study, clinical features of sepsis were present in 58 (78.3%) of the 74 newborns with C-NS bacteremia. In view of these findings, it appears that recovery of C-NS in newborn blood, even on single culture, should not be discarded as contaminant and every such patient should be carefully evaluated for clinical and laboratory evidence of sepsis.

Previous published results of nasal and umbilical cultures(18), have revealed that more than 90% of babies are colonized with C-NS by the third hospital day. Onset of C-NS sepsis after first week in the present study, is consistent with nosocomial infections rather than merely a contamination(19). However, were contamination a significant problem, a precipitous increase in positive cultures would be expected in the first five days of life as C-NS rapidly colonizes the skin by 5th day(18). Only sixteen babies (21.6%) in the present

series had asymptomatic C-NS bacteremia within first four days of life and are compatible with a probable contamination, since none had any hematological or clinical evidences of sepsis and all recovered without appropriate antibiotic coverage. Few studies(9,20), however, have documented early onset sepsis with C-NS which was not seen in the present study.

Our findings are well substantiated by some earlier studies that have implicated C-NS as a cause of late onset nosocomial sepsis secondary to prolonged hospitalization, total parental nutrition or prolonged intravenous therapy, umbilical catheterization, and mechanical ventilation, *etc.*(1,20-24). Thus 34 (58.6%) of the 58 neonates with C-NS septicemia in the present study, were hospitalized for longer than 10 days, 32 were on prolonged intravenous (>7 days) therapy, 14 had undergone umbilical catheterization, and 15 required mechanical ventilation before the diagnosis of C-NS was made.

Further analysis of cases with C-NS sepsis revealed that a majority (>2/3rd) of them were premature and LBW. Others(3,5,21,24), have also reported an increased susceptibility of LBW and premature infants to C-NS sepsis probably due to a relatively longer hospital stay and excessive exposure to diagnostic and supportive procedures that characterize intensive care. In the present study, various perinatal factors were ruled out as predisposing to C-NS sepsis since no case of early onset sepsis was recorded. The role played by these factors, if any, was in prolonging the duration of hospitalization and intravenous line.

Clinical presentation of C-NS sepsis is non specific. Although few cases of focal sepsis have been reported in literature(4,9), they were not seen in our cases.

Though previous workers have observed high survival rates for neonates with nosocomial C-NS septicemia, 17.24% of the neonates with C-NS sepsis in the present study died. Outcome, however, was poorer in babies with hyaline membrane disease and those requiring ventilator support ($p<0.05$), which is not untrue for such babies even if they are free from sepsis.

Treatment of C-NS sepsis has been complicated recently by organisms that are multidrug resistant(3-5,15,21). In the present study, sensitivity tests were carried out for 12 antibiotics (2 recently introduced) and all but 6 (1.34%) isolates were susceptible to at least one of these antibiotics. The maximum sensitivity (90-100%) was for newer antibiotics (ceftriaxone, cefuroxime, amikacin, ciproflox) followed by cloxacillin, getamicin and cephaxin (60-80%). Vancomycin remains the most effective single agent in antimicrobial therapy for a serious C-NS infection, though cephalosporins in combination with aminoglycosides are also highly effective, as also shown by the sensitivity reports in our cases(3,5,21,25).

In conclusion, recovery of C-NS from blood culture of a newborn infant with signs of sepsis should not be considered a contaminant. The newborn infant, especially the premature and LBW neonates with relatively longer hospital stay and excessive exposure to diagnostic and supportive procedures should be added to the list of high risk patients for septicemia with C-NS.

REFERENCES

1. Dunham EC. Septicemia in the newborn. AM J Dis Child 1933, 45: 229-253.
2. Eitzman DV, Smith RT. The Significance of blood cultures in the newborn period. Am J Dis Child 1957, 94: 601-603.

3. Baumgart, Hall SE, Campos JM, Polin RA. Sepsis with Coagulase negative staphylococci in critically ill new born. AM J Dis Child 1983, 137: 461-463.

4. Noel GJ, Edelson PJ. *Staphylococcus epidermidis* bacteremia in neonates: Further observations and the occurrence of focal infection. Pediatrics 1984, 74: 832-837.

5. Munsan DP, Thompson TR, Johnson DE, *et al*. Coagulase-negative staphylococcal septicemia: Experience in a newborn intensive care unit. J Pediatr 1982, 101: 602-605.

6. Fleer A, Senders RC, Visser MR. Septicemia due to coagulase-negative staphylococci in a neonatal intensive care unit: Clinical and bacteriological features and contaminated parenteral fluids as source of sepsis. Pediatr Infect Dis 1983, 2: 426-431.

7. Ponce DeLeon S, Wenzel RP. Hospital acquired blood stream infections with *Staphylococcus epidermidis*. Am J Med 1984, 77: 639-644.

8. Schmidt BK, Kirpalani HM, Corey M, *et al*. Coagulase-negative staphylococci as true pathogens in newborn infants: A cohort study. Pediatr Infect Dis 1987, 6: 1026-1031.

9. Agarwal M, Chaturvedi P, Dey SK, Narang P. Coagulase-negative staphylococcal septicemia in newborn. Indian Pediatr 1990, 27: 163-169.

10. Geme JW, Bell LM, Baumgart S, Angio CT, Harris MC. Distinguishing sepsis from blood culture contamination in young infants with blood cultures growing coagulase negative staphylococci. Pediatrics 1990, 86: 157-162.

11. Cruickshank R, Duguid JP, Marmion BP, Swain RHA. Medical Mircrobiology, Vol II, 12th edn. Edinburgh, Churchill Livingston, 1975.

12. Sidebottom DG, Freeman J, Platt R, Epstein MF, Goldmann DA. Fifteen-year experience with blood stream isolates of coagulase-negative staphylococci in neonatal intensive care. J Clin Microbiol 1988, 26: 713-718.

13. Anagnostakis D, Kamba A, Petrochilou V, Arseni A, Matsaniotis N. Risk of infection associated with umbilical vein catheterization–A prospective study in 75 newborn infants. J Pediatr 1975, 86: 759-763.

14. Prince EH. Staphylococcal epidermidis infection in cerebrospinal fluid shunts. J Host Inf 1984, 5: 7-17.

15. Karchmor AW, Archer GL, Dismuker WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis-micro biologic and clinical observations as guidelines to therapy. Ann Intern Med 1983, 98: 447-455.

16. Archer GL, Karchmor AW, Vishniavoky N, Johnston JL. Plasmid pattern analysis for the differentiation of infection from non infecting *Staphylococcus epidermidis*. J Infect Dis 1984, 149: 913-920.

17. Koshi G. Blood culture updated. Indian J Pediatr 1986, 53: 429-431.

18. Goldmann DA, Leclair J, Macone A. Bacterial colonization of neonates admitted to an intensive care environment. J Pediatr 1978, 93: 288-293.

19. Freeman J, Mc Gowan Jr JE. Day specific incidence of nosocomial infection estimated from a prevalence survey. Am J Epidemiol 1981, 114: 888-901.

20. Battisi O, Mitchison R, Davies PA. Changing blood culture isolates in a referral neonatal intensive care unit. Arch Dis Child 1981, 56: 775-778.

21. Christo GG, Chandran S, Shivananda PG, Baliga M, Venkatesh A. Coagulase-Negative staphylococcal sepsis in infants. Indian Pediatr 1988, 25: 338-342.

22. Hall RT, Rhodes PG. Total parental nutrition via indwelling umbilical catheters

in the newborn period. Arch Dis Child 1976, 51: 929-934.

23. Davies AJ, Ward Platt M, Kirk R, *et al.* Is coagulase negative staphycococcal bacteremia in neonates a consequence of mechanical ventilation? J Hosp Infect 1984, 3: 260-270.

24. Freeman J, Epstein MF, Smith NE, *et al.* Extra hospital stay and antibiotic usage with nosocomial coagulase-negative staphylococcal bacteremia in two neonatal intensive care unit populations. Am J Dis Child 1990, 144: 324-329.

25. Schaad UB, McCracken GH Jr, Nelson JD. Clinical pharmacology and efficacy of vancomycin in pediatric patients. J Pediatr 1980, 96: 119-126.

NOTES AND NEWS

CHAPTER ON DEVELOPMENTAL PEDIATRICS

Over the past few years there has been a growing awareness that a rational approach to Developmental Medicine has to be evolved at multidisciplinary level of practising professionals in the field. An ideal set up for the practice of Developmental Medicine needs inputs from all branches of medicine, psychology, therapy services, special educators and medico-social workers. The cost of establishing such a Unit even at Medical College level is exhorbitant and at the peripheral centre a dream beyond our reach. Such a set up has been an exclusive privilege of scattered few centres in the country. Drawing from the lessons learnt at such centres, one has to evolve a need based socio-culturally relevant economically feasible system of early diagnosis and management programmes that are widely known and practised at grass root levels also.

Towards this end, in the year 1992 which happens to be the last year of the international decade of the disabled persons, the Indian Academy of Pediatrics will be convening a National Disability Workshop followed by the formation of Chapter on Developmental Pediatrics. The Chapter intends to evolve a multidisciplinary forum for exchange of knowledge and promoting research in developing service models and community approaches. Interested Pediatricians and other professionals are requested to contact the following persons for further details.

Dr. (Mrs) G. Shashikala,
Consultant Developmental Neurologist,
M.S.S. Children's Orthopedic Hospital,
71, Rashmi Dongre Layout,
Abhyankar Nagar,
Nagpur 440 010
Tel. 521271

Prof. M.S. Mahadeviah,
Head, Department of Pediatrics,
Kempe Gowda Institute of Medical Sciences,
518 Rajmahal Vilas Extension,
Sadashiranagar,
Bangalore 560 080
Tel. 365301