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RESEARCH ARTICLE

NOSOCOMIAL OUT BREAK OF NEONATAL SEPTICEMIA SENSITIVE ONLY TO QUINOLONES IN A TERTIARY CARE NURSERY

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ABSTRACT

Background: Nosocomial infections are an important cause of morbidity and mortality in neonatal intensive care units (NICUs). A Nosocomial outbreak of neonatal septicemia occurred in theNICUs of a tertiary care hospital in Kashmir during Nov-Dec 2008.

Aims and objectives: The present study was undertaken to study various aspects of this nosocomial infection outbreak.

Materiel and Methods: This was a retrospective observational study carried out in NICU of a tertiary care referral pediatric hospital in Srinagar Ja nd K, India.Total of 31 patients who developed nosocomial sepsis during the study period of 2 months were taken as subjects. The neonates whose diagnosis at admission was probable sepsis or who were obviously septic were excluded from the study. Cultures from all the newborns were obtained by sterile vein puncture technique and incubated for 24-48 hours for identification of the organism and determination of sensitivity pattern by disc diffusion method. Antibiotics tested included cephalosporins, aminoglycosides, aminopenicillins, vancomycin, sulbactam and quinolones. Routine investigations like Haemogram, urine culture, CSF exam and culture, X-ray chest, CRP and liver and renal function tests were done when indicated.

Results: 31 neonates developed sepsis during the hospital stay. Klebsiella was the predominant organism isolated in 25 cases (81%).Acinetobacter was isolated from 2 cases (6.5%) E-coli from 2 cases (6.5%) and Pseudomonas and Staph.aureus in one case each. All the cases that grew Klebsiella from blood had thrombocytopenia (platelet count<50,000) with the predominant presentation being purpura and upper GI bleed. Cholestasis was frequently seen associated with Klebsiella sepsis. All the isolates were uniformly resistant to aminopenicillins. Aminogylcoside resistance was also very high i.e. 90%. Cephalosporin's showed an intermediate resistance pattern with some showing 80-90 %(cefotaxime-ceftriaxone) and some showing only 30-40% resistance (cefperazone-salbactam and ceftazidime). The outbreak was caused by Klebsiella which was multi drug resistant with sensitivity only to quinolones. The number of neonates infected was thirty one and the mortality was 55%. Majorty of the neonates had thrombocytopenia and cholestasis. The outbreak was traced to a common source of an intravenous solution used for diluting drugs. Our study helped to change nosocomial infection control policy in this hospital.

Conclusion: The outbreak was caused by Klebsiella which was multi drug resistant with sensitivity only to quinolones. The number of neonates infected was thirty one and the mortality was 55%. Majorty of the neonates had thrombocytopenia and cholestasis. Our study helped to change nosocomial infection control policy in this hospital.

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INTRODUCTION

Nosocomial infections are a major problem for hospitalized patients due to increasing duration of hospitalization and costs of treatment. These infections make the treatment of patients difficult due to increasing mortality and morbidity particularly in neonatal intensive care units (NICUs).Various factors such as prematurity, low weight, prolonged hospitalization, use of broad-spectrum antibiotics, and particularly the use of invasive procedures such as intubation, ventricular shunt, intra-vascular catheter, and parenteral nutrition with fat emulsions facilitate the development of such infections, and increase their incidence. Prevention and control of nosocomial infections in NICUs will not be possible without identifying the current status of these infections and their predisposing factors.

The emergence of resistant strains of enteric gram negative bacteria has considerably jeopardized the therapeutic armamentarium against such infections and narrowed down the choices.

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There is increasing evidence that cephalosporin resistant gram negative strains are causing nosocomial infections through out the world (Waggoner *et al*., 1997; Toltzis and Blumer, 2001 and Flidel- Rimon *et al*., 1996). Information regarding clinical and molecular characterization of nosocomial outbreaks due to multiresistant strains in India is limited.

MATERIALS AND METHODS

This was a retrospective observational study carried out in NICU of a tertiary care referral pediatric hospital in Srinagar JandK,India. Total of 31 patients who developed nosocomial sepsis during the study period of 2 months were taken as subjects. The neonates whose diagnosis at admission was probable sepsis or who were obviously septic were excluded from the study. Cultures from all the newborns were obtained by sterile vein puncture technique and incubated for 24-48 hours for identification of the organism and determination of sensitivity pattern by disc diffusion method.

Antibiotics tested included cephalosporins, aminoglycosides, aminopenicillins, vancomycin, sulbactam and quinolones. Routine investigations like Haemogram, urine culture, CSF exam and culture, X-ray chest, CRP and liver and renal function tests were done when indicated. During the study period 65 neonates were admitted in the neonatal intensive care for various problems .The neonates whose diagnosis at admission was probable sepsis or who were obviously septic were excluded from the study.

RESULTS

31 neonates developed sepsis during the hospital stay and they were studied for the characteristics of the outbreak.14 of these newborns were preterm and 17 were term.80% of them were admitted in the first week of life and 20% after the first week.71% were low birth weight(<2.5Kg) on admission and 29% were >2.5Kg on admission. The sex ratio of the studied population was 68:32 male and female (Table 1).

Table 1. Patient details (total admissions 65)

		n	%
1.	Developed sepsis (infection rate)	31	47.7
2.	Gest. Age	14	
a)	Preterm	17	45
b)	Term		55
3.	Age on admission		
a)	< 7days	25	80
b)	>7days	6	20
4.	Sex		
a)	Male	21	68
b)	Female	10	32

The admitting diagnosis was asphyxia in 8(26%). Prematurity in 14(45%) meconium aspiration syndrome in 2(6.5%) neonatal jaundice in 2(6.5%) and respiratory distress syndrome in 5(16%) (Table 2).

Table 2. Diagnosis on admission

Diagnosis	n	%
Asphyxia	8	26
Prematurity	14	45
MAS	2	6.5
Neonatal jaundice	2	6.5
RDS	5	16

Cultures from all the newborns were obtained by sterile vein puncture technique and incubated for 24-48 hours for identification of the organism and determination of sensitivity pattern by disc diffusion method. Antibiotics tested included cephalosporins, aminoglycosides, aminopenicillins, vancomycin, sulbactam and quinolones. Routine investigations like Haemogram, urine culture, CSF exam and culture, X-ray chest, CRP and liver and renal function tests were done when indicated.

Klebsiella was the predominant organism isolated in 25 cases (81%). Acinetobacter was isolated from 2 cases (6.5%) E-coli from 2 cases (6.5%) and Pseudomonas and Staph.aureus in one case each .CSF culture was positive in 6 cases (19%) with all growing Klebsiella. All patients had received ampicillin and gentamicin parentally for 48 hrs after admission, which were stopped after negative septic work up and sterile blood culture reports. Single use vials were used. However the diluting solution was common. None of these patients had central catheter. All the cases that grew Klebsiella from blood had thrombocytopenia (platelet count<50,000) with the predominant presentation being purpura and upper GI bleed. Cholestasis was frequently seen associated with Klebsiella sepsis (Table 3).

Table 3. Most commonly reported pathogen and complication

Organism	Blood stream infection		CSF		Thrombocytopenia		Cholestasis	
	n	%	n	%	n	%	n	%
Klebsiella	25	81	6	19	25	81	19	61
Acinetobacter	2	6.5	–	–	–	–	–	–
Pseudomonas	1	3	–	–	–	–	–	–
Staphylococcus	1	3	–	–	–	–	–	–
E.Coli	2	6.5	–	–	–	–	–	–

The bilirubin levels in newborns ranged from 15-35mg/dl with highest rise (>20%) in conjugated levels. Enzymes were also deranged with predominant rise of alkaline phosphatase levels (>1000 i.u). Cholestasis was already present before starting treatment with quinolones. All the isolates were uniformly resistant to aminopenicillins**.** Aminogylcoside resistance was also very high i.e. 90%. Cephalosporin's showed an intermediate resistance pattern with some showing 80-90 %(cefotaxime-ceftriaxone) and some showing only 30-40% resistance (cefperazone-salbactam and ceftazidime). Vancomycin resistance was also 80-90%.Quinolones showed a good sensitivity to the isolates with ciprofloxacin and pefloxacin showing 80-100% sensitivity and ofloxacin showing 70-80% sensitivity (Table 4).

Table 4. Culture sensitivity (%) pattern of patients with nosocomial sepsis

Antibiotic	Klebsiella	Acinetobacter	Pseudomonas	Staphylococcus	E.coli
Ampicillin	0	0	0	0	0
S	100	100	100	100	100
R					
Gentamicin	12	21.4	11	10	0
S	88	78.6	89	90	100
R					
Amikacin	14	20	10	11	0
S	86	80	90	89	100
R					
Cefotaxim	32	20	10	50	0
S					
R	68	80	90	50	100
Ceftriaxone	25	18	33	22	0
S	75	82	67	78	100
R					
Oflaxacin					
S	80	82	76	80	90
R	20	18	24	20	10
P-floxacin					
S	80	76	80	73	90
R	20	24	20	27	10
Cefperazone					
S	24	30	28	30	0
R	76	70	72	70	100
Cefperazone + Sulbactum					
S	60	63	70	80	32
R	40	37	30	20	68
Ceftazidime					
S	33	40	90	36	0
R	67	60	10	64	100
Vancomycin					
S	6	28	7	100	0
R	94	72	93	0	100

Ciprofloxacin was given intravenously using 10mg/Kg/d for 14 days in septic neonates and for 21 days in those with meningitis.17 of the 31 infected neonates expired giving a mortality of 55% whereas 14(45%) were discharged home (Table 5).

Table 5. Out come of patients who developed nosocomial sepsis

	n	%
Discharged home	14	45
Expired	17	55

Infection control measures in the nursery were intensified and the nursery was closed for admission till the epidemic was over. Surface cultures from all **accessible areas in the nursery, infants, basins, solutions etc** were taken and cultured. The infection was traced to a common solution used for diluting drugs which also grew Klebsiella.

Typing was not possible in our lab. The solution was discarded and after the control of epidemic, whole nursery was fumigated. Microbiological surveillance is now regularly carried out in our nursery.8 out of the discharged patients are reporting for follow up and do not have any bony deformities or defects in linear growth that could be ascribed to quinolone use.

DISCUSSION

Nosocomial infections result in considerable morbidity and mortality among neonates. Although most Nosocomial infections are maternal in origin, an increasing proportion is being acquired in nurseries (Gaynes *et al*., 1996). Center for Disease control and prevention has arbitrarily defined all neonatal infections whether acquired during delivery or during hospital (intra partum or post partum) as Nosocomial unless known or proven to be transplacentally acquired as in CMV or Toxoplasmosis (Garner *et al*., 1988). Reported infection rate in the NICU varies from 1.8 to 39.8/ 100 admissions or discharges (Goldman *et al*., 1981). Nosocomial infections caused by gram-negative bacilli account for 18-19% of blood stream infections (Beck Sague *et al*., 1994). These infections are associated with high mortality rates ranging from 40-90%. E.coli, Klebsiella, Enterobacter cause the majority of gram negative endemic Nosocomial infection in the NICU (Gaynes *et al*., 1996; Flibel Rimo *et al*., 1996; Al-Rabeen *et al*., 1998 and Fok *et al*., 1998).

Nosocomial gram negative enteric pathogen in newborn nurseries particularly those causing epidemics often are resistant to multiple antibiotics.aminiglycoside resistance was observed early on, often due to plasmid mediated production of aminoglycoside inactivating enzymes (Toltzis and Blummer, 1995; Cook *et al*., 1980; Mckee *et al*., 1982; Savavolatz *et al*., 1984).

There is a need, therefore to scrutinize the problem so as to be able to plan for the future (Musoke and Revanthi, 2000). Neonatal intensive care units provide many portals of infection entry. There have been various reports of nosocomial sepsis traced to intravenous fluids (Ross *et al*., 1977), although anything and everything including air conditioners (Mc Donald *et al*., 1998), breast milk (Donowitz *et al*., 1981), and hand lotions (Morse *et al*., 1967) have been incriminated in causing outbreaks. Care givers contaminate their hands with pathogens, colonize the infants under their care, fail to wash their hands and inoculate new arrivals, who require pharyngeal or gastro intestinal instrumentation such as bag resuscitation, suctioning or nasogastric feeding (Mayhall *et al*., 1980).

Relationship between infection and hyperbilirubinemia is well known. Possible mechanisms of cholestasis in sepsis include changes in hepatic microcirculation,direct effects from bacteria products and effects caused by endotoxin induced mediators (Karpen, 2002). Shamir (Shamir *et al*., 2000) reported gram negative bacteremia was commonly associated with liver enzyme abnormalities in premature infants, Klebsiella accounting for majority of cases.

Pawa *et al* (Pawa *et al*., 1997) reported nosocomial sepsis with multi drug resistant Klebsiella as the infectious agent in 68% of cases. Silna *et al* (Silva *et al*., 2001) reported an outbreak of Klebsiella resistant to multiple drugs in Mexico with a fatality rate of 62%. Benerjee *et al* (Banerjee *et al*., 1993) reported septicemia due to Klebsiella pneumonia in 70% of neonates admitted in their units with multiple drug resistance in all cases.

Quinolones are a class of drugs that are currently very sparsely used in children because of concerns regarding their toxicity on bone and cartilage.However literature reports are present where they have been used in extremely compelling situations with no other choice. Our nosocomial outbreak presented a similar dilemma.

Khaneja *et al* (Khaneja *et al*., 1999) report successful treatment of resistant K-pneumonia sepsis in an ELBW infant with ciprofloxacin; other documented uses in children include meningitis by Black *et al* (Black *et al*., 1990), multidrug resistant typhoid by Cheesbrough *et al* (Chessbrough *et al*., 1991) and infectious episodes in cystic fibrosis by Black *et al* (Black *et al*., 1990).

Martell M *et al* (Martell *et al*., 1996) demonstrated that ciprofloxacin and Pefloxacin for life saving treatment of sepsis in preterm infants were not associated with osteo articular problems or joint deformities. The arthropathic problems associated with quinolones are mainly from animals studies.Quinolones offer an advantage over exciting antibiotics by effectively eradicating many multiresistant pathogens.

Conclusion

Nosocomial nursery outbreaks are a challenge to combat; gram negative organisms are the major offender's .Amongst the various incriminated factors involvement of intravenous fluids is a possibility. It is an endless struggle to combat neonatal infection.

Strict asepsis and infection control policies should be enforced and vigorously followed in nurseries. More judicious selection and use of antibiotics should be implemented. In life threatening situations where the choice is limited, quinolones offer a way out. Animal data is not in concorelance with human data with respect to quinolone induced arthropathy and significant toxicity is not common.

Conflicts of interest: None.

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