Neonatal meningitis

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ABSTRACT

Objective: To determine the prevalent bacterial agents of neonatal meningitis and their antibiotic susceptibility in a referral intensive care unit in Assir Central Hospital, Saudi Arabia, during the years 1993-1998.

Methods: Records of newborn infants with positive cerebrospinal fluid culture during the period were retrospectively studied.

Results: There were 1473 nursery admissions, of which 32 episodes of meningitis occurred amongst 31 neonates. *Klebsiella pneumoniae* (31%) and *Serratia marcescens* (21%) were the main pathogens. The incidence of concurrent septicemia among these infants was 58%. *Klebsiella pneumoniae* appears to dominate in both early and late onset infections. The sex incidence was equal and the mortality rate was 48%.

Conclusion: The survey identifies *Klebsiella pneumoniae* and *Serratia sp.* as the leading bacterial agents of neonatal meningitis in our environment. The relatively high frequency of *Serratia* infection in the present survey appears unique as this organism is comparatively rare in other reports across the globe. No *Group B Streptococcus* was isolated, which is in contrast to reports obtained in Europe, America and Australia where it is the predominant organism of neonatal sepsis or meningitis. Antibiogram identified imipenem and cefotaxime as the empirical antibiotics in infants with a clinical diagnosis of neonatal sepsis in our hospital; no more conventional use of ampicillin. In view of the changing bacterial pattern of infant infection with time even in the same environment, a periodic review of this subject is advocated.

Keywords: Neonatal meningits, bacterial pathogens, antibiotic susceptibility.

Neurosciences 2000; Vol. 5 (3): 162-165

Bacterial meningitis is known to be more common in neonates than any other age group.[1] In spite of considerable advances in antimicrobial treatment, neonatal meningitis remains a scourge with a high mortality and frequent permanent neurological sequelae. The causative agents of neonatal sepsis vary between geographical areas and with time in any particular locality. In North America and Europe, the prevalent bacterial agents of early-onset neonatal sepsis are *Group B Streptococcus* (GBS), *Listeria monocytogenes* and *Escherichia Coli* and those of late-onset sepsis include coagulase negative *Staphylococcus*, *Klebsiella sp* and *Escherichia coli*.[1-4] There have been isolated studies of childhood meningitis in the Riyadh area (Southeastern) of Saudi Arabia but none have been comprehensively focused on newborns.[5,6] To our knowledge, there has been no documented survey on neonatal meningitis from the Southwestern region of Saudi Arabia. The main focus of this survey was to determine the prevalent bacterial agents of neonatal meningitis in our environment. A foreknowledge of the bacterial pattern of meningitis is a prerequisite in formulating a most appropriate antibiotic policy in order to reduce handicap and fatality. Only neonates with positive spinal fluid culture were considered; autopsy was not conducted on any of the deceased infants.

Assir Central Hospital serves as a tertiary and referral centre for all the other 18 hospitals and 238 primary health care centres in Assir Province of

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Saudi Arabia. It is the only hospital in this catchment area with a Level III neonatal intensive care unit (NICU) though it has no maternity service of its own. The NICU is entirely a referral unit and therefore admits infants requiring specialized investigations and care from all over Assir region (population 2 million). It has a capacity to accommodate 20 patients and the unit admits an average of 250 newborns per year. There are adequate facilities for incubator care, artificial ventilation, intravenous alimentation, stand-by portable radiography, ultrasonography and CT scan. Laboratory facilities in the hospital include those for aerobic and anaerobic cultures and sensitivity among others.

Methods. The study covers a period of 6 years (January 1993 to December 1998). All the neonates with bacteriologically positive cerebrospinal fluid (CSF) cultures were first identified from the Microbiology Laboratory registers. The charts of these infants were then pulled out for a detailed study. The following data was abstracted from the charts: place of birth (home or medical institution), age at diagnosis, sex, gestational age, birth weight, management and outcome. Details on clinical features and CSF biochemistry including cell count were not studied as these were considered to be non-specific. As a unit policy, every new admission in the unit was subjected to either partial (blood and urine culture) or full (blood, urine and CSF culture) sepsis screening. Lumbar puncture was undertaken only if the infant looked ill or septic at any stage of hospitalization. Also, whenever the initial blood culture was reported as positive in any patient, it was promptly followed by a spinal tap. All cerebrospinal fluid samples were cultured aerobically using blood agar (Difco Lab. Detroit Cat. No. 0690-17) and MacConkey's agar (BBL Cat. No.11387). Bacterial isolates were characterized and identified by the conventional procedures described in Lennette et al (1985).[10] Antibiotic susceptibility testing was performed using the disc diffusion method described by Bauer et al (1966).[11] The standard reference strains, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853, were tested regularly for monitoring the accuracy and precision of the disc diffusion test. The medium used was Mueller-Hinton agar (Difco, Cat. No.02520/4).

During the period, all new admissions received a combination of ampicillin and gentamicin after sepsis work up. The infants were on this regimen for 5 days or until culture was negative. If culture was positive, treatment was later adjusted according to the isolate's susceptibility results and continued for a total duration of 2 to 3 weeks. Infants with myelomeningocoele and ventriculoperitoneal shunts were excluded from the final analysis.

Results. The total number of newborns with bacteriologically proven meningitis during the 6-year period was 31 (15 male, 16 females). The overall admission in the corresponding period was 1473; thus the incidence of neonatal meningitis in the NICU was 21 per 1000 admissions. The 31 patients (16 term and 15 preterm) had 32 episodes of meningitis. One preterm had *Klebsiella pneumoniae* followed by *Serratia meningitis* after 3 weeks. The indications for the admission of these infants were: prematurity (n = 11), major congenital malformation (n = 8), sepsis (n = 5), severe birth asphyxia (n = 3), necrotizing enterocolitis (n = 2), acute renal failure and hemorrhagic disease of the newborn (n = 1 each). In 6 of the infants the meningitis was proven to be of early onset (< 48 hours of age) while in the remaining 25 infants the infection was of late onset (> 48 hours of age) thus suggesting nosocomial acquisition. All the patients had received various combinations of antibiotics, which included ampicillin in every case, before they were transferred.

The cerebrospinal fluid of the 31 newborns yielded *Klebsiella pneumoniae* (10 or 31% of cases) and *Serratia marcescens* (8 or 25% of cases) as the most prevalent pathogens (Table 1). Eighteen (58%) of the 31 infants had simultaneous positive CSF and blood cultures as demonstrated in Table 1. The incidence of concurrent septicemia was as high as 80% with *Klebsiella* and 75% with *Serratia*. The 6 isolates of early-onset infection were *Klebsiella sp* (n = 5) and *coagulase negative Staphylococcus(CONS)*

Table 1 - Bacterial isolates (32 cases) and outcome in 31 neonates with meningitis.

Type of organism	Total number (+)		No. of deaths
Klebsiella pneumoniae	10	(8)	5
Serratia marscesens	8	(6)	6
Pseudomonas aeruginosa	3	(1)	1
Enterobacter agglumerans	2	(1)	0
Escherichia coli	2	(0)	0
Haemophilus influenza	1	(0)	1
Citrobacter freundii	1	(1)	0
Total Gram negative	**27**	**(17)**	13
CONS	3	(2)	0
Staphylococcus aureus	2	(0)	2
Total Gram positive	**5**	**(2)**	2
Grand Total	**32**	**(18)**	15

(+) cases with simultaneous septicemia in parenthesis
CONS - *coagulase negative staphylococcus*

Table 2 - Antibiogram showing susceptibility first 4 leading isolates from CSF.

Antibiotics	***Klebsiella pneumonie*** **(n =10)**	***Serratia sp*** **(n=8)**	***Pseudo sp*** **(n=3)**	***CONS*** **(n=3)**
Imipenem	94	81	52	NT
Cefotaxime	40	83	24	NT
Cefoxitin	44	14	32	NT
Ceftriaxone	4	5	7	12
Ceftazidime	5	12	10	23
Gentamicin	28	9	29	23
Amikacin	26	31	54	62
Aztreonam	26	40	39	54
Ampicillin	0	1	5	4
Ciprofloxacin	80	69	51	50
Choramphenicol	30	16	27	38
AM-CL	12	2	10	4
Vancomycin	NT	NT	NT	100
Cloxacillin	NT	NT	NT	70

NT - not tested; AM-CL - Amoxicillin-clavulanic acid; CONS - coagulase negative staphylococcus

(n = 1) which were isolated on admission.

Outcome. Fifteen of the infants died giving an overall mortality rate of 48%. The fatalities in association with *Klebsiella* and *Serratia* were 50% and 75%. Of the 16 survivors, 6 developed hydrocephalus requiring shunt insertion, 10 were discharged home without any apparent sequelae and were all lost to follow-up. The in vitro susceptibility tests results (Table 2) revealed a resistance rate of 95% and more to ampicillin by each of the prevalent pathogens of neonatal meningitis in our environment. *Klebsiella sp*, and *Serratia sp*, the 2 major isolates in this survey show 94% and 81% susceptibility to imipenem and with cefotaxime they demonstrated 40% and 83% susceptibility. Other cephalosporins and the aminoglycosides did not demonstrate any impressive activity on the isolates. The *CONS* and *Staphylococcus aureus* were 100% susceptible to vancomycin as expected.

Discussion. The study has identified *Klebsiella pneumoniae* and *Serratia marcescens* as the important organisms of neonatal meningitis in Assir Central Hospital. Since most cases of neonatal meningitis result from bacteremia, pathogens involved in neonatal septicemia are commonly the same for neonatal meningitis in a given environment.[1-3] This observation is corroborated by a parallel study (1993-1998) which also identified *Klebsiella pneumoniae* and *Serratia marcescens* as the most frequent pathogens of neonatal septicemia in the same unit. The bacterial isolates in the present study are at variance with the experience in North America,[1] Europe,[2-4] and Australia[7] where *GBS* is the leading pathogen of neonatal sepsis. This survey identified no case of *GBS* meningitis. We cannot fully explain the reason for this; probably this organism may be rare in the Assir region of Saudi Arabia or perhaps the frequent use of ampicillin in suspected cases of neonatal infection could have stifled the isolation of this organism. Interestingly, in a study of childhood meningitis, 2 separate hospitals in Riyadh identified *GBS* in 11%[5] and 57%[6] of the newborn population in their series. Neonatal infection due to *GBS* therefore may not be a rare entity in Saudi Arabia.

The relatively high frequency of *Serratia meningitis* in this survey is rather startling and noteworthy. To our knowledge, this particular organism appears to hold a very low position in the list of organisms that cause neonatal sepsis in other published series across the globe.[1-11] It therefore appears unique that this bacterial agent is comparatively so rampant in our environment. From the present survey, it appears to carry a poor prognosis for concomitant septicemia and a high fatality frequency.

Clinical examination alone cannot distinguish septicemic infants with coexisting meningitis from those without meningitis. As reported by others, 70-85% of neonates with meningitis will have positive blood culture.[1,2] The comparatively low incidence of simultaneous septicemia (58%) among the patients in our series may be a feature of a referral unit whereby the babies had received antimicrobials before they were transferred. Antimicrobial medication is capable of sterilizing the blood stream without simultaneously affecting the CSF. Nevertheless, a bacteriological diagnosis can rest on blood culture which, if positive, should be an indication for spinal tap when judged prudent and if this is not possible, the infant can be treated as if meningitis were present with 2 to 3 weeks of intravenous antibiotics.

The overall mortality rate of 48% in this series is unacceptably high even though it falls within the 20-70% figure in the literature.[1,12] This high rate in our series should not be construed as being due to infection only but should be viewed in the context of a multiplicity of factors operating in concert. The newborns in this study were admitted largely for conditions, other than infection, which carry poor prognosis; for example, all the shortcomings of severe birth asphyxia, severe congenital malformation and the concomitants of prematurity had obviously conspired to make the infants particularly vulnerable. The study is handicapped in

determining long term neurological sequelae since a majority of the cases preferred to return to their local hospitals for follow up.

The high degree of resistance demonstrated by the isolates in this survey to a majority of the antimicrobials available in our setting is rather disturbing. The indiscriminate use of antimicrobials by the referring hospitals may be an underlying cause for this. It will be interesting to know if this is the experience of other purely referral NICUs such as ours. From the antibiotic profile, it can be recommended that the traditional use of ampicillin as one of the first line antibiotics for cases of systemic infection in our NICU should be suspended. It appears imipenem and cefotaxime are the only 2 drugs worth recommending empirically for neonates in our environment with suspected sepsis or meningitis. However, in the management of meningitis, drug penetration of the blood brain barrier is an important factor hence imipenem cannot be recommended for this purpose since it penetrates poorly into the CSF even in the presence of meningeal inflammation. In contrast, cefotaxime and its metabolite, desacetyl-cefotaxime, adequately penetrates the blood-brain barrier especially with inflamed meninges.

In view of the changing pattern of bacterial agents of infection in any given environment, the findings of this study need to be reviewed periodically.

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