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An observational study for evaluation of antibiotic utilization and growing resistance against antibiotics in pediatric patients suffering from meningitis in a tertiary care hospital

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ABSTRACT

Background: Meningitis, inflammation of the meninges with systemic septicemia, from the bacterial, viral, or fungal origin, is a fatal disease in all age groups, particularly infants and children. The present study was done to evaluate the usage of antibiotics in pediatric patients with meningitis in a tertiary care hospital. **Aims and Objectives:** The study was conducted to evaluate the prescription pattern of antibiotics for pediatric patients suffering from meningitis. The efficacy of antibiotics, combination of antibiotics, and the resistance developed against them were reevaluated. **Materials and Methods:** An observational, noninterventional study with 34 pediatric patients (The mean age of the patients were 6.17 year. ±4.84 SD) admitted in Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar from September 2012 to February 2014 were evaluated. Data were collected after the approval of the research protocol by the Institutional Ethics committee, KIMS from case sheets of patients from the ward as well as the Medical Record and Data section. Comparative statistical analysis was done by using student's t-test in respect of data measured on a continuous scale. All differences with $P<0.05$ were labeled as statistically significant. **Results:** Ceftriaxone ± ß lactamase inhibitor (βLI) (77.4%), and Cefoperazone ± βLI (12.9%) were the most frequently used cephalosporin. In 55.8% of patients, three or more antibiotics in combination were given. Two drugs regimen like β lacatam + aminoglycoside in 23.5% of patients and β lactam + anti-Methicillin-resistant *Staphylococcus aureus* (MRSA) in 20.6% were given. Emerging resistance pattern against both Gram-positive cocci and Gram-negative bacilli to penicillins, cephalosporins, and aminoglycosides which are the primary first-line drugs has been observed. **Conclusion:** Very severe meningitis patients were treated with multiple antibiotics including anti-MRSA agents. High resistance (≥60%) was observed against β lactams.

Key words: Meningitis; Antibiotics; Resistance; Pediatric patients

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INTRODUCTION

Meningitis is a very serious infection of the meninges that surround the brain and the spinal cord. It is usually caused by viral, bacterial, or fungal pathogens. Aseptic meningitis predominantly is caused by viruses, usually is a diagnosis of exclusion based on the lack of bacterial findings, and generally has lower rates of case fatality and neurologic sequelae.

Bacterial meningitis can be quite severe and may result in brain damage, hearing loss, or learning disability, and death if not treated early. Bacterial meningitis is a medical, neurologic, and sometimes neurosurgical emergency that requires the multidisciplinary approach of treatment.[1]

The clinical presentation of meningitis in newborn infants is frequently nonspecific, and spinal fluid abnormalities may be difficult to differentiate from values typically seen

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in newborn infants.[2] Signs of meningeal irritation like the Kernig sign or Brudzinski sign are less prominent than in adults in infants and young children. Although the rate of disease associated with meningitis is lower than other major causes of childhood, mortality there are high case fatality rates and neurologic sequelae in survivors.[3]

Aims and objectives

1. To evaluate the prescription pattern of antibiotics for pediatric patients suffering from meningitis.
2. To evaluate the efficacy of antibiotics, combination of antibiotics, and the resistance developed against them.

MATERIALS AND METHODS

Within the study period from September 2012 to February 2014 about 34 patients have been evaluated. Data were collected from case sheets of patients from the ward as well as the Medical Record and Data section of the Indoor patients receiving antibiotics along with supportive medications with provisional or confirmed diagnoses of Meningitis. Patients admitted in the pediatric ward, Pediatric intensive care unit and Neonatal intensive care unit with a provisional diagnosis of meningitis were included. Clinical signs with cerebrospinal fluid (CSF) positive gram stain, CSF cytology, and CSF culture were considered to include a patient.[4] Among the included patients who died or Discharged on Risk Bond within 48 h after admission were excluded. CSF gram stain, culture and sensitivity (C/S) and cytology were done after lumbar puncture (LP) routinely. CSF for viral marker or latex agglutination test (LAT) to detect bacterial antigen were done in the significant number of patients.[4,5] Routine blood count, Chest X-ray, were done in every patient. Computerized tomography (CT) scan of the brain was done in suspected patients of raised intracranial pressure (ICP).[6,7] Blood c/s, urine c/s were done when required. Electroencephalography were done when seizure develops in meningitis or sepsis patients. Fundoscopy was done before LP in meningitis patients to detect papilloedema due to increased ICP.[8] Audiometry[9] in most of the patients and brain-stem evoked auditory response (BERA)[10] in a few cases were done to detect sensorineural hearing impairment at the time of discharge from hospital.

RESULTS

Among the 34 patients there were 29 male patients and 5 female patients (M: F=6:1). Mean age of the patients= was 6.17 years. ±4.84 (SD). Mean weight =19 kg±12.16 (SD). The mean duration of stay in the hospital = 10 days. ±6.11 (SD).

The maximum density of cases in respect of time was found in the age group of 1 month-1 year (23.5%). Similar findings (44.4%) were seen in the age group of 1 month to 1 year in a study done by Tajdin et al.,[11] 11.7% of patients were within the neonatal age group, 14.8% of patients observed in age group 1–5 year, 26% in the age group 5–10 years and 24% in the age group >10 years. The preponderance of male patients suffered from pyogenic meningitis compared to females, a finding reported by other study was observed in our study also (M: F=6:1).

It has been evaluated that along with meningitis about 26.7% patients had sepsis, 13.3% patients had pneumonia and 3.3% patients had co-existing illness like malaria. The patients included were mostly suffering from bacterial meningitis (76.4%). 20.5% of patients were of aseptic meningitis while TB meningitis patients were very few (2.9%).

Clinical presentation of meningitis in pediatric patients[1-3] are often less prominent than in adults. Fever was present in 70% of patients. Headache and vomiting were present in about 40% of patients. Lesser number of children than adults usually develop Kernig's or Brudzinski's sign and neck rigidity.[12] In our study, a total of 53% of patients had at least any one of the meningeal signs +ve (either of neck rigidity/Kernig/Brudzinski). 13% of children were in the stage of shock during admission. 6.7% of children presented with altered sensorium. 10% of children had raised ICP with bulging anterior fontanelle.

Blood culture was done in 18 (60%) patients. Among them, in 9 (50%) patients, the sample was taken after the patient has received at least the first dose of antibiotic. In 4 (22.2%) cases the culture was positive. Urine culture was done in 9 (30%) patients. Among them, 7 patients had received at least the first dose of antibiotic, before the sample was collected. One pathogen was isolated, however. Bacterial meningitis usually leads to a neutrophil predominance in CSF, typically between 80% and 95%; however low neutrophil count found in our study (Table 1). CSF polymerase chain reaction for the viral marker was done when there was suspicion of viral meningitis.

Different species of Staphylococci (4) were predominantly found in Gram-positive isolates. Among Gram-negative bacteria, *Enterobacter* (1) from CSF culture and *Neisseria meningitidis* Antigen (1) was detected in CSF by LAT. CSF culture positivity in our study was 2 from 34 patients (5.8%). Among these 34 patients, in the case of 25 patients I.V. antibiotic was administered before LP was performed .CSF samples from 13.94% of patients were positive on culture in a similar study done by Modi et al.[13] Several studies from India report culture-negative cases of meningitis or a low CSF culture positivity, ranging from 6% to 50%.[5] Culture and gram stain were positive in 7 (14%) and 4 (8%) cases of bacterial meningitis, in another study done by Fitzwater

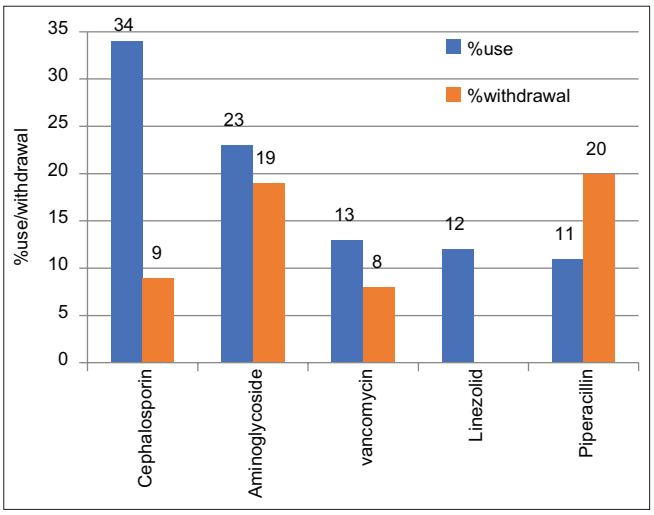

Figure 1: % usage of different antibiotics and % of discontinuation

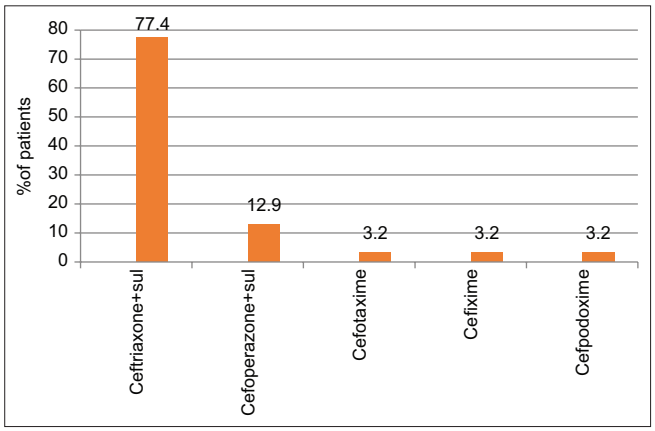

Figure 2: Use of different types of cephalosporin in meningitis

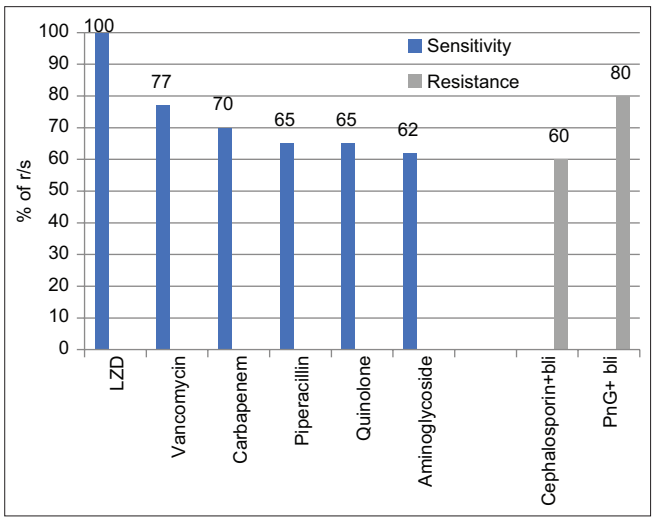

Figure 3: Sensitivity/resistance pattern seen in gram +ve isolates

et al.[3] In our study, CSF culture and gram stain are positive in 5.8% and <5% cases. Blood C/S and urine C/S were done in 18 and 9 patients, respectively. Among them in blood c/s 4 samples (22%) and in urine c/s 1 sample (11%) were positive. Being a tertiary care hospital, most of the referred patients from other hospital where treatment was started, received antibiotics. Low positivity of CSF culture could be due to this reason. Meningitis being an emergency infective condition, combination of antibiotics were given aggressively by I.V (intravenous) route.[14,15] Different types of Cephalosporins (34% of total antibiotic use) are the most frequently used antibiotics followed by Aminoglycoside (23%), Vancomycin (13.2%), Linezolid (12%), and Piperacillin (11%) (Table 2).[14]

Vancomycin was discontinued in 8.3% of the total no of use. Stoppage of other antibiotics are: Piperacillin (20%), Aminoglycoside (19%), and Cephalosporin (8.8%) (Figure 1).3rd generation Cephalosporins were mostly used, among them Ceftriaxone±ß lactamase inhibitor (βLI) (77.4%) were the most frequently used antibiotic. Its use was restricted in patients <3 months of age due to fear of hyperbilirubinemia. Cefoperazone±βLI (12.9%) was the second most frequently used antibiotic. Cefotaxime, cefixime, and cefpodoxime (3.2%) were used in a few cases (Figure 2). Injection (Inj) Amikacin was the most frequently used aminoglycoside. These combinations of antimicrobials used are categorized into 4 groups

A. β-lactam+aminoglycoside n=8
   In 8 patients (23.5%) β-lactam+aminoglycoside was used.
B. anti-Methicillin resistant *Staphylococcus aureus* (MRSA)+β-lactam n= 7 (20.6%)
C. β-lactam+aminoglycoside+anti-MRSA n=13 (38.2%)
D. β-lactam+aminoglycoside+macrolide/quinolone n=6 (17.6%).

DISCUSSION

In 25 (78%) patients, the CSF sample was collected after the patient has received the first dose of antibiotic. Fundoscopy was done routinely before LP to detect papilledema (due to raised ICP and to prevent cerebral herniation). CT or Magnetic resonance imaging (MRI) was done before LP in suspected cases of raised. ICP to detect any space occupying lesion, cerebral abscess or herpes simplex encephalitis. However, in severe meningitis cases when improvement was not obtained after considerable period of antibiotic administration, CT or MRI was also done to detect underlying pathology.[6] Most of the patients were examined by audiometry and BERA to rule out any sensorineural hearing loss due to meningitis[9] before discharge. It takes 24–36 h after administering the IV antibiotic for CSF sterilization. When clinical improvement was not satisfactory, LP and CSF culture was repeated.[5,8] In patients of very severe bacterial meningitis who presented with shock with altered sensorium, neck rigidity with

Table 1: CSF cytology of present study

CSF cytology	Normal value	Bacterial meningitis (mean±SD)	Aseptic meningitis (mean±SD)
WBC count	0–5/μL	285.7±222.45	21.33±8.14
Neutrophil	0%	27.7±22.17	17.5±10.4
Lymphocytes		72.2±22.17	88.33±10.41
Protein	15-45 mg/dl	43.72±15.85	24.6±3.19
glucose	40-70mg/dl	64±13.15	73.6±23.67

CSF: Cerebrospinal fluid

Table 2: Use of β-lactam+aminoglycoside

β-lactam+aminoglycoside	Use (%)
a. Cephalosporin+aminoglycoside	7 (20.5)
b. Piperacillin+aminoglycoside	1 (2.9)

Table 3: Use of anti-MRSA

Antibiotics	Use (%)	From starting (%)	Added later (%)
Vancomycin	10 (33.3)	9 (26.5)	1 (2.9)
Linezolid	7 (23.3)	4 (11.7)	3 (8.8)

MRSA: Methicillin-resistant *Staphylococcus aureus*

the positive meningeal sign, seizure, hypothermia with unfavorable CSF findings, were treated aggressively with multiple of antibiotics. 3rd generation Cephalosporin (ceftriaxone/cefotaxim/cefoperazone±βLI) or injection (inj) Piperacillin+tazobactum with anti-MRSA agents like inj Vancomycin or Injection Linezolid in combination were most frequently used for multidrug resistant strain[16,17] along with injecton Dexamethasone. Inj Clarithromycin and injection Ciprofloxacin were given to 2 patients with β-Lactam+Aminoglycoside. Syp Clarithromycin was added in a few cases. Anti-MRSA agents were started initially along with β-Lactam in 13 patients with severe bacterial meningitis, among them injection Vancomycin in 9 patients and inj Linezolid in 4 patients (Table 3). Injection Vancomycin/Linezolid is recommended to be started empirically with β-Lactam±Aminoglycoside in severe bacterial meningitis infection where Gram-positive bacteria like different species of staphylococcus are predominantly prevalent and resistance to 3rd gen. Cephalosporin was anticipated.[18-20] In about 9 patients Aminoglycoside was combinedly used with anti-MRSA and β-Lactam. In 4 patients anti-MRSA agents were added later on when Gram-positive cocci were found.

In one patient Neisseria Ag was detected by LAT of CSF. Vancomycin was discontinued in that patient. In a patient with history of TB meningitis, injection Vancomycin+inj Meropenem+inj Chloramphenicol were given with ATT. Inj Metronidazole was used in a few patients for anaerobic coverage. IV acyclovir was used in patients suffering from aseptic meningitis in a similar study by Tajdin et al.[11] β- lactam+aminoglycoside+anti-MRSA was found to be used in 7% patients (our study it is 38%), β-lactam+anti-MRSA was used in 59% patients (our study it is 17.6%), β-lactam+aminoglycoside was used in 22% (our study it is 23%). A combination of two β-Lactams (Ceftriaxone+Benzyl-penicillin) was used in 12.5% of patients in similar study by Tajdin et al.,[11] in our study this combination was not used. In about 60% patients in our study empirical use of Aminoglycoside, for synergistic activity, was observed (in combination with other drugs). Amikacin can be used in meningitis due to Gram-negative bacilli like *Escherichia coli*, *Enterobactor,* etc. as well as in Gram-positive cocci infection. In our study, significant sensitivity against both Gram-positive cocci (60%) and Gram-negative bacilli for Aminoglycoside was observed. Therefore, the use of Aminoglycoside in different combinations (like β-Lactam+aminoglycosie±anti-MRSA) has been appropriate and effective. When the sensitivity of isolated bacteria to β-Lactam (or anti-MRSA) is confirmed then Aminoglycoside can be discontinued from the combination therapy to avoid unnecessary toxicity.[21] In our study, Aminoglycoside were withdrawn in 19% of total use when the isolated bacteria had shown sensitivity to β-lactam. In our study, high resistance observed against commonly used antibiotics are: Cephalosporin, co-trimoxazole, and macrolide Quinolone, Penicillin (no of c/s reports were very few for statistically percentage calculation). The sensitivity observed: linezolid(100%),vancomycin(75%) and aminoglycoside(60%). In other study by Khan et al.[22] The pattern of sensitivity against Gram-positive cocci observed: vancomycin(100%),aminoglycoside(84%),fluo roquinolone(75%),macrolide(48%),cephalosporin (42%) and Penicillin(30.6%).

Very few Gram-negative bacteria were isolated in our study namely *Enterobacter* and *N. meningitidis* showing high resistance against Penicillin and Cephalosporin.

Considerable sensitivity was observed to Imipenem, Aminoglycoside, Piperacillin, and Quinolone. In a similar study,[22] sensitivity of Gram-negative bacteria observed to Imipenem (100%), Aminoglycoside (75%), Cefotaxime (68%) Cefoperazone-sulbactam (60%), Fluoroquinolone (62.5%), and Co-trimoxazole (52%) (Figure 3).

Thus, in two similar studies[22,23] along with our study demonstrate the emerging resistance pattern against both

gram +ve cocci and Gram-negative bacilli to Penicillins, Cephalosporins and Aminoglycosides which are the primary 1st line drugs in such condition.

Dexamethasone is used frequently in severe cases of pyogenic meningitis in anticipation to lessen neurological complications. In many clinical trials dexamethasone was observed to lessen the severity of infection and decrease the stay in the hospital. Steroids are given before or at the same time of receiving the first dose of antibiotic. In few clinical trials improved neurological sequelae was observed in severe meningitis cases, particularly those suffering from *Streptococcus pneumoniae* and *Haemophilus influenzae* patients.[24,25] Here, 46% of patients who were suffering from severe meningitis, received the dexamethasone whereas 54% who were suffering from the moderate grade of meningitis did not receivedexamethasone. The group who received dexamethasone have a mean duration of hospitalization 13.4 days and that of non-dexamethasone receiving group of 7.6 days. To know if there is any statistically significant difference between two means, students t-test was applied. It was found that the first group had significantly longer duration of hospitalization than the second group ($P<0.05$). It can be concluded that the administration of dexamethasone might have decreased the neuronal damage but did not have a significant effect to decrease the duration of hospitalization. Again, Injection of Dexamethasone was applied to those very very severe meningitis patients with an obvious prolonged course of ailment and Inj Dexamethasone was of little help to lessen the duration of hospitalization.[24]

Limitations of the study

No of patients are less. More no of patients to be evaluated.

CONCLUSION

CSF culture positivity in our study was 2 from 34 patients (5.8%). Among these 34 patients, in case of 25 patients I.V. antibiotic was administered before L.P was performed. Being a tertiary care Hospital, most of the referred patients from other Hospital where treatment was started, received antibiotics. Low positivity of CSF culture could be due to this reason. Most of the patients were examined by audiometry and BERA to rule out any sensori-neural hearing loss due to meningitis[9] before discharge. In a similar study[11] β-lactam+ aminoglycoside+ anti-MRSA was found to be used in 7% patients (our) study it is 38%), β-lactam+anti-MRSA was used in 59% of patients (our study it is 17.6%), β-lactam+aminoglycoside was used in 22% (our study it is 23%). Combination of two β-Lactams (Ceftriaxone+Benzyl- penicillin) was used in 12.5% of patients in a similar study,[11] in our study this combination was not used. In about 60% of patients in our study empirical use of Aminoglycoside with β-lactam, for synergistic activity. Like two similar studies[22,23] our study demonstrates the emerging resistance pattern against both gram +ve cocci and Gram-negative bacilli (>60%) to Penicillins, Cephalosporins, and Aminoglycosides which are the primary 1st line drugs in such condition. Here, 46% of patients who were suffering from severe meningitis, received the dexamethasone. However, the beneficial effect of steroids on neurological sequleae could not be evaluated due to incomplete data.

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SB- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data and statistical analysis, manuscript preparation and submission of article; **AG-** Design of study, statistical analysis and interpretation; review manuscript.

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