

## **RECENT TRENDS IN THE MANAGEMENT OF ACUTE BACTERIAL MENINGITIS**

Acute bacterial meningitis (ABM) continues to be a major life-threatening illness in children. Although the introduction of new antimicrobial agents has had an impact, the outcome of meningitis has not improved appreciably. Recent research on animal models has given a significant insight into the pathogenesis which may, hopefully, lead to the development of innovative modalities for the management of meningitis. The management issues that currently confront us in our endeavour to reduce the morbidity and mortality of ABM are: early diagnosis, choice of initial antibiotics, use of adjunctive anti-inflammatory agents, effective supportive therapy including role of fluid restriction and the role of neuroimaging.

### **Diagnosis**

Prompt diagnosis is the cornerstone for effective management. The clinical features of meningitis are often non-specific, especially in infants. A lumbar puncture (LP) performed at the earliest suspicion is, therefore, important for making a presumptive diagnosis and starting treatment. This is based mainly on the finding of CSF polymorphonuclear leukocytosis and hypogly-

corrachia. Care must be taken to examine the CSF soon after doing the LP as the cell count tends to fall over a period of time and may be falsely low after 30-60 min. The cell count is best done by manual methods as electronic cell counters are inaccurate below counts of 1000 cells/cu mm. The normal CSF of children contains less than 6 WBC/ml and in 95%, there are no polymorphonuclear leukocytes(1). Thus, the presence of even a single polymorph may be regarded as abnormal in a febrile child, to initiate therapy pending the results of CSF culture(2). In neonates the average WBC count in the CSF is  $8/\mu\text{l}$  (range 0-32), 60% of which may be polymorphs(3). A CSF cell count of  $>20/\mu\text{l}$  and/or polymorphs  $>5/\mu\text{l}$  are considered abnormal(4). As there is a considerable overlap of all CSF indices between infected and non-infected neonates, it is advisable to treat whenever the CSF parameters are suggestive of ABM. It must be remembered, that in the early stages of ABM, the CSF may be normal or may at times show lymphocytosis and also that cases of aseptic meningitis may have 30-90% polymorphs in their initial CSF. A normal initial LP does not exclude ABM, and in the presence of a strong clinical suspicion, it should be repeated few hours later.

Hypoglycorrachia is present when CSF glucose value is less than 50-60% of blood glucose in the older child and less than 75% in the neonate. In any case, a CSF glucose less than 40 mg/dl is considered definitive hypoglycorrachia. Blood samples for glucose estimation must be drawn before the LP as the procedure may result in elevation of blood glucose levels.

Gram stain of the CSF, if done properly

by an experienced person, is a highly sensitive and specific, rapid and cheap bedside diagnostic test. Fluorescent staining of bacterial DNA with acridine orange may show the bacterial morphology in cases where the Gram stain is negative(5).

The LP may have to be withheld or delayed in children with signs of raised ICP and/or focal deficits because of the risk of brain herniation. Control of intracranial pressure (ICP), and a CT scan is required before doing the LP. Postponement of the LP is also indicated in children with hemodynamic instability, local infection at LP site, or DIC, until the conditions are managed and the procedure can be tolerated. *However, the treatment of ABM must be started immediately, without waiting for the LP.* Administration of few doses of antibiotics does not appreciably alter the results of the LP(2,5). The Gram stain and culture positivity yield may however be reduced. As blood cultures reveal the bacterial pathogen in >80% cases of untreated meningitis, these should be drawn before initiating antibiotic therapy(2,5).

The definitive etiologic diagnosis of meningitis is made by isolation of organisms from cultures of the CSF. Even a cytologically and biochemically normal CSF, presumably done in the early stage of ABM, may grow bacteria. Hence, culturing of all CSF samples is important. A survey of ABM in our country revealed isolation of causative organisms in only 15.8%(6). The causes of such a poor yield are non-availability of CSF culture facilities round the clock, delayed and faulty inoculation of CSF in culture media, and majority of cases having received antibiotics before hospitalization and LP. Some improvement in yield can be achieved by direct plating of CSF.

Culture results take at least 24-48 hours. Rapid diagnostic immunological tests are useful for quick detection of bacterial antigen or antibody even in partially treated cases. The antigen does not disappear rapidly after killing of the bacteria, and may persist for few days after antibiotic therapy.

Latex particle agglutination (LPA), countercurrent immunoelectrophoresis (CIEP), enzyme-linked immunosorbent assays (ELISA) and coagglutination (CO) tests detect bacterial antigen. The diagnostic yield of these tests has been variably reported from 45-97%(7). It increases when the CSF, blood and urine are examined concomitantly. The LPA is more sensitive than CIEP especially in detecting PRP antigen of *H. influenzae* b(2). However, false positive results are not uncommon, and negative results do not exclude meningitis. Specific antibody detection tests are available for anti PRP antibody of *H. influenzae* and IgM antibody to *N. meningitidis* Group A. The Indian experience in this area is limited(7,9). The cost of these tests prohibits their routine use in our country. They may have a useful role in partially treated cases and where the Gram stain is negative.

### **Antibiotic Therapy**

It is imperative to start early and adequate antibiotic therapy sometimes even before the results of CSF examination become available. The initial regimen has to be broad enough to affect all the likely pathogens anticipated according to the age of the child. Even though Gram stain smears or immunological tests may indicate a specific pathogen, broad-spectrum therapy is started until results of culture and sensitivity are available.

### ***Birth to 3 months age***

In neonates a combination of penicillin

and an aminoglycoside—generally ampicillin and gentamicin or amikacin have been conventionally used. This has been based on the bacteriological profile of ABM in this age group as seen in Western countries. This includes group B Streptococcus, *Listeria monocytogenes* and Gram negative pathogens. From the limited data available from our country, Group B streptococcus and *Listeria* are not significant pathogens whereas Gram negative organisms are the commonest(6). Ampicillin along with an aminoglycoside has been an effective regimen. However, recently, due to the emerging resistance of Gram negative organisms to ampicillin, and reduced sensitivity to aminoglycosides, we have switched over to using a third generation cephalosporin either alone or in combination with aminoglycosides. Cefotaxime is preferred in neonates, both because it has been used more extensively and because it is not excreted by the bile(2). Infants 1-3 months of age may have pathogens commonly encountered in the neonatal period or those seen beyond the neonatal period. Indian data shows that most cases of ABM in this age group also are caused by Gram negative organisms(6). Hence, the same regimen as for neonates is recommended.

#### ***Beyond 3 months of age***

The main causative organisms are meningococcus, pneumococcus, and *H. influenzae*; sometimes Gram negative bacilli and staphylococcus. *H. influenzae* is rarely seen after 5 years of age. A combination of ampicillin 300-400 mg/kg/day (or penicillin 3,00,00 U/kg/day) and chloramphenicol 75-100 mg/kg/day has traditionally been used. The use of ampicillin and chloramphenicol has been dictated by the need to cover *H. influenzae* type b which may be resistant to either one of these antibiotics. However,

resistant *H. influenzae* is rare in our country. Chloramphenicol has the advantage that it can be used orally after the initial 3-4 days of IV therapy, when the child can tolerate oral feeds. It may be noted that a study from Delhi has found the use of chloramphenicol alone as initial therapy to be as effective as the combination of penicillin and chloramphenicol, with fewer side-effects(10). Multicentric data are, however, needed before a general recommendation can be made.

#### ***Newer Antibiotics***

In developed countries, third generation cephalosporins are now the preferred initial antibiotics for meningitis. Both cefotaxime (150-200 mg/kg/day) and ceftriaxone (100 mg/kg/day) are effective against most of the bacteria causing meningitis, including multiple resistant *H. influenzae* type b and penicillin resistant pneumococcal strains(2,5). The advantage of ceftriaxone is its once a day dosage. Due to their cost, it may not be possible to use them as first line antibiotics in all cases of meningitis in our country. They would, however be preferred in Gram negative ABM, and if affordability is not a problem. Aztreonam, a synthetic monocyclic B lactam antibiotic has also been shown to be effective against Gram negative pathogens, with good penetration into CSF. Improvement in outcome has not yet been documented.

At times specific conditions or clinical clues towards specific organisms may warrant a change in the initial empiric therapy, viz., cover for staphylococcus in children having meningitis with CSF shunts, and use of ceftazidime for suspected pseudomonas in nosocomial infections and immunocompromised children.

#### ***Subsequent Antibiotic Therapy***

Once the organism is isolated, specific

antibiotic therapy can be used according to its sensitivity. A minimum of 14-21 days therapy is needed for neonates and 10-14 days for older infants and children. The period may need to be extended as a result of complications.

Repeat CSF examination either during, or prior to cessation of therapy, is not needed if the child responds appropriately. It should be done only if the clinical course indicates reason to doubt effectiveness of therapy.

### ***Adjunctive Therapy***

An improved understanding of the pathophysiology of meningitis(11,12) has focussed attention on non-antibiotic management in search for a better outcome. Research has shown that much of the cellular damage in meningitis results from the release of toxic inflammatory mediators from macrophages, astrocytes and microglia in response to bacterial products and circulating endotoxin. CSF levels of endotoxin, interleukin (IL-1) and tumor necrosis factor (TNF) correlate with an adverse outcome. It is of particular concern that levels rise further following the administration of antibiotics(13).

The consequences of the inflammatory reaction, *viz.*, severe cerebral edema, raised intracranial pressure, and reduced cerebral blood flow (CBF) with loss of autoregulation further add to neuronal injury. It is hoped that severe and irreversible neuronal injury may be prevented by modalities directed at interrupting the inflammatory cascade and timely correction of raised ICP and cerebral edema.

### ***Steroids***

The efficacy of dexamethasone in

reducing brain water content, CSF pressure, pleocytosis and lactate concentration, TNF activity and other indices of meningeal inflammation has been proven in animal studies(12) and has formed the basis of several clinical trials. It is now recognized that dexamethasone when used in the initial stages of ABM, concomitantly with antibiotics, reduces the incidence of neurologic and/or audiologic sequelae of meningitis due to *H. influenzae* and probably also pneumococcus(14,15). A dose of 0.15 mg/kg of dexamethasone is given IV along with antibiotic administration, and repeated every 6 hourly for 4 days. In the rare (<1%) instance of gastrointestinal bleeding, steroids should be stopped(2).

### ***Pentoxifylline***

This is a phosphodiesterase inhibitor which decreases adherence of leukocytes to endothelial cells, reduces production of superoxide and other toxic oxygen radicals and attenuates the release of proteolytic substances from neutrophils. It also suppresses JNF production, and has been shown to reduce meningeal inflammation in animals(16).

Non-steroidal anti-inflammatory agents including indomethacin, monoclonal antibodies (anti-endotoxin, anti-TNF, anti-IL-1B, and anti-CD), oxygen radical scavengers and pharmacologic agents to modulate intracellular calcium flux are other areas of active research. Applicability of these modalities in human beings has yet to be established. The use of human intravenous immunoglobulin may be important in neonates and immune deficiency states.

### ***Supportive Therapy***

This is particularly directed at control of raised ICP and seizures, and ensuring hemo-

dynamic and metabolic stability. Repeated evaluation during the first 48-72 hours is essential. A rapidly progressive or complicated course, deep coma, intracranial hypertension, shock or DIC warrant admission to the Pediatric Intensive Care Unit (PICU), and expeditious management (17). One of the important issues currently under discussion is that of fluid therapy.

### **Fluids**

The frequent occurrence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in meningitis has led to the recommendation of giving restricted fluids during the initial stages of the disease(2,5). However, this concept is now being questioned. Powell *et al.* (18) assumed that children with meningitis have hypovolemia, and should therefore receive normal maintenance plus replacement fluids. This was based on the finding that these patients had high plasma arginine vasopressin (AVP) levels which rapidly normalized after IV administration of sodium and fluids equal to 1.4 times maintenance requirements. However, no direct proof of hypovolemia in meningitis has ever been presented. On the other hand it has been clearly shown that a majority of these patients have increased body water and extracellular fluid (ECW), which correlates with the severity of the disease(19). At the same time, however, our studies have not shown any benefit of fluid restriction on the outcome of meningitis, even in those with SIADH(20,21). It is possible that the increase in ECW is a compensatory response to reduction in cerebral flow and selective hypoperfusion of the cortex(19). Restriction of fluids could then have adverse effects on hemodynamic stability and cerebral blood flow and might lead to cerebral ischemia and more

sequelae. Indeed, in experimental meningitis in rabbits, fluid restriction has been shown to cause lowering of mean arterial blood pressure as well as cerebral blood flow and increase in CSF lactate(22).

The last word on fluid administration has yet to be said. It might be prudent to administer enough fluids to maintain normal blood pressure and thereby achieve adequate cerebral perfusion. All manipulations of fluids and electrolytes must be accompanied by careful monitoring of the hydration status, hemodynamic variables, and plasma and urine electrolytes and osmolarity.

### **Role of Neuroimaging**

Ultrasonography in infants with open fontanelle is being increasingly used as an important tool for early detection and monitoring of complications especially cerebral edema, and ventriculitis(23,24). It also has a therapeutic role in doing guided aspirations of ventricular fluid and brain abscesses, and shunt placements. It may, however miss subdural effusions and infarcts(25). CT scan is needed where the sonographic findings are doubtful. In older children, a CT is indicated whenever the course is complicated, *viz*, significant and persistent raised ICP, focal seizures or deficits, increasing head circumference, and unexplained high and/or prolonged fever.

### **Conclusions**

Management of meningitis warrants immediate and appropriate antibiotic therapy, judicious use of dexamethasone, and effective supportive therapy to control raised ICP and seizures. The traditional concept of fluid restriction needs re-examination. A consistent aggressive approach towards management of raised ICP and the use of therapeutic agents targeted against

the inflammatory cascade are expected to improve the outcome of this serious disease.

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