Role of Dexamethasone in Acute Bacterial Meningitis in adults

T. Ahsan,M. Shahid,T. Mahmood,R. Jabeen,U. Jehangir,M. Saleem,N. Ahmed,A. Shaheer (Medical Unit 2, Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi.)

Abstract

Objective: To evaluate the role of dexamethasone as adjunctive therapy in adult acute bacterial meningitis (ABM) in two groups of patients treated with antibiotics alone or a combination of antibiotics and dexamethasone. Design: Systematic sampling interventional open cohort study.
Setting: Department of Medicine (Medical Unit II), Jinnah Postgraduate Medical Centre, Karachi.
Patients: Sixty eight patients aged 12-85 years admitted in Medical Unit II and diagnosed to have ABM. Patients were divided into two groups. Group A received anti-microbial therapy for 14 days (a combination of benzyl penicillin 6 million units IN 6 hourly and chloramphenicol 1 gm IN 6 hourly) and group B received the same antimicrobial therapy with dexamethasone 0.6 mg/kg/day in 3 divided doses for 4 days.
Main Outcome Measures: Differences in mortality and morbidity in the two groups and differences in the CSF inflammatory parameters between the two groups of patients.
Results: There was early resolution of fever, headache and altered consciousness in group B as compared to group A. Cranial nerves involvement was lower in group B. There was no difference in the occurrence of other focal neurological deficits between the two groups. CSF inflammatory parameters (glucose, protein and WBC count) were significantly better in group B by day 5. No complications attributable to dexamethasone were seen in group B.
Conclusion: There was early resolution of symptoms and CSF inflammatory parameters in the group that received dexamethasone as adjuvant therapy. Mortality was lower in the group treated with dexamethasone but the difference was not statistically significant. Dexamethasone should be administered to all adults patients with ABM(JPMA 52:233;2002).

Introduction

Pyogenic Meningitis is a dreaded disease not only because of its mortality but also because of its long term morbidity. Dexamethasone is used as adjunctive therapy in many infectious and inflammatory disorders to improve the ultimate outcome of treatment. Although routinely used for tuberculous meningitis, its role in pyogenic meningitis in adults is not defined. Inflammation of the subarachnoid space is largely responsible for the pathological consequences and clinical features of bacterial meningitis including increased permeability of blood brain barrier (BBB), cerebral oedema, increased intracranial pressure, cerebral vasculitis, loss of auto-regulation of cerebral blood flow, cortical hypoxia and CSF acidosis[1,2]. Subarachnoid space inflammation is induced by certain bacterial constituents. These pro-inflammatory agents include gram positive cell wall peptidoglycans and teichoic acid and endotoxins of gram negative bacteria. These constituents induce inflammation through the release of various inflammatory cytokines within the CSF, such as interleukin (IL)-IB , tumour necrosis factor (TNF), IL-6 and platelet activating factor[3,4]. CSF is an area of impaired host resistance due to the virtual absence of antibodies and complement. This allows rapid bacterial proliferation. Brisk bacteriolysis after the administration

of bactericidal antibiotics may accelerate the release of pro-inflammatory cell wall components into the CSF. Increased cytokine production ensues and thus exacerbates inflammation with its patho-physiological consequences. Antibiotic therapy therefore has the potential for exacerbating the consequences of CSF infection. Administration of glucocorticoids as an anti-inflammatory agent to ameliorate these effects of infection has been evaluated by many groups particularly in children[5-10].

This study was undertaken to determine the role of dexamethasone in all adult cases of ABM at the very outset, in order to minimize the short and long term sequelae of ABM.

Methodology

Study design

This was an open, interventional cohort study conducted in Medical Unit II of Jinnah Postgraduate Medical Centre, Karachi over a period of 2 years from May 1998 to April 2000. This is a 50 beded unit which receives medical patients on every third day. All patients admitted with a clinical diagnosis of ABM subsequently confirmed by a lumbar puncture and CSF examination, were included in the study. A total of 68 patients were recruited over a 2 year period. Exclusion criteria were gram negative septicemia shock or meningococcaemia; previous history of seizures (> 1); pre-existing focal neurological deficit; concomitant debilitating disease; conditions requiring immuno-suppressive therapy; conditions requiring cytotoxic chemotherapy; patients with contraindications to steroid therapy and pregnancy. Four patients of ABM were excluded, from the study; 3 had meningococcal septicemia; and 1 had severe chronic obstructive pulmonary disease (COPD).

Systematic sampling was done in which every alternate patient was assigned to either group A or group B irrespective of their age, sex or disease severity.

Treatment protocol

Group A

Patients assigned to group A received a combination of benzyl penicillin in a dose of 6 million units I/V 6 hourly (after giving a test done of 0.1 ml s/c) and chloramphenical I g I/V x 6 hourly. In case of penicillin hypersensitivity, ceftriaxone 2 g twice daily intravenously was substituted. Antibiotics were reviewed appropriately after culture and sensitivity reports were received. The minimum duration of treatment was 14 days. Chloramphenicol was discontinued if gram negative diplococci were identified in CSF smear.

Group B

Patients in this group were given the same antibiotic regimen and additionally received dexamethasone intravenously in a dose of 0.6 mg/kg/day in three divided doses for the first 4 days of treatment. The first dose of dexamethasone was administered concomitant with the first dose of antibiotic.

All patients received optimal supportive therapy and nursing care . Paracetamol was used as an antipyretic at a dose of 0.5-1 g x 8 hourly. Mannitol was given at a dose of I g/kg twice daily in cases of altered consciousness. Lumbar puncture was done in all patients before starting treatment, after excluding papilloedema or focal neurological signs. CSF was sent for biochemical analysis, microscopy, gram staining, culture and sensitivity. CSF analysis was repeated on the 5th day of treatment. Other investigations done on day 1 and day 5 were complete blood count, glucose, urea, creatinine and electrolytes. Blood culture sample was also taken on day 1.

Patients were followed up for changes in symptoms and signs including fever, headache, vomiting, skin rash, joint pains, signs of meningeal irritation, altered consciousness, melaena or haem atochezia.

Statistical Analysis

For comparison of two means, student's t-test was employed. The chi-square test of proportion was used for comparison of difference in percentages.

Results

A total of 72 patients with ABM were admitted in Medical Unit II over a 2 year period from May 1998 to April 2000. Four patients were excluded from the study (3 patients had meningococcaemia and 1 patient additionally had severe COPD). The mean duration of symptoms prior to presentation in group A and B was 2.1 and 1.8 days in 29 patients in group A and 33 patients in group B. The pace of respectively. In group A male to female ratio was 4.5:1 while in group B it was 16:1. Mean age of the study population was 29.82 ± 17.43 with a range of 12-85 years. Mean age of group A was 33.3 ± 19.33 and that of group B was 26.4 ± 14.8, thus showing no significant age difference between the two groups.

At the time of presentation mean systolic BP was 115±20 and diastolic BP was 71±13 while mean temperature was 100.37 ± 1.19° F. Seventeen percent of patients had the typical skin rash of meningococccal infection (8 in group A and 9 in group B). Arthritis affecting the knee joints was observed in 3% of the cases (1 in group A and 2 in group B). Neck rigidity was present in 33 patients in each group, whereas Kernig's sign was positive

Cranial nerve involvement was much lower in group resolution of these signs with treatment is shown in Figure 1.

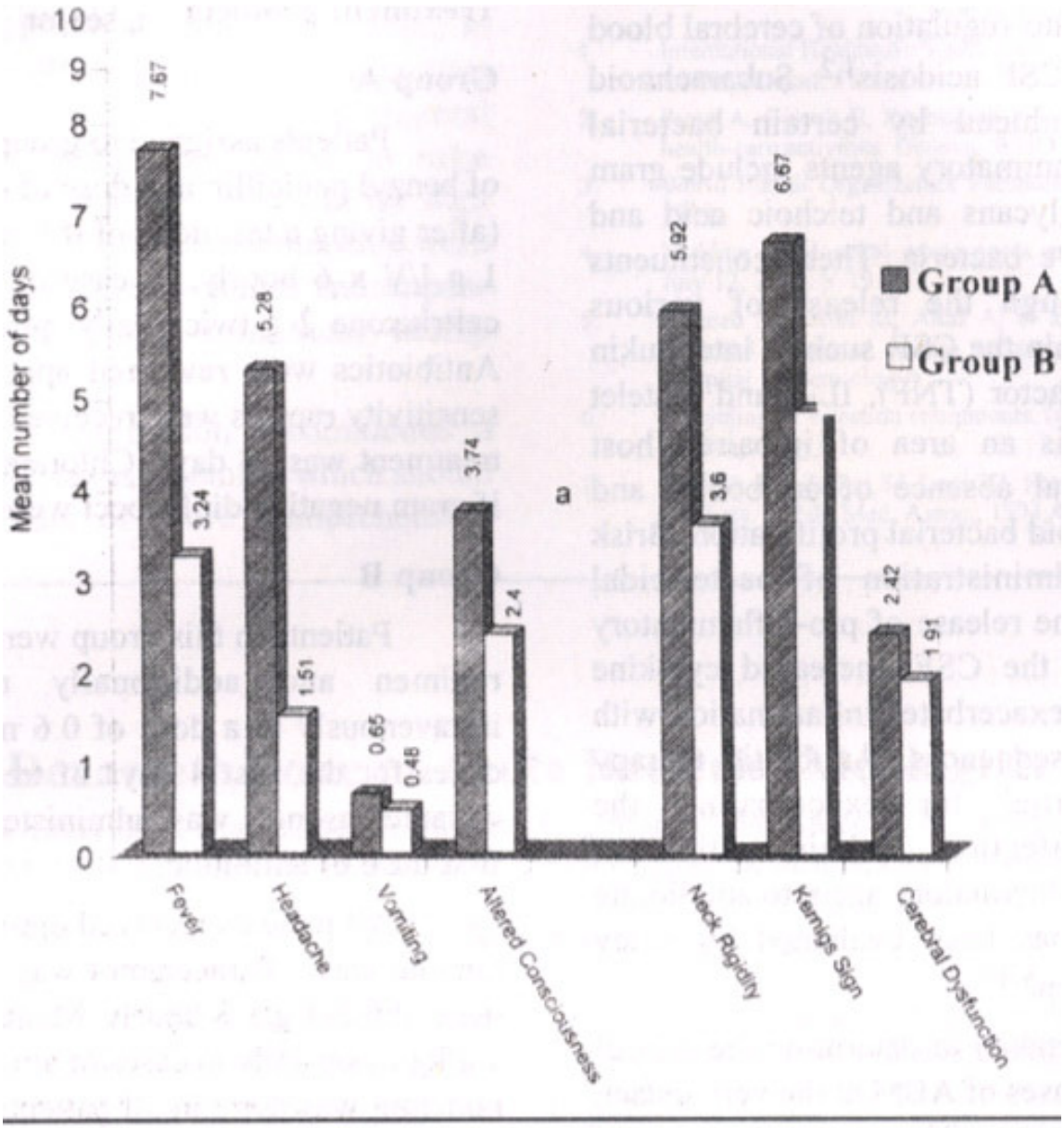

Figure 1. Resolution of symptoms and signs in Group A and B patients.

Cerebral dysfunction was assessed in accordance with Glasgow Coma Scale (GCS) at the time of presentation. Twenty one patients in group A and 19 patients in group B had a GCS score of < 15. Early restoration of cognition in group B was observed as compared to group A, although the difference was not statistically significant.

B being 17.6% (6 patients) as opposed to 29.4% (10 patients) in group A. All cranial nerve palsies appeared during the course of treatment. Nerve deafness was recorded in 2 patients in each group. One patient in group A developed persistent dysphasia and right crural monoparesis. Similarly 1 patient in group B developed paraplegia which persisted beyond day 14. Therefore, there was no difference in the development of focal neurological deficit between the two groups and the overall frequency of this complication was very low in this study. Overall seizure activity was 2.9% (2 patients in group A). No patient in group B had seizures. Herpes labialis was frequent and occurred in 30% of cases overall by day 3. No adverse effects attributable to dexamethasóne were documented.

Table. Comparison of CSF inflammatory indices between two groups on day 1 and 5.

Laboratory investigations		Group A	Group B	P-value
Glucose	Day 1	21.02+27.02	22.65+34.38	P> 0.32
(mg/dl)	Day 5	41.16+18.40	64.00+26.62	P< 0.001
Proteins	Day 1	336.87+253.32	417.19+269.64	P> 0.20
(mg/dl)	Day 5	115.80+79.51	68.78+35.98	P < 0.003
TLC/µl	Day 1	8823.92+10823.08	12026+10790.97	P > 0.022
	Day 5	400.23+782.63	279.65+703.97	P < 0.53

The CSF changes on day 1 and day 5 are shown in Table. CSF was turbid in almost all patients in both groups and clarity was restored by day 5. On day 5 the CSF glucose showed a statistically significant improvement in group B as compared to group A (P<0.003). The difference in the fall of CSF leucocyte count although greater in group B by day 5 did not achieve statistical significance (P>0.53). Gram stain of CSF showed gram negative diplococci in approximately half the patients in each group studied (44.11%). CSF culture was positive for N. meningitidis in 4 cases in group A and 9 cases in group B. The isolate in all 13 cases was sensitive to penicillin, ceftriaxone and chioramphenicol. Blood culture was positive only in 1 case in group A and a coliform organism
was identified which was sensitive to cephalosporins, gentamycin and co-amoxiclav. Mean creatinine level in group A was 2.13 ± 6.34 and in group B 1.08±0.35. Creatinine was normal on day 5 in both groups . There was no significant drop in the haemoglobin level in both groups on day 5 . The fall in peripheral WBC count was also not significant in group A and B patients on day 5. Four patients in group A and 2 patients in group B died constituting a mortality of 11.7% and 5.8% respectively. Although the mortality was lower in group B the difference was not significant in view of the small number of cases. The distribution of cases of ABM during the 2 years of the study is shown in Figure 2,

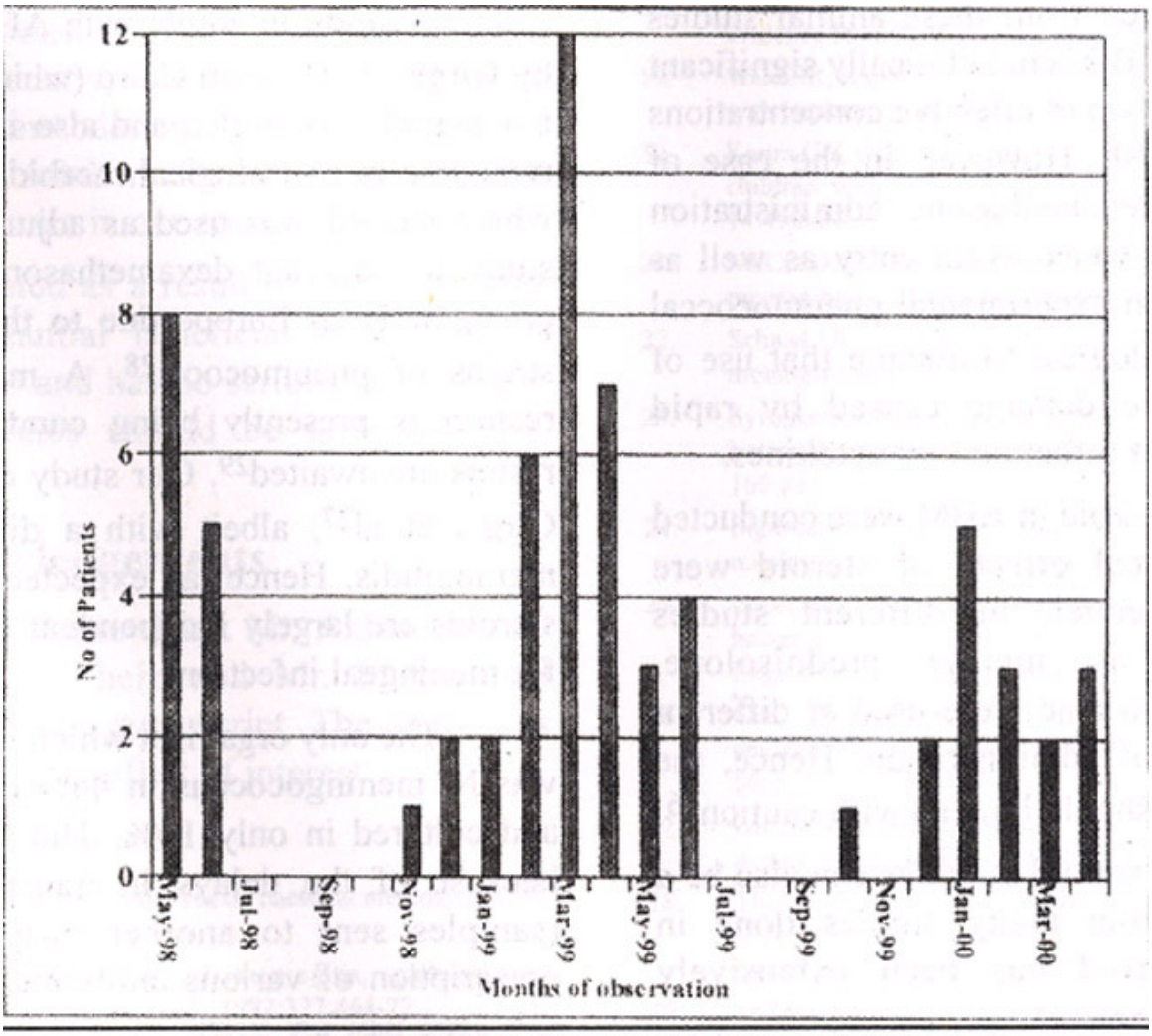

Figure 2. Monthwise distribution of meningitis cases from May-98 to April 00.

depicting a clustering of cases in late winter through to early summer months in Karachi.

Discussion

In view of the better understanding and ever expanding knowledge of the pathophysiology of inflammation in ABM and damage caused by products of bacteriolysis and inflammatory mediators, evaluation of routine use of steroids as an anti-inflammatory agent in ABM in adults is imperative. Despite the availability of multiple effective antibiotics the mortality of ABM remains at around 10-25% with an additional 10-30% suffering from serious long term consequences, such as cognitive deficit, focal neurological deficit, deafness and seizures[11]. Improvement in this scenario will probably ensue only with more effective modulation of immune responses to bacterial infection of the meninges, by interventions such as early use of steroid, anti-endotoxin antibody, plasmapheresis, protein C and S administration. While most of these modalities are experimental at the present moment, the use of steroid has been extensively investigated. Steroids inhibit the generation of IL-i and TNF by bacterial lipopolysaccharide stimulated macrophages. Various animal studies have confirmed in experimentally induced S. Pneumoniae and H. Influenza meningitis that adjunctive steroid treatment in animals led to

significantly less brain oedema, intracranial pressure and CSF lactate levels[2,12,13]. However, efficacy of steroid in experimental animal models of meningococcal meningitis has not been studied. It has also been shown in two animal studies that the early normalization of homeostatic derangements did not adversely affect the penetration of antibiotics through the (BBB)[14-17]. It can be deduced from these animal studies that this early restoration of BBB is not clinically significant in terms of reducing the build up of effective concentrations of anti-microbials in the CSF. However, in the case of vancomycin, concomitant dexamethasone administration has been shown to decrease vancomycin entry as well as rate of bactericidal activity in experimental pneumococcal meningitis[18]. It is therefore logical to assume that use of steroids would mitigate the damage caused by rapid bacteriolysis and activation of inflammatory cytokines.

The early trials with steroid in ABM were conducted before the pathophysiological effects of steroid were properly understood. Moreover, in different studies different steroids such as methyl prednisolone, hydrocortisone and dexamethasone were used at different doses and different timing of administration. Hence, the results of these early studies should be read with caution[16].

The use of adjunctive steroid in adults can also be a reasonable extrapolation from many studies done in children. The use of steroid has been extensively investigated in children by many investigators[8,19-23], even though the majority of children in these studies had H. nfluenzae or pneumococcal meningitis. Qazi et al[10] conducted a double blind placebo controlled study in children with meningitis and concluded that no benefit accures in children on mortality as well as morbidity when treated with adjuvant steroid. They attributed it to the late presentation of the patients. The mean duration of the illness was 5-7 days prior to being diagnosed. Our results differ from this study even though one drawback of our study is that it was not a double blind placebo controlled trial. The overall mortality in our study was only 8.8% which is much lower than that reported by Qazi et al. The difference in mortality may be attributed to the greater vulnerability of the very young and very old and the delay in diagnosis which is invariably more at the extremes of age. In our study mortality in the steroid group was 5.8% as opposed to study by Qazi et al[10] where 25% mortality was recorded in the steroid group. In the antibiotic alone group; mortality in our study was 11.7% with a comparable mortality of 12% in the study by Qazi et al. This difference in mortality is not statistically significant in view of the small number of cases, however it is an outcome measure which is not influenced by any observation bias. Moreover, the mean duration of illness prior to presentation in our study was 2 days as opposed to > 4 days in the study by Qazi et al. In Qazi's study duration of illness prior to diagnosis was an independent predictor of mortality alongwith unconsciousness.. Our mortality is comparable to those of most European studies[8,24-26]. Mortality in studies from Pakistan has been reported much higher at between 18-29%.

A study in adults with ABM due to S. Pneumoniae by Girgis et al[27] from Cairo (which was not double blinded nor placebo controlled and also included children) showed reduction in neurological morbidity and mortality in cases where steroid was used as adjunctive treatment. Another study of adjuvant dexamethasone in adults was stopped prematurely in Europe due to the emergence of resistant strains of pneumococci[28]. A multi centre study in this respect is presently being conducted in Europe and its results are awaited[29]. Our study corroborates the results of Girgis et al[27], albeit with a different organism i.e., N. meningitidis. Hence, as expected the beneficial effects of steroids are largely independent of the causative organism for meningeal infection.

The only organism which was identified in this study was N. meningococcus in 44% of cases on gram staining and cultured in only 19%. The low culture yield may be because of the delays in

transportation of the samples (samples sent to another hospital laboratory), or the prescription of various antibiotics by general practitioners prior to reaching hospital. It is reasonable to conclude that N. meningitidis is the most common organism causing
meningitis in adults in Karachi. Similar results were reported from Lahore[30], Karachi[31] and Sindh[32] previously. The sensitivities were also similar to our study. Penicillin can safely be advocated as the first line drug to be used in all cases of adult ABM before microbiological feed back is available.

Our study shows a dramatic improvement in the symptomatology of the patients. The duration of pyrexia and headache were halved by the administration of dexamethasone, thus restoring a sence of well being much earlier in the group of patients treated with dexamethasone. Patients became apyrexial much quicker with steroids. This effect was not shown in the Egyptain study. Restoration of full consciousness was also marginally quicker in this group. Cranial nerve involvement was lower in the steroid group. No seizure activity was noted in this group either. These differences were not statistically significant in view of the small number of cases. Studies should be undertaken to explore these differences in larger number of patients so that firm evidence based guidelines regarding routine use of dexamethasone in adults with ABM can be formulated.

The overall male to female ratio of 7.5: 1 in ABM cases is in agreement with previous study for Lahore where the ratio was 7:332. In the Egyptian trial male to female ratio was 2:1, whereas in a large study from Iceland the ratio was 1:1.233. The prominence of male affectees in our country may be related to the different life styles of women and men, women being less exposed because they are largely house bound. Men may work in crowded poorly ventilated working conditions, or in the case of workers from other parts of the country, may also be dwelling in small over crowded accommodation, thus expediting the naso-pharyngeal spread. Adult males therefore bear the brunt of this infectious disease in our country.

It can be safely stated as a result of our study that dexamethasone has substantial beneficial effects as an adjuvant in ABM in adults and has no serious side effects. Larger double blind studies should be undertaken to corroborate our results.

Acknowledgements

The authors would like to thank Mr. Akhtar Anwer for his invaluable statistical help and Mr. Muhammad Anwer for patiently typing the manuscript. The study was self funded and there was no conflict of interest.

References

1.Quagliarello VJ, Scheld WM. New perspectives on bacterial meningitis. Clin. Infect. Dis., l993;17:603-10.

2.Quagliarcllo VJ, Scheld WM. Bacterial meningitis, pathogenesis, pathphysiology and progress. N. EngI. J. Med., 1992;327:864-72.

3.Scheld WM. Bacterial meningitis, brain abscess and other suppurative intracranial infections. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin iB, Kasper DL, et al, (eds.). Harrisons principles of internal medicine. Vol 1, 14 ed. New York: McGrawHill, 1998, pp.2419-26.

4.Low PS, Lee BW, Yap HK. inflammatory response in bacterial meningitis: Cytokine levels in

Cerebrospinal fluids, Ann. Trop. Paediatr., 1995;15: 55-59.
5.Roos KL. The Use of adjunctive therapy to alter the pathophysiology of bectenal meningitis. Clin. Neouropharmacol., 1995;18:138-47.
6.Macaluso A, Pivetta S, Maggi RS. Dexamethasone adjunctive therapy for bacterial meningitis in children. Ann. Trop. Paediatr., 1996; 16: 193-98.
7.Townsend GC, Scheld WM. Adjunctive therapy for bacterial meningitis; rationale for use, current status and prospects for the future. Clin. Infect. Dis., 1993; 17(Suppi 2) S 537-49.
8.Mcintyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis: A meta-analysis of randomised clinical trials since 1988. JAMA., 1997; 278: 925-3 1.
9.Ciana G, Parmar N, Antonio C. Effectiveness of adjunctive treatment with steroids in reducing short term mortality in a high risk population of children with bacterial meningitis. J. Trop. Pediatr., 1995 ; 41: 164-68.
10.Qazi SA, Khan MA, Mughal N. Dexamethasone and bacterial meningitis in Pakistan. Arch. Dis. Child., 1996; 75: 482-88.
11.Begg N, Cartwright KAy, Cohen J, et at. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. J. Infect., 1 999;39: 1-15.
12.Tauber MG, Khayam-Bashitt, Sande MA. Effects ofampicillin and corticosteroids on brain water content, CSF pressure and CSF lactate levels in experimental pneumococcal meningitis. J. Infect. Dis., 1985;151:528-34.
13.Saez-Lorens X, Ramilo 0, Mustafa MM, et al. Molecular pathophysiology of bacterial meningitis; current concepts and therapeutic implications, J. Pediatr., 1990: 116: 671-84.
14.Mustafa MM, Ramilo 0, Mertsola J, et al. Modulation of inflammation and cachectin activity in relation to treatment of experimental Haemophilus influenzae type b meningitis. J. Infect. Dis., 1989; 160: 818-25.
15.Tunkel AR, Wispelwey B, Scheld WM. Bacterial meningitis: recent advances in pathophysiology and treatment. Ann. Int. Med., 1990; 112: 610-23.
16.Gregory C, Townsend, Scheld WM. Adjunctive corticosteroida for adult bacterial meningitis. Infect. Med., 1995 ,12:701 -10.
17.Cabelos C, Lacasa JM, Martos A, et al. Influence of dexamethasone on efficacy of ceftriaxone and vancomycin therapy in experimental pneumococcal meningitis. Antimicrob Agents Chemother., 1995;39:2158-60.
18.Tauber MG, Sande MA. Dexamethasone in bacterial meningitis; increasing evidence for a beneficial effect. Pediatr. Infect. Dis. J., 1989; 8:842-45.
19.Wald ER, Kaplan SL, Mason EO Jr, et al Dexamethasone therapy for children with bacterial meningitis. Paediatrics, 1995; 95: 2 1-28.
20.Kanra GY, Ozen H, Secmeer G, et al. Beneficial effects of dexamethasone in children with pneumococcal meningitis. Paediatrics, Infect. Dis. J., 1995; 14:490-94.
21.McCracken Gil Jr, Lebel MH. Dexamathasone therapy for bacterial meningitis in infants and children. Am. J. Dis. Child., 1989;143:287-89.
22.Schaad UB, Lips U, Gnehm HE, et al. Dexamethasone therapy for bacterial meningitis in children. .Lancet, 1993;342:457-61.
23.Syrogiannopoulos GA, Athanassia NL, et al Dexamethasone therapy for bacterial meningitis in children: 2-versus 4-day regimen. J. Infect. Dis., 1994; 169:853-58.
24.Sigurdardottir B, Bjomsson OM, Jonsdottir KE, et al. Acute bacterial meningitis in adults, a

20 year review. Arch. Intern. Med., 1997;157:425-50.
25.Lebel MH, Freij BJ, Syrogiannopoulos GA. Dexamethasone therapy for bacterial meningitis, results of two double blind placebo controlled trials. N. EngI. J. Med., 1988;319:964-71.
26.Odio CM, Faingezicht I, Paris M, et al The beneficial effects of early dexamethasone in infants and children with bacterial meningitis. N. EngI. J. Med., 1991 ;324:1525-31.
27.Girgis NI, Farid Z, Mikhail LA, et al. Dexamethasone therapy for bacterial meningitis in children and adults. Pediatr. Infect. Dis. J., 1989;8:848-51.
28.Thomas R, Le Tuizo Y, Bouget J, et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults; adults meningitis steroid group. Intensive Care Med., 1999;25:475-80.
29.Moller K, Skinhoj P, (Editorial). Guidelines for managing acute bacterial meningitis, speed in diagnosis and treatment is essential. Br. Med.
J.,2000;320: 1290.
30.Randhawa MS. Pattern of acute bacterial meningitis in adults. Pak. J. Med. Sci., 1998; 14:213-22.
31.Jehan Q, Jaleel KA. A bacteriological study of meningitis. Med. Spectrum, 1989; 10:11-13.
32.Rajper GM, Khaskheli AA, Shiekh RB, et a!. Bacterial pyogenic meningitis and drug sensitivity, one year study at People's Medical College Nawabshah, Pakistan. Specialist, 1997;13: 123-28.
33.Sigudardottir B, Bjornsson OM, Jonsdottir KE, Acute bacterial meningitis in adults; a 20 year review. Arch. Intern. Med., 1997;157:425-50.