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Dexamethasone in Adults with Community-Acquired Bacterial Meningitis

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Abstract

Bacterial meningitis in adults is a severe disease with high fatality and morbidity rates. Experimental studies have shown that the inflammatory response in the subarachnoid space is associated with an unfavourable outcome. In these experiments, corticosteroids, and in particular dexamethasone, were able to reduce the inflammatory cascades in the subarachnoid space. The use of corticosteroids as adjunctive therapy in adults with bacterial meningitis has been evaluated in six studies, performed over a time period of 40 years. Most studies on adjunctive dexamethasone therapy in adults with bacterial meningitis were limited by methodological flaws. In 2002, a study with sufficient statistical power to show significant differences was published. This European Dexamethasone Study showed that adjunctive dexamethasone therapy reduced the rate of unfavourable outcomes in adults with bacterial meningitis from 25% to 15%. In this study, adjunctive treatment with dexamethasone was given before or with the first dose of antibacterials, without serious adverse effects. A quantitative review showed a consistent beneficial effect of dexamethasone on mortality and a borderline statistical beneficial effect on neurological sequelae. On the basis of the available evidence, adjunctive dexamethasone therapy should be initiated before or with the first dose of antibacterials and continued for 4 days in all adults with suspected or proven bacterial meningitis, regardless of bacterial aetiology. In patients with both meningitis and septic shock, dexamethasone therapy cannot be unequivocally recommended, but the use of lower doses seems reasonable at present. Since prompt use of dexamethasone and appropriate antibacterials improves the prognosis of adults with bacterial meningitis, hospitals will require protocols to include dexamethasone with the initial antibacterial therapy.

Bacterial meningitis has been uniformly lethal up to the introduction of antimeningococcal antisera in the early 20th century.[1] In 1940, mortality rates were further reduced to a rate of approximately 20% with the introduction of penicillin.[1] Since then, mortality rates in patients with bacterial meningitis have been stable, despite advances in critical care and imaging techniques such as cranial computed tomography and magnetic resonance imaging.[1,2] Since the 1980s, experimental studies have unraveled pathogenesis and pathophysiological mechanisms in bacterial meningitis.[3] The inflammatory

response in the subarachnoid space was found to be associated with unfavourable outcome.[4] In these experiments, corticosteroids, and in particular dexamethasone, were able to reduce the inflammatory cascades in the subarachnoid space.[5] This knowledge has led to clinical trials of dexamethasone as adjuvant therapy. In four trials in children with *Haemophilus influenzae* meningitis conducted in the early 1990s, dexamethasone did reduce the frequency of neurological sequelae (principally, sensorineural hearing loss) but did not change mortality; however, mortality among included children was low (<1%).[6] In 2002, it was shown that in adults with bacterial meningitis, adjunctive dexamethasone therapy reduced the rate of unfavourable outcomes from 25% to 15%.[7] Despite these results, the role of dexamethasone in the treatment of bacterial meningitis remains controversial, at least in some subgroups of patients.[8,9] In this paper we summarise the current evidence for and against the use of adjunctive dexamethasone in adults with community-acquired bacterial meningitis.

1. Bacterial Meningitis

1.1 Epidemiological Aspects

The estimated incidence of bacterial meningitis is 2.6–6 per 100 000 adults per year in developed countries, and is up to ten times higher in less developed countries.[1,2,10-12] In the developed world, the epidemiology of bacterial meningitis has changed in recent decades.[1,2,10-13] Meningitis due to *H. influenzae* type b (HiB) has nearly been eliminated since routine vaccination with the conjugate HiB vaccine was initiated (figure 1).[10,12] The introduction of conjugate vaccines against seven most common and resistant serotypes of *Streptococcus pneumoniae* is expected to reduce the burden of childhood pneumococcal meningitis substantially.[13] As a consequence, in developed countries, bacterial meningitis has become a disease predominantly of adults rather than of infants and children.[2] Although the pneumococcal seven-valent conjugate vaccine is highly effective in children, the high costs

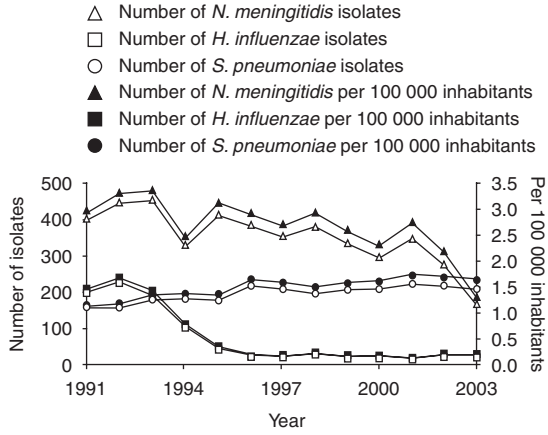

Fig. 1. Number of cerebrospinal fluid isolates from meningitis patients as received by the Netherlands Reference Laboratory for Bacterial Meningitis from 1991 to 2003. In the Netherlands, routine vaccination with the conjugate *Haemophilus influenzae* type b (*H. influenza*) vaccine started in 1993, led to a sharp decline of *H. influenza* cases. After 1994, the most common bacterial species isolated from bacterial meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis*.

of this vaccine limit its implementation in healthcare in developing countries.[14]

In different regions in the developed world, invasive infections due to *Neisseria meningitidis* serogroup C strongly increased over the last 10 years.[15-17] Routine immunisation with the meningococcal serogroup C protein-polysaccharide conjugate vaccines has been undertaken in several countries.[15-17] This vaccine strategy seems to reduce the disease burden of bacterial meningitis substantially.[17] Concerns that routine vaccination may result in an increase in meningococcal disease due to non-C serogroups have not been realised.[17] An important advance is the approval in 2005 of a conjugate meningococcal vaccine against serogroups A, C, Y and W135 that may further decrease the incidence of this devastating infection.[9] The vaccine offers the potential for addressing epidemic meningococcal disease in sub-Saharan Africa due to serogroup A and W135, and would also be useful in controlling W135 strains, which have been associated with the Hajj, and serogroup Y, which has been particularly prevalent in the USA.[17]

In adults with community-acquired bacterial meningitis, most common aetiological agents are *S.*

pneumoniae and *N. meningitidis*, which cause 80–85% of all cases.[2,9,10] *S. pneumoniae* primarily causes respiratory infections, including otitis media, sinusitis and pneumonia.[2,18-21] Groups at increased risk of pneumococcal infection include the elderly, immunocompromised patients (including those with HIV type 1 infection), smokers and certain other demographic groups.[20] As individuals advance in age, the rate of pneumococcal infections increases, including meningitis.[2,20] In contrast, *N. meningitidis* most commonly causes meningitis in young adults.[2,11] Nasopharyngeal carriage of meningococci is an important factor that leads to the development of invasive disease.[20,21] The estimated prevalence of meningococcal carriage is 5–10% under nonepidemic conditions.[20,21]

Another epidemiological trend is the emergence of antibacterial-resistant strains of *S. pneumoniae*.[22] Pneumococcal resistance to penicillin, due to changes in its penicillin binding proteins, was first reported in 1965.[23] The prevalence of such resistance was limited until an epidemic of highly resistant pneumococci occurred in South Africa in 1977.[23] Since then, resistance has developed worldwide and in some regions it occurs with a frequency of up to 70%.[23] Reports of reduced susceptibility of pneumococci to several antibacterials, including broad-spectrum cephalosporins, have also been published.[24] In response to this epidemiological trend, recommendations for suspected and confirmed bacterial meningitis have necessarily evolved.[9]

1.2 Clinical Aspects

Early diagnosis is vital in the treatment of bacterial meningitis.[9,25,26] Therefore, clinical recognition is important to complete further investigations efficiently and initiate appropriate therapy as soon as possible, with the goal of minimising adverse outcomes.[9] Bacterial meningitis is often considered but remains difficult to recognise.[2,9,27] The classic triad of fever, neck stiffness and an altered mental status is infrequent (44%); however, almost all patients present with at least two of the signs and symptoms of headache, fever, neck stiffness and an altered mental status (defined as a score on Glasgow coma scale <14).[2] Most patients with pneumococcal meningitis have underlying conditions, such as distant foci of infection (otitis, pneumonia) or an immunocompromised state.[2,18,19] Rashes occur more frequently in patients with meningococcal meningitis, with reported sensitivities of 63–80% and with specificities of 83–92%.[2,27]

Seizures before admission occur in 5–9% of all patients and 15–23% of patients develop seizures during their clinical course.[2,9,11,18-20] Cranial nerve palsy is relatively rare; most commonly affected are cranial nerves VIII (6–10%), III (4%), IV (3%) and VII (2%).[2,9] Focal cerebral findings (aphasia, hemiparesis and monoparesis) on admission occur in approximately 15–23% of patients.[2,9,11,18-20] Papiloedema is uncommon in patients with acute bacterial meningitis (3–4% of patients; however, in most studies the results of fundoscopic examination were not recorded).[2,11,19] Systemic manifestations, such as hypotension and tachycardia, occur frequently in community-acquired bacterial meningitis (table I).[9]

Community-acquired bacterial meningitis in adults is a severe disease with high fatality and morbidity rates.[2,9,11,18-20] Meningitis caused by *S. pneumoniae* has the highest case fatality rates, reported to range from 19% to 37%.[2,9,18,19] Of those who survive, up to 50% develop long-term neurological sequelae, including cognitive impairment.[2,9,18,19,28-30] For meningococcal meningitis, mortality and morbidity rates are lower, with rates up to 5% and 7%, respectively.[2,9] The strongest risk factors for an unfavourable outcome in patients with

Table I. Clinical findings on admission in patients with pneumococcal and meningococcal meningitis[2,18]

Characteristic	Relative frequency (%)	
	pneumococcal meningitis (n = 352)	meningococcal meningitis (n = 257)
Seizures before admission	7	2
Otitis or sinusitis	44	4
Pneumonia	18	5
Immunocompromised	22	5
Rash	2	64
Coma	19	7
Focal neurological deficits	43	20

bacterial meningitis are those indicative of systemic compromise, impaired consciousness, low cerebrospinal fluid (CSF) white-cell count, and infection with *S. pneumoniae*.[2]

1.3 Pathophysiology

Experiments in animal models increased knowledge about the pathogenesis and pathophysiological mechanisms in bacterial meningitis.[3-5,20,31] Colonisation generally leads to asymptomatic carriage; however, in some cases and with specific conditions bacteria migrate through the respiratory epithelium and vascular endothelium, resulting in invasive disease.[3,20,31] Internalisation and migration by the bacterium is induced through the respiratory epithelium and vascular endothelium;[3,31] after the bacteria have crossed this mucosal barrier, they spread throughout the host tissues, facilitated by enzymes and virulence factors. Once in the bloodstream they must overcome several host defence mechanisms to survive.[3,31] The blood-brain barrier is formed by cerebromicrovascular endothelial cells, which restrict blood-born pathogen invasion.[3,31] Activated endothelial cells upregulate platelet-activating-factor receptor and bacteria are thought to invade via transcytosis.[3,31] Physiologically, concentrations of leucocytes, antibodies and complement components in the subarachnoid space are low; this condition facilitates multiplication of bacteria, which undergo autolysis under conditions such as growth to stationary phase or exposure to antibacterials (figure 2).[31] Administration of adequate antibacterial treatment leads to rapid bacteriolysis and releases high concentrations of inflammatory bacterial fragments.[3-5,31] This activates the downstream cascades of inflammation in the subarachnoid space, resulting in the release of tumour necrosis factor(TNF)-α, interleukin (IL)-1β, IL-6, lipopolysaccharide and lipoteichoic acid, which are considered the major early response cytokines that trigger inflammatory cascades.[3-5,31,32] As a consequence, various pathophysiological alterations are induced, such as increased blood-brain barrier permeability causing brain oedema and raised intracranial pressure.[5] Both the inflammatory reactions and pathophysiological alterations are associated with unfavourable outcome.[5] Adjunctive treatment with anti-inflammatory agents, such as dexamethasone, reduces CSF inflammation and thereby improves neurological outcome (figure 2).[5]

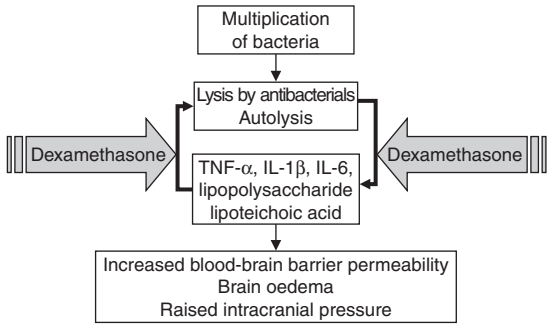

Fig. 2. Mechanisms of action of dexamethasone in bacterial meningitis: inflammatory reaction in the subarachnoid space and pathophysiological alterations. Dexamethasone inhibits production of tumour necrosis factor (TNF)-α and interleukin (IL)-1, reverses development of brain oedema, and limits the increase in cerebrospinal fluid lactate and leucocyte concentrations.[3,33]

2. Dexamethasone

2.1 Pharmacological Properties

Dexamethasone is a glucocorticoid. The pharmacological properties of glucocorticoids have been extensively reviewed previously.[34] Glucocorticoids are used in a wide variety of clinical conditions where it is thought that their immunosuppressive properties account for their beneficial effect. The effects of glucocorticoids are mediated by genomic and possibly nongenomic mechanisms.[34] Genomic mechanisms include activation of the cytosolic glucocorticoid receptor that leads to activation or repression of protein synthesis, including cytokines, chemokines, inflammatory enzymes and adhesion molecules. Thus, both inflammation and immune response mechanisms may be modified. Nongenomic mechanisms might play an additional role in glucocorticoid pulse therapy. Clinical efficacy depends on glucocorticoid pharmacokinetics and pharmacodynamics;[34] of glucocorticoids, dexamethasone has superior penetration in the CSF.[35]

2.2 Mechanisms of Action

Dexamethasone inhibits the production of TNF-α and IL-1, reverses development of brain oedema and limits the increase in CSF lactate and leucocyte concentrations (figure 2).[3,5,31]

In animal models, potential factors to influence this immunomodulatory effect of dexamethasone are the timing of dexamethasone dose in relation to the first antibacterial dose, the kinds of antibacterials used with regard to their effect on the amount of early response cytokines released, and the cerebrospinal bacterial concentrations at the start of therapy.[32,36-38] Timing of dexamethasone dose administration in relation to the first antibacterial dose is critical. Studies in *H. influenzae* meningitis showed that the downstream cascades of inflammation in the subarachnoid space, partly triggered by the lysis of bacteria by antibacterials (in these studies, third generation cephalosporins), was prevented only if dexamethasone was given simultaneously with the fist dose of antibacterials.[32] Less attention has been given to possible differences between various kinds of antibacterials with regard to the amount of immunostimulatory components and response cytokines released. Because some antibacterials, in addition to bacterial killing, may induce filament formation, whereas others induce rapid cell lysis after spheroplast formation, antibacterials at concentrations inducing equivalent killing of the bacterial inoculum may differ considerably in the total amount of immunostimulatory components released and the kinetics of this release.[36,37] Although components of the inflammatory response may contribute to the deleterious effects of bacterial meningitis, the clinical significance is uncertain. Finally, viable bacteria play a crucial role in the induction and maintenance of the metabolic and pathophysiological alterations.[38] A recent study in experimental pneumococcal meningitis suggested that cerebrospinal bacterial concentrations at the start of therapy are more important than the timing of adjunctive dexamethasone therapy in influencing the antibacterial-induced inflammatory response.[38] In this study, the antibacterial-induced secondary inflammatory response occurred only in animals with high bacterial concentrations before the start of ampicillin therapy.

In conclusion, adjunctive dexamethasone therapy down-regulates meningeal inflammation in experimental bacterial meningitis, reduces cerebral oedema and intracranial pressure, and improves outcome.

3. Clinical Evidence

3.1 In Children

Since publication of the experimental studies, several controlled trials have been performed to determine whether adjunctive corticosteroid therapy is beneficial in children with bacterial meningitis.[6] In 1997, a meta-analysis of randomised controlled trials performed since 1988 showed a beneficial effect of adjunctive dexamethasone therapy on severe hearing loss in children with HiB meningitis and suggested a protective effect in those with pneumococcal meningitis, only if the drug was given before or with parenteral antibacterials.[39] However, meningitis due to HiB has nearly been eliminated since routine vaccination with the conjugate HiB vaccine was initiated (see section 1.1). More recently, a Cochrane review, including 1853 patients of whom 1474 were children, showed a beneficial effect of corticosteroids on severe hearing loss in children with bacterial meningitis caused by HiB (relative risk [RR] 0.31; 95% CI 0.15, 0.62), as well as in meningitis caused by bacteria other than HiB (RR 0.42; 95% CI 0.20, 0.89).[6] In children, adjuvant corticosteroid treatment of 20 patients would prevent one case of severe hearing loss.[6] No beneficial effect on mortality was found; however, mortality rates were low, which suggests selection bias. In nine studies, mortality rates were ≤3%, whereas mortality rates in childhood bacterial meningitis in previously reported studies ranged from 8% to 20%.[40] Inclusion of patients with less severe illness in the meta-analysis, as reflected by the low case fatality rates, will underestimate the protective effect of corticosteroids.[6]

An additional large controlled trial showed no beneficial effect of adjunctive corticosteroid therapy

in children.[41] This Malawian study included mainly children in whom treatment began late, HIV-positive children and children receiving inappropriate antibacterial therapy. Therefore, the results of this trial are not representative for the typical meningitis population in industrialised countries. For patients admitted in a late stage of disease, adjunctive corticosteroid therapy is less protective and might even be harmful.[6]

Although in the Cochrane review the clearest effect was seen on severe hearing loss, a consistent trend towards a beneficial effect of corticosteroids in reducing mortality and neurological sequelae among children with acute bacterial meningitis was found, in the absence of significant adverse effects.[6] On the basis of the current evidence, early corticosteroid treatment in children with suspected bacterial meningitis is advised in developed countries (0.4 or 0.6 mg/kg/day for 4 days, see section 3.5).

3.2 In Adults

The use of corticosteroids as adjunctive therapy in adults with bacterial meningitis has been evaluated in six studies, performed over a time period of 40 years.[7,42-46] The first study included both children and adults from Boston and Chicago, USA; 85 adults were randomised for treatment with hydrocortisone or placebo.[42] The hydrocortisone regimen consisted of a 6-day regimen with 300mg on the first day (intravenously), 250mg on the second day (intravenously), 200mg on the third day (orally), and so on in dosages that decreased by 50mg per day. The timing of hydrocortisone therapy was described imprecisely; the protocol required that study therapy was administered at the time that antibacterial agents were first administered or at the time that a major change of antibacterial therapy occurred. Neither withdrawals from therapy nor information about antibacterial therapy was stated. Only the effect of corticosteroids on mortality was described: 16 of 38 (42%) of patients died in the corticosteroid group versus 22 of 47 (47%) in the placebo group (RR 0.9; 95% CI 0.56, 1.46) [table II].

In 1989, an Egyptian study was published showing an impressive protection by adjunctive dex-

Table II. Studies on corticosteroids as adjunctive therapy in adults with bacterial meningitis

Study (year)	Country	Randomisation	Blinded	No. of adults	Timing corticosteroids before/with antibacterials	Antibacterial regimen	Relative risk of mortality	95% CI
Bennet et al.[42] (1963)	US	Yes	Yes	85	No	NS	0.9	0.56, 1.46
Girgis et al.[43] (1989)	Egypt	Yes	No	147	Yes	Ampicillin and chloramphenicol	0.3	0.13, 0.82
Bhaumik and Behari[45] (1998)	India	Yes	No	30	No	Various	0.3	0.04, 3.36
Thomas et al.[46] (1999)	France and Switzerland	Yes	Yes	60	No	Amoxicillin	0.6	0.15, 2.14
Gijwani et al.[44] (2002)	India	No	No	40	Yes	Cephalosporin	NA	NA
de Gans and van de Beek[7] (2002)	Europe	Yes	Yes	301	Yes	Various	0.5	0.24, 0.96

NA = not available; **NS** = not stated.

amethasone therapy against death.[43] Children and adults were assigned to adjunctive treatment or no adjunctive treatment according to a redesigned randomisation chart. Antibacterial therapy consisted of ampicillin and chloramphenicol, administered intramuscularly. Dexamethasone was given intramuscularly as well, simultaneously with the first dose of antibacterial, at a dosage of 12mg every 12 hours for 3 days. Although the effect of dexamethasone was impressive, the study had several methodological flaws, being neither blinded nor placebo controlled. Information on withdrawals was lacking. Only two pathogens were cultured from the CSF, suggesting considerable selection bias. In total, 147 adolescents and adults were included in this study: 108 patients with meningococcal meningitis (73%) and 39 patients with pneumococcal meningitis (27%). Results showed a significant beneficial effect of dexamethasone; 5 of 68 patients (7%) died in the dexamethasone group versus 18 of 79 (23%) in the placebo group (RR 0.3; 95% CI 0.13, 0.82).

The third and fourth trials were performed in India and were limited by very poor methodology.[44,45] Randomisation was performed in only one study, which included 30 patients.[44] Patients received multiple antibacterial therapies and dexamethasone was started after the first dose of antibacterials. Results were nonsignificant, with 1 of 14 patients (7%) dying in the dexamethasone group and 3 of 16 (19%) in the placebo group (RR 0.3; 95% CI 0.04, 3.36).

The first study on dexamethasone in adults that followed current principles of evidence-based medicine was published in 1999.[46] It was a randomised, double-blind, multicentre trial conducted in emergency or intensive care units throughout France and Switzerland. The standard antibacterial therapy consisted of amoxicillin and the trial was ended prematurely because of emerging resistant *S. pneumoniae* strains. Dexamethasone 10mg was given four times daily for 3 days and was started up to 3 hours after the first dose of antibacterial therapy. The primary outcome measure was the rate of patients cured without any neurological sequelae 30 days after initiation of therapy. The required sample size was calculated to be 256; after enrolment of 60 patients, the study was ended prematurely. Five adverse effects were observed, two in the dexamethasone group and three in the placebo group. Two patients had gastric ulcers with overt haemorrhage, both in the placebo group. Results were inconclusive, with 3 of 31 (10%) patients dying in the dexamethasone group compared with 5 of 29 (17%) in the placebo group (RR 0.6; CI 0.15 to 2.14).

In 2002, results of the European Dexamethasone Study were published.[7] This was a randomised, double blind, multicentre trial involving 301 adults with suspected meningitis in combination with cloudy CSF, bacteria in the CSF on Gram stain or a CSF leukocyte count of >1000/mm^3, which compared adjuvant treatment with dexamethasone or placebo. Dexamethasone 10mg or placebo was administered 15–20 minutes before or with the first dose of antibacterial, and was given every 6 hours for 4 days. The primary outcome measure was the score on the Glasgow outcome scale at 8 weeks after admission (a score of 5, indicating favourable outcome, vs a score of 1–4, indicating an unfavourable outcome). A total of 108 participants (36%) had meningitis due to *S. pneumoniae*, 97 (32%) due to *N. meningitidis*, 29 (10%) due to other bacteria and 65 patients had negative CSF cultures (22%). Initial antibacterial therapy consisted in most patients of amoxicillin or penicillin (77%); antibacterial resistance among isolates was low (<1%). In this study, treatment with dexamethasone was associated with a reduction in the risk of an unfavourable outcome (RR 0.59; 95% CI 0.37, 0.94) and with a reduction in mortality (RR 0.48; 95% CI 0.24, 0.96). In patients with pneumococcal meningitis, an unfavourable outcome was found in 26% of the patients treated with dexamethasone as compared with 52% in the placebo group (RR 0.50; 95% CI 0.30, 0.83). No significant beneficial effect was found on neurological sequelae in patients with pneumococcal meningitis (RR 0.67; 95% CI 0.33, 1.37). The benefit of adjunctive dexamethasone therapy was not undermined by an increase of severe neurological disability in patients who survived or by any corticosteroid-induced complication. Gastrointesti-

nal tract bleeding occurred in two of the dexamethasone-treated patients and in five patients in the placebo group (table II).

A quantitative review on this topic has recently been published, which included five clinical trials.[47] Treatment with corticosteroids was associated with a significant reduction in mortality (RR 0.6; 95% CI 0.4, 0.8) and in neurological sequelae (RR 0.6; 95% CI 0.4, 1). The reduction in case fatality in patients with pneumococcal meningitis was 21% (RR 0.5; 95% CI 0.3, 0.8). In meningococcal meningitis, mortality (RR 0.9; 95% CI 0.3, 2.1) and neurological sequelae (RR 0.5; 95% CI 0.1, 1.7) were both reduced, but not significantly. Adverse events were equally divided between the treatment and placebo groups (RR 1.0; 95% CI 0.1, 1.7; p = 0.03).[47]

In summary, most available studies on adjunctive dexamethasone therapy in adults with bacterial meningitis were limited by methodological flaws. Only one study was methodologically sound with sufficient statistical power to detect a clinically significant effect. In this European Dexamethasone Study, the proportion of patients with bacterial meningitis who had an unfavourable outcome was reduced when given adjunctive treatment with dexamethasone, without serious adverse effects. A quantitative review showed a consistent beneficial effect of dexamethasone on mortality and a borderline statistical beneficial effect on neurological sequelae.

3.3 Disease-Modifying Effects

In the European study, patients treated with dexamethasone developed the following symptoms less frequently than patients in the placebo group: impairment of consciousness, seizures and cardiorespiratory failure during clinical course.[7] A *post hoc* analysis of this study showed that the beneficial effect of dexamethasone on mortality in pneumococcal meningitis was attributable to a reduction in systemic complications, rather than neurological complications.[48] In a categorisation of death of patients with pneumococcal meningitis who died within 14 days after admission, the percentage of patients who died as a result of neurological causes was similar between groups. The percentage of patients who died as a result of a systemic cause was significantly smaller in the dexamethasone group than in the placebo group (2% vs 16%; RR 0.11; 95% CI 0.04, 0.25). The systemic complications that were potentially preventable by dexamethasone were pulmonary complications and septic shock.

A multivariate analysis of patients with pneumococcal meningitis included in the European study, showed tachycardia, advanced age, low level of consciousness, bacteraemia and absence of dexamethasone therapy as independent risk factors for death in pneumococcal meningitis.[49] In this analysis, treatment with adjunctive dexamethasone in adults with pneumococcal meningitis mainly reduced systemic complications but also reduced seizures. In a stepwise multivariate model of dexamethasone-treated patients included in the study, only focal cerebral abnormalities were prognostic for unfavourable outcome.[50] Other prognostic factors previously identified failed to achieve statistical significance, although this may be because the study was insufficiently powered. The biological meaning of this finding is likely to be that patients presenting with focal neurological signs have brain damage even before high-dose dexamethasone is administered.

3.4 Timing of Dexamethasone Therapy

Starting corticosteroids before or with the first dose of parenteral antibacterial therapy is more effective than starting corticosteroids after the first dose of antibacterial therapy.[6] In the European study, dexamethasone (or placebo) was administered 15–20 minutes before or with the first dose of antibacterial. However, it is possible that benefit may still accrue even if dexamethasone is administered after the first dose of antibacterials. In a *post hoc* analysis of the European Study, the beneficial effect of dexamethasone on mortality in patients with pneumococcal meningitis was attributable to a reduction in systemic complications.[7,36] The possible implication of this is that the effect of dexamethasone is not restricted to the first hours after administration, although there are no supporting

data. In experimental pneumococcal meningitis, CSF bacterial concentrations at the start of therapy appeared to be more important than the timing of dexamethasone therapy in influencing the antibacterial-induced inflammatory response (see section 2.2).[48] Hence, there is a time period beyond which dexamethasone loses its effectiveness after the first (parenteral) administration of an antibacterial agent but this interval has not clearly been defined. Therefore, dexamethasone should be started with or before the first dose of antibacterials.[9]

3.5 Dose and Duration of Dexamethasone Therapy

The available studies do not address two important issues: the optimum dosage and the duration of dexamethasone therapy. In most studies, a 4-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day for children; 40 mg/day for adults) divided into four daily doses was used.[6,7,47] One randomised, prospective study involving 118 children with bacterial meningitis showed a 2-day and 4-day regimen of dexamethasone to be similarly effective.[51] In this study, physicians were not blinded for treatment groups. Long-term neurological sequelae, or moderate or more severe unilateral or bilateral hearing impairment (or both), were found in 1.8% and 3.8% of patients treated with dexamethasone for 2 and 4 days, respectively. However, results of the studies on dexamethasone in adults with bacterial meningitis are only applicable to a 4-day regimen. If corticosteroids are indicated, a 4-day regimen of dexamethasone therapy (10mg four times daily) should be given and this treatment should be started before or with the first dose of antibacterials.

4. Practical Implications

What are the practical implications of studies on adjunctive dexamethasone in adults? Firstly, in patients with bacterial meningitis who meet the inclusion criteria of the European study, dexamethasone 10mg should be initiated before or with the first dose of antibacterial therapy (figure 3). Inclusion criteria were suspected bacterial meningitis in combination with cloudy CSF, bacteria in the CSF on Gram stain or a CSF leukocyte count of >1000/mm^3. The large majority of patients who were included had bacterial meningitis. Of the 65 of 301 patients (22%) with negative CSF cultures, 43 (66%) had at least one individual CSF finding that was predictive of bacterial meningitis (a glucose level <34 mg/dL [1.9 mmol/L], a glucose ratio [the ratio of glucose in the CSF to that in blood] <0.23, a protein level >220 mg/dL, a white-cell count >2000/mm^3, or a neutrophil count >1180/mm^3).[7,52] Secondly, in patients with suspected meningitis, the results of the studies support the administration of adjunctive dexamethasone with or before the first dose of empirical antibacterials, although the study did not specifically address this issue.[9] This course will result in the unnecessary treatment of patients who do not have bacterial meningitis, however, the potential benefits outweigh any potential risks associated with dexamethasone therapy. Data from all trials of adjunctive dexamethasone treatment indicate that its use is generally safe.[6,7,9] Thirdly, dexamethasone should be continued for 4 days in patients with bacterial meningitis, regardless of microbial cause.[9] As the European study showed no significant beneficial effect in the meningococcal subgroup, several experts advise discontinuation of dexamethasone ther-

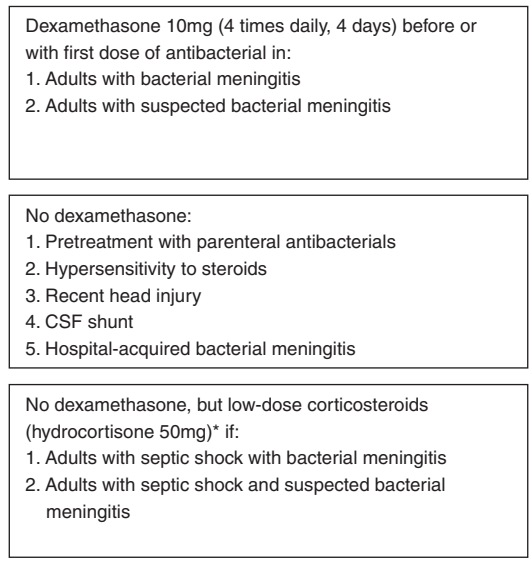

Fig. 3. Recommendations for adjunctive corticosteroid treatment in adults. **CSF** = cerebrospinal fluid; * Annane et al.[56]

apy if bacterial meningitis is not caused by *S. pneumoniae*.[8,53-55] However, the European study was not powered to analyse all subgroups of interest, so the absence of a significant benefit in any subgroup, such as with the subgroup of patients with *N. meningitidis* infection, does not rule out a beneficial effect of dexamethasone in subgroups. Therefore, on the basis of the available evidence, adjunctive dexamethasone therapy should be initiated before or at the time of the first dose of antibacterials and continued for 4 days for all adults with suspected or proven acute bacterial meningitis, regardless of microbial aetiology.

There are exceptions; for some adults with suspected meningitis, the beneficial effect of adjunctive dexamethasone is less certain and, for some, dexamethasone can even be harmful. We do not recommend the use of adjunctive (high-dose) corticosteroid treatment in patients who have already received parenteral antimicrobial therapy. Post-neurosurgical patients or those with CSF shunts were excluded in all studies;[47] since meningitis in these patients has different pathophysiology and predominant bacteria,[57] we do not recommend routine use of corticosteroids in these groups. Neither do we recommend the use of corticosteroids in patients with hospital-acquired acute bacterial meningitis or in those who have a hypersensitivity to corticosteroids.

Current evidence provides no support for the use of high-dose corticosteroids in patients with sepsis or septic shock, and suggests that their use may be harmful.[58,59] However, patients with septic shock and adrenal insufficiency benefit from corticosteroid therapy in physiological doses and with longer duration, whereas, in those with no evidence of relative adrenal insufficiency, therapy with corticosteroids may be detrimental.[56,59] There are no controlled studies of the effects of corticosteroid therapy in a substantial number of patients with both meningitis and septic shock and, therefore, corticosteroid therapy in that group cannot be unequivocally recommended. However, the use of lower doses as employed by Annane et al.[56] seems reasonable at present (figure 3).

Special consideration should be given to patients with pneumococcal meningitis caused by bacterial strains that, based on local epidemiology, are likely to be highly resistant to penicillin or cephalosporin (see section 4.1).

4.1 Penicillin-Resistant Pneumococci

By reducing the inflammation, dexamethasone may prevent opening of the blood-brain barrier and, thereby, may impede the penetration of antibacterials into the subarachnoid space.[7,9] Decreased concentrations of antibacterials may lead to delayed or even failed CSF sterilisation.[24] This is of particular concern in patients with pneumococcal meningitis caused by highly resistant strains who require combination therapy with vancomycin.[8,9] With the worldwide increase in the prevalence of penicillin-resistant pneumococci, combination therapy that includes vancomycin has become more and more important.[8,9,22-24] In experimental studies, dexamethasone significantly reduces vancomycin penetration in the CSF.[36,60] Treatment with dexamethasone did not reduce vancomycin levels in CSF in a study in children with bacterial meningitis;[61] however, treatment failures have been reported in adults who received vancomycin and adjunctive dexamethasone.[62] We recommend that adjunctive dexamethasone should be administered to most adults with bacterial meningitis, even if the pneumococcal isolate is later found to be highly resistant to penicillin and cephalosporins.[9] Patients with pneumococcal meningitis who are treated with vancomycin containing regimens and dexamethasone should be carefully observed throughout therapy.[9] In addition, rifampicin added to the empirical combination of vancomycin plus a third generation cephalosporin may be reasonable, pending culture results and *in vitro* susceptibility testing, although there are no clinical data to support this.[9]

4.2 Cognitive Impairment

Cognitive impairment occurs frequently after bacterial meningitis.[28-30] Dexamethasone may potentiate ischaemic injury to neurons and influence neurogenesis as well.[63,64] In infant rats, dex-

amethasone as an adjunct to antibacterial treatment aggravates neuronal damage in the hippocampal formation, leading to learning abnormalities.[44] In various models of brain injury, neurogenesis is increased in response to noxious stimuli, reflecting an endogenous potential of cell replacement.[63] The clinical relevance of these findings is not clear. A long-term follow-up study of the European Dexamethasone Study has been started to evaluate possible late adverse effects of adjunctive dexamethasone therapy on cognition; results are expected in 2006.

5. Future Directions

Since routine use of dexamethasone is warranted in most adults with bacterial meningitis, this may lead towards a new situation in which risk stratification for unfavourable outcome in adults with bacterial meningitis is no longer reliable.[21,50] A well designed and large cohort study is needed to evaluate the implementation and the effect of adjunctive dexamethasone in clinical practice.

Over the last few years, important advances in experimental bacterial meningitis have been made, including the role of oxygen-glucose deprivation of hippocampal neurons as a complication of meningitis, the role of cytokines, and the protective role of nuclear factor (NF)-κB and brain-derived neurotrophic factor.[3,33,65-67] However, it is unclear whether these adjuvant strategies will prove their efficacy in clinical practice.

To target new therapeutic interventions and to identify populations at prior risk, other risk factors than clinical features should be studied. Genetic factors of patients and causative bacteria are potentially essential factors in the susceptibility and outcome of bacterial meningitis.[68,69] In sepsis, polymorphisms concerning antibody receptors, lipopolysaccharide binding receptors or proteins, complement proteins and cytokines have been described as potential determinants of outcome.[70-75] Activation of inflammation and coagulation are closely related and mutually interdependent.[76] In bacterial meningitis, research on the associations between genetic polymorphisms and outcome is scarce,[68,69,71] and the relationship between polymorphisms and presentation or clinical course has not been investigated. Exploration of the genetic factors in bacterial meningitis may provide insight in the complex disease of bacterial meningitis, and may lead to different treatment and vaccination strategies and further decline of mortality and morbidity rates among patients with bacterial meningitis.

However, future progress is most likely to come from preventive measures, i.e. the implementation of the use of available vaccines and the development of new vaccines.[9] The approval in 2005 of a conjugate meningococcal vaccine against serogroups A, C, Y and W135 is also an important advance that may decrease the incidence of this devastating infection.[9,17] A promising approach is the development of vaccines directed against noncapsular antigens common to all pneumococcal species.[18]

6. Conclusion

Adjunctive dexamethasone is an advance in therapy for adults with bacterial meningitis. Hospitals will require protocols to include dexamethasone with the initial antibacterial therapy, since the causative organism in many cases will not be known when treatment is started. This may result in the unnecessary treatment of patients who do not have bacterial meningitis but the potential benefits for patients with meningitis outweigh any potential risks associated with dexamethasone therapy. Therapy should be discontinued if the patient is found not to have bacterial meningitis.

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