

The role of adjunctive dexamethasone in the treatment of bacterial meningitis: an updated systematic meta-analysis

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Background: Bacterial meningitis is a serious infection in children and adults worldwide, with considerable morbidity, mortality, and severe neurological sequelae. Dexamethasone is often used before antibiotics in cases of this disease, and improves outcomes.

Objective: Although several studies have identified the role of adjunctive dexamethasone therapy in the treatment of bacterial meningitis, the results are still inconclusive. The aim of this study was to systematically evaluate the therapeutic and adverse effect of adjunctive dexamethasone in patients with bacterial meningitis.

Materials and methods: Relevant randomized, double-blind, placebo-controlled trials of dexamethasone in bacterial meningitis published between 2000 and 2016 were retrieved from the common electronic databases. The odds ratio (OR) and risk ratio (RR) with their 95% confidence interval (CI) were employed to calculate the effect.

Results: A total of ten articles including 2,459 bacterial meningitis patients (1,245 in the dexamethasone group and 1,214 in the placebo group) were included in this meta-analysis. Our result found that dexamethasone was not associated with a significant reduction in follow-up mortality (292 of 1,245 on dexamethasone versus 314 of 1,214 on placebo; OR =0.91, 95% CI =0.80–1.03, $P=0.14$) and severe neurological sequelae (22.4% versus 24.1%, OR =0.84, 95% CI =0.54–1.29, $P=0.42$). However, dexamethasone seemed to reduce hearing loss among survivors (21.2% versus 26.1%; OR =0.76, 95% CI =0.59–0.98, $P=0.03$). No significant difference was found between these two groups in adverse events.

Conclusion: Our results suggested that adjunctive dexamethasone might not be beneficial in the treatment of bacterial meningitis. Future studies with more data are needed to further prove the role of dexamethasone in bacterial meningitis.

Keywords: bacterial meningitis, dexamethasone, treatment, meta-analysis

Introduction

Bacterial meningitis is a serious life-threatening disease with severe neurological emergency such as hearing loss, developmental disorders, and neuropsychological impairment, occurring in up to 50% of survivors of the disease.¹ The clinical signs of bacterial meningitis include fever, headache, meningismus, an altered level of consciousness, and so on.² It is ranked fourth as a cause of disability, and the estimated incidence is 1–2 million cases per year worldwide.³ *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* are the leading causes, still resulting in unacceptably high levels of human mortality and morbidity.⁴ Although routine vaccination against the common pathogens has decreased the burden of disease, improved the outcomes, and had a notable effect on the prevalence of bacterial meningitis,^{5,6}

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due to global emergence of multidrug-resistant bacteria, an estimated 1.2 million cases occur worldwide every year and 180,000 deaths in children aged 1–59 months were reported in 2010.^{7,8} In addition, bacterial meningitis often causes hearing loss and is fatal in 5%–40% of children and 20%–50% of adults despite treatment with adequate antibiotics.⁹ Early diagnosis and rapid initiation of empiric antimicrobial and adjunctive therapy are vital. Therefore, therapy should be initiated as soon as blood cultures have been obtained, preceding any imaging studies.

Corticosteroids, which have metabolic and regulatory functions in humans, are a class of steroid hormones that are produced in the adrenal cortex of vertebrates and the synthetic analogs of these hormones. They are implicated in a wide range of physiological processes such as stress response, immune response, inflammation regulation, carbohydrate metabolism, and protein catabolism.¹⁰ Corticosteroids can also attenuate the intrathecal inflammatory response caused by infection and are used as an adjunct to antibiotics in the treatment of bacterial meningitis, reducing the mortality and morbidity.¹¹ Dexamethasone is a type of corticosteroid medication.^{12,13} The use of dexamethasone was significantly associated with improved cancer-related fatigue and quality of life.¹⁴ Dexamethasone therapy has been implemented as adjunctive treatment for bacterial meningitis and is correlated with a lower mortality and fewer neurological and auditory sequelae in adults and children.¹⁵ Moreover, the adjunctive dexamethasone therapy can improve survival for years in the acute phase in adults with community-acquired bacterial meningitis.¹⁶

Although several studies have shown that dexamethasone was used as a complementary therapy to antibacterials, it is still not clear whether it is effective in the treatment of bacterial meningitis because of the disparate findings from clinical trials and clinical evidence,¹⁷ and empirical use of dexamethasone in bacterial meningitis appears controversial.^{18,19} Borchorst and Møller²⁰ found that dexamethasone treatment might be correlated with lower mortality and fewer neurological and auditory sequelae in adults and children from high-income countries, especially in adults suffering from pneumococcal meningitis. However, Peterković et al²¹ did not substantiate the reported benefits of adjunctive dexamethasone in adult bacterial meningitis based on 20 years of experience in daily practice. Therefore, we conducted this meta-analysis to systematically evaluate the role of dexamethasone in bacterial meningitis.

Materials and methods

Literature search

The electronic databases of PubMed, Embase, Medline, and the Chinese biomedicine literature were used to retrieve relevant articles published between January 2000 and 2016. The MeSH terms were “bacterial meningitis”, “dexamethasone or corticosteroids”, “treatment or therapy”, and their combinations. We also manually searched the references of retrieved articles to obtain more resources. We considered only those studies that were written in English and Chinese.

Inclusion criteria

The eligible articles must meet the following criteria: 1) randomized, double-blind, placebo-controlled trials of dexamethasone in the treatment of bacterial meningitis; 2) the diagnosis of bacterial meningitis was accepted in the presence of positive cerebrospinal fluid (CSF) culture, positive blood culture, positive latex agglutination test, or suggestive CSF cytology and biochemical profile;²² 3) the primary outcomes were death at the time of first follow-up, severe neurological sequelae at first follow-up, and severe bilateral hearing loss at first follow-up; and 4) the search was focused on studies that had been conducted in humans.

Data extraction

Two of our authors independently assessed the quality of the included studies based on the descriptions provided by the authors of the included trials. Any disagreement was subsequently resolved by discussion with a third author to reach a final consensus on each item. The following information was extracted from each included article: the name of first author, year of publication, country, study period, age range, sample size, diagnostic criteria, dexamethasone dose, and primary outcomes.

Statistical analyses

Statistical analyses were conducted in Review Manager (Version 5.2, The Cochrane Collaboration). The overall effect was measured by odds ratios (ORs) and risk ratios (RRs) with their 95% confidence interval (CI). The significance of the pooled ratios was determined by the Z-test with a *P*-value <0.05 considered statistically significant. The *I*² test and the *Q*-statistic test were employed to calculate the between-study heterogeneity. The fixed-effect model was used when the *P*-value for the *Q*-test was >0.10 and *I*² for the *I*² test was <50%; otherwise, the random-effect model was used when the effect was heterogeneous.

The evidence of publication bias was assessed by visual funnel plot inspection. The sensitivity analysis was used to assess whether our results were substantially influenced by the presence of any individual study.

Results

Characteristics of included studies

After applying the inclusion criteria, a total of ten articles were finally screened out, including 2,459 patients (1,245 in the dexamethasone group and 1,214 in the placebo group) with bacterial meningitis. Figure 1 presents the process of literature search. The ten articles (two were written in Chinese^{23,24} and eight in English^{25–32}) were conducted in six countries (the Netherlands, India, Malawi, Vietnam, Brazil, and the People's Republic of China). All the patients were confirmed by clinically suspected bacterial meningitis plus CSF or blood criteria. The characteristics of the studies included in this analysis are listed in Table 1.

Curative effect analysis of dexamethasone in the treatment of bacterial meningitis

Follow-up mortality

All the ten articles reported the follow-up mortality of dexamethasone in the treatment of bacterial meningitis. No significant between-study heterogeneity was observed, and the fixed-effect model was used. Overall, we found that the

frequency of follow-up mortality in the dexamethasone group was a little lower than that in the placebo group (23.5% versus 25.9%), but the statistical analysis proved that dexamethasone was not associated with a significant reduction in death ($OR=0.91$, 95% $CI=0.80–1.03$, $P=0.14$) as shown in Figure 2. Subgroup analysis by age group showed that dexamethasone was not correlated with follow-up mortality reduction either in adults ($OR=0.93$, 95% $CI=0.79–1.09$, $P=0.39$) or in children ($OR=0.88$, 95% $CI=0.71–1.08$, $P=0.22$).

Hearing loss

Nine articles reported the incidence of hearing loss. Our result found that the frequency of hearing loss in the dexamethasone group was lower than that in the placebo group (21.2% versus 26.1%), and the statistical analysis found that dexamethasone was associated with a significant reduction in hearing loss ($OR=0.76$, 95% $CI=0.59–0.98$, $P=0.03$) as shown in Figure 3.

Neurological sequelae

Eight articles considered the role of dexamethasone in severe neurological sequelae of patients with bacterial meningitis. Our result demonstrated that dexamethasone was not associated with a significant reduction in severe neurological sequelae (22.4% versus 24.1%, $OR=0.84$, 95% $CI=0.54–1.29$, $P=0.42$) in the random-effect model as shown in Figure 4.

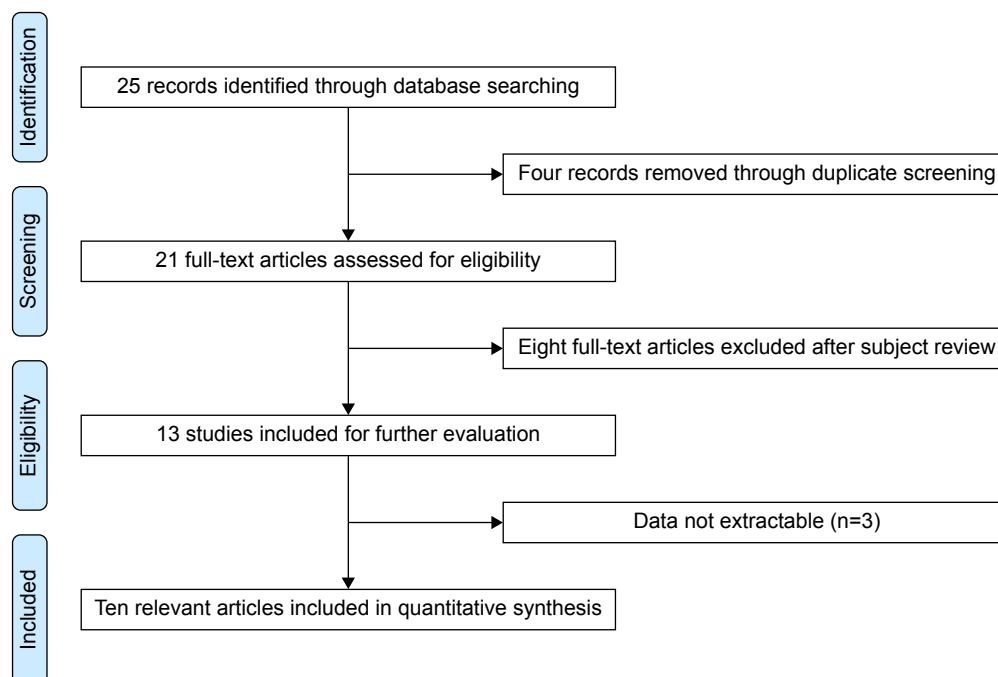
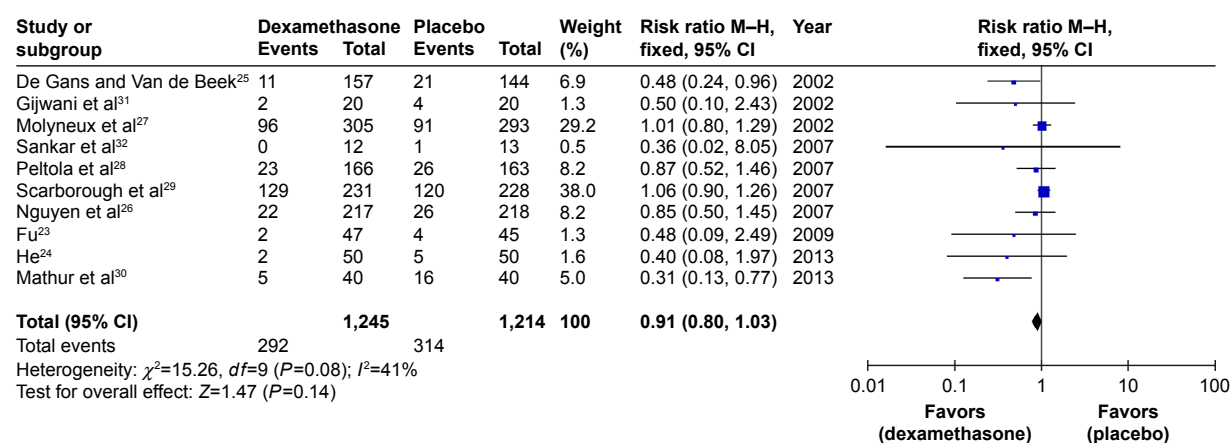


Figure 1 Flow chart of selection process in this meta-analysis.

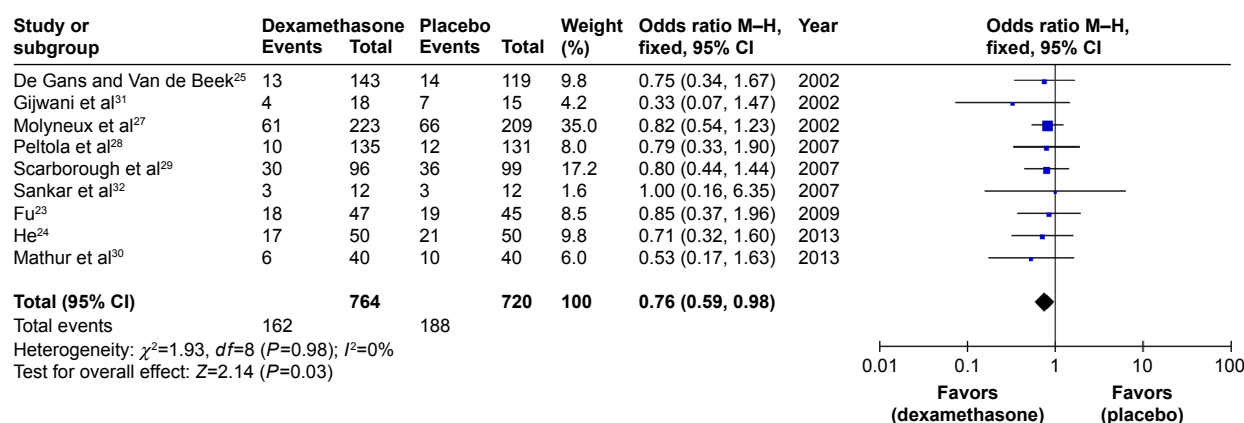
Table 1 Main characteristics of included studies in this meta-analysis

First author	Year	Country	Study period	Age range (years)	Sample size	Criteria	Dexamethasone dose	Primary outcome
De Gans and Van de Beek ²⁵	2002	The Netherlands	1993–2001	≥17	301	Clinically suspected BM plus CSF criteria	10 mg three times daily for 4 days	Death at 8 weeks
Gijwani et al ³¹	2002	India	1998–1999	>10	40	Clinically suspected BM plus CSF criteria	0.15 mg/kg four times daily for 4 days	Death at 4 weeks
Molyneux et al ²⁷	2002	Malawi	1997–2001	0.16–13	598	Clinically suspected BM plus CSF criteria	0.4 mg/kg twice daily for 2 days	Death at 4 weeks
Nguyen et al ²⁶	2007	Vietnam	1996–2005	≥14	435	Clinically suspected BM plus CSF criteria	0.4 mg/kg twice daily for 4 days	Death at 4 weeks
Peltola et al ²⁸	2007	Brazil	1996–2003	0.16–16	329	Clinically suspected BM plus CSF or blood criteria	0.15 mg/kg four times daily for 2 days	Death at 4–8 weeks
Sankar et al ³²	2007	India	2002–2003	0.16–12	25	Clinically suspected BM plus CSF or blood criteria	0.15 mg/kg four times daily for 5 days	Death at 4 weeks
Scarborough et al ²⁹	2007	Malawi	2002–2005	>15	459	Clinically suspected BM plus CSF criteria	16 mg twice daily for 4 days	Death at 6 weeks
Fu ²³	2009	People's Republic of China	Not reported	14–60	92	Clinically suspected BM plus CSF criteria	0.2 mg/kg four times daily for 4 days	Death at 8 weeks
He ²⁴	2013	People's Republic of China	2008–2012	<15	100	Clinically suspected BM plus CSF or blood criteria	0.2 mg/kg three times daily for 4 days	Death at 8 weeks
Mathur et al ³⁰	2013	India	2008–2009	<1	80	Clinically suspected BM plus CSF criteria	0.15 mg/kg four times daily for 2 days	Death at 4–6 weeks

Abbreviations: BM, bacterial meningitis; CSF, cerebrospinal fluid.

**Figure 2** Meta-analysis of the effect of adjunctive dexamethasone therapy on follow-up mortality.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

**Figure 3** Forest plot of the relative strength of adjunctive dexamethasone therapy on hearing loss in the statistical analysis.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

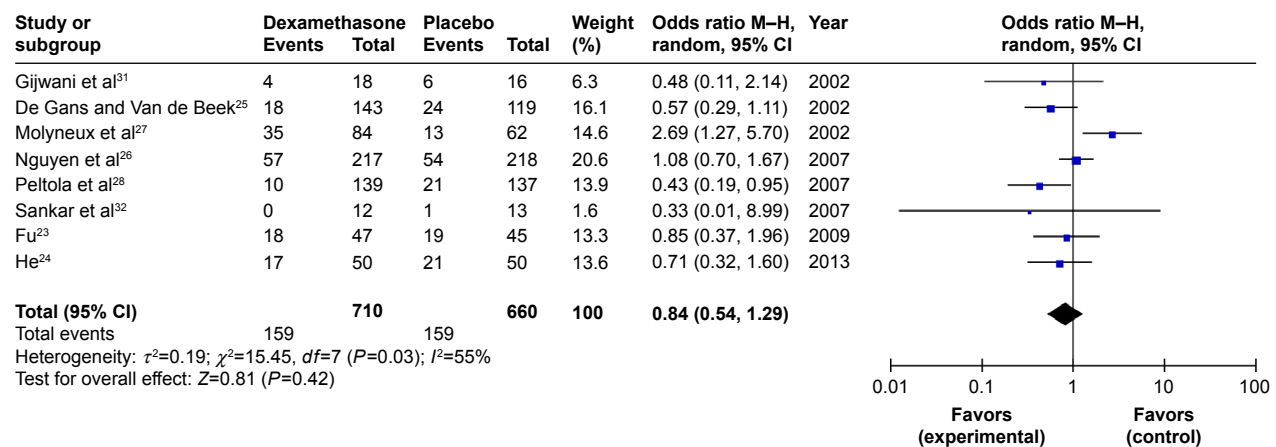


Figure 4 Meta-analysis of correlation of adjunctive dexamethasone therapy on severe neurological sequelae.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Adverse effect

Adverse events included gastrointestinal bleeding, hyperglycemia, hydrocephalus, blindness, second fever, and so on. These adverse events showed no significant difference between the dexamethasone group and the placebo group ($P>0.05$).

Sensitivity analysis and publication bias

We conducted a sensitivity analysis by systematically removing each study and recalculating the significance of the result to confirm whether each study influenced the overall results. Our result found that the pooled RRs and ORs were not significantly changed. The funnel plots were used to evaluate the publication bias. All the plots were found to be roughly symmetrical, indicating no publication bias as shown in Figure 5.

Discussion

In this meta-analysis, we totally screened out ten articles, including 2,459 patients. Our result found that dexamethasone

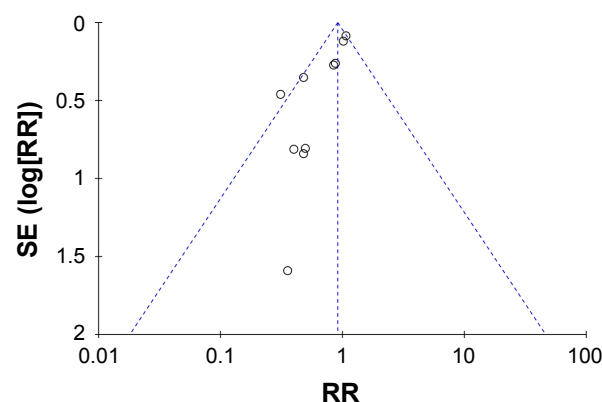


Figure 5 Funnel plot of publication bias in this meta-analysis.

Abbreviations: SE, standard error; RR, relative risk.

was not associated with a significant reduction in follow-up mortality ($P=0.14$) and severe neurological sequelae ($P=0.42$). However, dexamethasone seemed to reduce hearing loss among survivors ($P=0.03$). No significant difference was found between these two groups in adverse events. Our results were consistent with those of previous meta-analysis, which showed that adjunctive dexamethasone in the treatment of acute bacterial meningitis did not seem to significantly reduce death or neurological disability but reduced the hearing loss among survivors.³³

Bacterial meningitis is a severe acute infectious disease. The intense inflammatory host's response is potentially fatal and contributes to the neurological sequelae. The poor outcomes are mainly due to secondary systemic and intracranial complications resulting from a consequence of the inflammatory response to the invading pathogen and release of bacterial components by the pathogen itself.³⁴ The inflammatory reaction involving the meninges, the subarachnoid space, and the brain parenchymal vessels was shown to contribute to neuronal injury.³⁵ The harmful inflammatory response is initiated by the recognition of bacterial products through pattern recognition receptors.³⁶ Despite effective antimicrobial therapy, the morbidity and mortality still remain high. Adequate and prompt treatment of bacterial meningitis is critical to outcome.

Dexamethasone is used to treat many inflammatory and autoimmune conditions. It can trigger a wide cellular response modulating the expression of genes involved in the innate immune system, growth, and stress and increases susceptibility to bacterial disease.³⁷ High-dose dexamethasone was shown to modulate serum cytokine profile in patients with primary immune thrombocytopenia.³⁸ Dexamethasone is often administered before antibiotics in cases of bacterial

meningitis. It then acts to reduce the inflammatory response of the body to the bacteria killed by the antibiotics (bacterial death releases proinflammatory mediators that can cause a response that is harmful to the patient), thus improving prognosis and outcome.³⁹

Many studies have identified the role of dexamethasone in the treatment of bacterial meningitis. However, the results still remain inconclusive. Bodilsen et al⁴⁰ proved that patients treated with dexamethasone were more likely to have a favorable outcome. Baunbæk-Knudsen et al⁴¹ indicated that adjuvant corticosteroid treatment in acute bacterial meningitis improved the outcome and could safely be administered in an elderly population with high levels of immunosuppressive comorbidity. Heckenberg et al⁴² suggested that adjunctive dexamethasone was widely prescribed for patients with meningococcal meningitis, was not associated with harm, and the rate of arthritis had decreased after the implementation of dexamethasone. Weisfelt et al⁴³ showed that treatment with adjunctive dexamethasone was not associated with an increased risk for long-term cognitive impairment. Brouwer et al⁴⁴ demonstrated that the corticosteroid dexamethasone did not significantly reduce the death rate, but patients treated with corticosteroids had significantly lower rates of severe hearing loss, any hearing loss, and neurological sequelae.

The combination of dexamethasone plus other antibodies might be the new treatment strategy for patients with bacterial meningitis. Kasanmoentalib et al⁴⁵ found that adjunctive treatment with dexamethasone plus anti-C5 antibodies improved the survival in severe experimental meningitis caused by *S. pneumoniae* serotype 3. Vivas et al⁴⁶ showed that low-dose daptomycin was affected by concomitant use of dexamethasone, suggesting that the combination appeared to be a good choice for the treatment of pneumococcal meningitis. Du et al⁴⁷ suggested that dexamethasone could downregulate the expression of AQP4 in the brain tissue of rats with meningitis and provided evidence for the mechanism of protective effect of dexamethasone on the central nervous system.

Dexamethasone may also have some adverse effect in the treatment of bacterial meningitis. Leib et al⁴⁸ demonstrated that dexamethasone as adjuvant therapy increased hippocampal cell injury and reduced learning capacity in the model of pneumococcal meningitis in infant rats. Spreer et al⁴⁹ found that dexamethasone increased the rate of apoptotic neurons in the granular layer of the hippocampal dentate gyrus in rabbits with *Escherichia coli* meningitis.

There were several limitations in our present meta-analysis. First, the event numbers of each included study were too small

to show whether results were positive or negative. Second, dexamethasone in the treatment of bacterial meningitis was all short-course therapy, thus less side effects were reported. Third, the performance of adjunctive therapy with dexamethasone in bacterial meningitis was shown to be dependent on circumstances;⁵⁰ therefore, other related factors should be considered. Finally, the dexamethasone dose and empiric antibiotic therapy were different in each study, which may have influenced our results.

Conclusion

Our results indicated that patients with bacterial meningitis neither benefit from nor are harmed by treatment with adjunctive dexamethasone. Future well-designed, large-sample studies are still needed to further evaluate the role of dexamethasone in the treatment of bacterial meningitis.

Disclosure

The authors report no conflicts of interest in this work.

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