International Journal of Medical and Health Research
ISSN: 2454-9142
Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 9; September 2017; Page No. 101-106

The effectiveness of dexamethasone in the management of acute pyogenic bacterial meningitis

Raghad Altayyar
Medical student, Collage of Medicine, Taibah University, Madinah, Saudi Arabia

Abstract
Acute bacterial meningitis is associated with significant morbidity and mortality rates despite the advances in antimicrobial therapy. Adjunctive corticosteroid therapy for acute bacterial meningitis is one of the most widely discussed controversial issues recently. Thus, the aim of this review is to evaluate the effectiveness of dexamethasone as an adjunctive treatment to improve the clinical outcome and prevent complications in acute bacterial meningitis patients. Dexamethasone is classified as glucocorticoid agonist; mostly indicated as an anti-inflammatory medication used specifically to decrease cerebral edema. Although many studies have supported the beneficial effect of adjuvant dexamethasone in preventing cerebral edema in acute bacterial meningitis, it has been reported that dexamethasone has major side effects and no significant evident effect in lowering mortality rates. In addition, it has a marked effect on limiting the penetration of antibiotics into the cerebrospinal fluid. All these results support the stance against using dexamethasone in acute bacterial meningitis.

Keywords: acute bacterial meningitis, dexamethasone, adjuvant treatment, clinical outcome, hearing loss, cerebral edema

1. Introduction

Meningitis is a critical condition with significant morbidity and mortality rate despite the advances in antimicrobial therapy [1]. It implies a serious infection of the meninges; dura, arachnoid and pia matter, and extend to the underlying cortex. The blood flow to the brain is reduced due to the inflamed tissue and the edema raises the intracranial pressure leading to several neurological manifestations. The typical presentation of meningitis cases is a stiff neck, confusion, hyperpyrexia, photophobia, seizures, confusion, headache and vomiting. Different microorganisms such as bacteria, virus and fungal may reach the meninges directly through the ear, nasopharynx and cranial injury or indirectly through blood stream spread [2]. Globally, one of the most common and severe types of meningitis is bacterial meningitis due to the widespread use of antibiotics. The incidence of bacterial meningitis varies throughout the world. As in the UK and Western Europe, 1–2 cases per 100 000 people each year, while it can extend to 1000 cases per 100 000 individual each year in the Sahel region of Africa [3]. In the Kingdom of Saudi Arabia, increase incident of bacterial meningitis cases have appeared after Alhaj and Alomra seasons, in which 48% of the cases reported in the holy areas both Makkah and Madinah [4]. Mainly caused by *Neisseria meningitidis*, *Streptococcus pneumonia*, and *Haemophilus influenza*.

Bacterial meningitis can lead to a good prognosis and less complication if diagnosed and treated early, although 5% to 10% die. However, the overall mortality rate remains at a high 70-100% for untreated cases with inferior prognosis for a patient in the extreme of age [5]. The leading cause of complications in acute bacterial meningitis is the congestion developed in pia matter with polymorph which may lead to adhesions [2] causing cranial nerve palsies as sensorineural hearing loss, the most frequent and permanent one, and learning disability in 10% to 20% of survivors [2]. Furthermore, the severity of the inflammation in subarachnoid space determines the clinical outcome. This means that most of the neurological damage in acute bacterial meningitis patients is due to edema, not the infection.

Acute bacterial meningitis treatment guidelines state that the first line of treatment is antibiotics, and many studies have looked at effect of adjuvant treatment as dexamethasone [6]. Dexamethasone is classified as a glucocorticoid agonist; it has anti-inflammatory action by inhibiting polymerphonuclear leukocytes infiltration in the inflammatory site. It has the ability to penetrate the CNS and can be used alone to manage cerebral edema [7].

Several studies have focused on assessing the dexamethasone effect. According to European guidelines, DEXA should be administrated with or shortly after a first dose of antibiotic in suspected cases of bacterial meningitis [8]. This is supported by a study concluding a reduction in risk of death by (Tinuade A Ogunlesi *at.al*) [7]. Meanwhile, a study done by (Esayas Gudina *at.al*) reported an increase in mortality rate and poor discharge Glasgow outcome scale scores at discharge in suspected cases [1]; a third suggestion that DEXA approved non-significant reduction of mortality [9]. Furthermore, two recent studies have addressed a side effect of using DEXA as an adjuvant drug, visible blood in the stool noted with recurrent fever [9, 10]. Nevertheless, no side effect was recorded according to the European guidelines [11]. In addition, another aspect was discussed covering the hearing loss improvement by DEXA. In high income countries, DEXA has reduced severe hearing loss and neurological damage [10, 11]. In contrast, no improvement in sensorineural hearing loss was reported by (Ogunlesi TA *et.al*) [8]. Lastly, the empirical use of DEXA is still controversial [12] and it is reported as a central nervous system protective by (Kai-Xian Du at.al) [13]. Thus,

inconsistent findings for adjuvant dexamethasone in preventing edema to ensure better prognosis have been reported.

The aim of this review is to evaluate the effectiveness of dexamethasone as adjunctive treatment to improve the clinical outcome and prevent complications in acute bacterial meningitis patients of all ages.

2. Literature review

2.1 Epidemiology of bacterial meningitis

Acute bacterial meningitis is a serious infectious disease of the membranes covering the brain resulting in a significant morbidity and mortality rates around the world [11]. Worldwide, the epidemiology of bacterial meningitis is not equally distributed [3]. In the Kingdom of Saudi Arabia, the incidence rises after Alhaj and Alomra seasons with 48% of the cases recorded in Makkah and Madinah [4].

Worldwide, the introduction of conjugated vaccines against N. meningitidis serogroup C and 7-, 10- and 13-valent pneumococcal and H. influenzae type b has altered the epidemiology of community-acquired bacterial meningitis in the past decades [14]. This has resulted in a considerable reduction in the incidence of bacterial meningitis in children [15]; thus currently adults form the majority of patients. The type of pathogenic bacteria in bacterial meningitis is based on the age group and predisposing factors [6].

The most common neonatal period for bacterial meningitis is in a range between the second and the sixth weeks [16]. Bacterial meningitis in neonates is commonly caused by streptococcus agalactiae (group B streptococcus, GBS) and Escherichia coli [6].

In the main three pathogens caused bacterial meningitis in childrenbeyond neonates' age historically, which were H. influenzae type b, Neisseria meningitides, and Streptococcus pneumoniae [6], but they have disappeared due to the introduction of vaccination in the 1990s [17]. Currently, both children and adult's cases are affected by the serogroup B meningococcal meningitis [18]. Similarly, the incidence of pneumococcal meningitis has become equal to the incidence of meningococcal meningitis in children beyond the neonatal age [19].

In the adult population, the majority of the affected cases are caused by S. pneumoniae [20]. Meanwhile, adolescents mostly are affected by Meningococcal meningitis [18]. Another causative pathogen found in old age and immunocompromised patients is Listeria monocytogenes [21]. In addition, 1-2% of bacterial meningitis of adult cases are caused by Haemophilus influenzae and Staphylococcus associated with underlying conditions as sinusitis [6]. Common bacterial meningitis organisms are summarized in Table.1.

Table 1: Common bacterial meningitis organisms

Organism	Age	Risk factors	Proportion of cases	Case fatality
S. pneumoniae	All ages	Immunoglobulin alternative complement deficiency, asplenia, alcoholism	57%	17.9%; higher if immunocompromised
N. meningitidis	Aged 11 to 17 years and younger adults	Multiperson dwellings, travel to Sub Saharan Africa	17%	10%
L. monocytogenes	Neonates and adults	Cell-mediated immunodeficiencies (e.g. steroids, HIV, alcoholism), newborns	4%	18%
H. influenzae	Children and adults	Newborns	6%	7%
Group B streptococcus	Neonates	86% of cases are in patients aged G2 months	17%	11%
Gram-negative rods (*E. coli*, K. *pneumoniae*)	Adults	Nosocomial infection; only 3% from community	33% of all nosocomial meningitis	35% nosocomial; 25% community acquired

***Source*:** Al Bekairy A M. *et al*., 2014 [4]

2.2 Risk factors of bacterial meningitis

The acquired risk factors for bacterial meningitis can be summarized as follows:

2.21 Age

The incidence of BM is highest in the extreme of age (young children <5 years, and elderly > 60 years) [4]. As mentioned before, children and infants have been protected by vaccination

against specific causative pathogens. In elderly patients the immunity declines, thus increasing the susceptibility to infection and reducing vaccine efficacy [22].

2.22 Immuno-compromising factors:

50% of bacterial meningitis patient have predisposing conditions, one-third of these have an immunodeficiency [22]. These conditions can be, post-splenectomy, malignancy, diabetes, alcoholism/cirrhosis and hematologic disorders such as sickle cell disease or thalassemia major [4, 22].

2.23 Medications

Such as nonsteroidal anti-inflammatory drugs (NSAIDs), and trimethoprim-sulfamethoxazole [4].

2.24 Exposure to pathogens

Recent colonization, contact with meningitis patient, sinusitis, CNS trauma and dural defect [4].

2.25 Disease

As systemic lupus erythematosus [4].

2.3 Pathogenesis of bacterial meningitis:

Numerous aspects of bacterial meningitis pathogenesis remain still undiscovered. Nevertheless, four main stages are known: colonization, invasion and survival in the bloodstream, and then affection of the subarachnoid space.

For further explanation, the bacteria initially colonize the upper respiratory tract mucous membranes and it is a combination of bacteria adherence to the cell surface and avoidance of the host's defense mechanism. Followed by the invasion into the bloodstream either transcellularly (through cells) or pericellularly (between cells). Then, evasion of the immune system is required to survive in the blood stream. Thus, most meningitis cases are followed by bacteremia. However, direct spread to CNS might occur in underlying conditions such as otitis media and sinusitis or from the nose through dural defects is also possible. The last stage is bacteria entry into the subarachnoid space, where the bacteria start to multiply because the lack of host defenses. Subsequently, recognition of bacterial components develops by pattern recognition receptors which present on microglia cells and other brain cells. This recognition leads to a cascade of events resulting in the release of pro-inflammatory mediators, for instance TNFα, interleukin 6, and interleukin 1β.

Therefore, the inflammatory process in the subarachnoid space reduces blood flow to the brain tissue developing three types of cerebral edema, which are vasogenic edema due to the increase in blood vessel permeability, interstitial edema due to increase in CSF pressure, and cytotoxic edema due to the disturbance in the cerebral vessels autoregulation, which, in turn, increase the intracranial pressure causing neurological damage [2, 3, 5].

2.4 Clinical manifestation of bacterial meningitis

The clinical presentation of bacterial meningitis is similar to several other illnesses; thus, it is difficult to diagnose clinically. Differential diagnosis involves viral and fungal meningitis, meningitis caused by autoimmune conditions, medications, for example, trimethoprim and non-steroidal anti-inflammatory drugs, and malignancy, as well as non-meningitic illnesses including sub-arachnoid hemorrhage, and migraine. However, a combination between any two of the signs and symptoms; headache, neck stiffness, fever, and disturbed consciousness are common in up to 95% of patients [3]. To confirm the diagnosis, laboratory tests with physical examination and the patient's medical history are required [4].

2.5 Management of bacterial meningitis

The gold standard for meningitis diagnosis is the examination of the cerebrospinal fluid. Typically, high protein and low glucose are reported in the CSF in the case of bacterial meningitis. Moreover, high white blood count in CSF is an indication of meningitis, although it must be noted that patients may be affected by bacteria without an elevated WBC count. Furthermore, measuring the opening pressure at the lumbar puncture time, which will be increased in bacterial meningitis cases, helps in the diagnosis [3].

Another marker useful to differentiate between bacterial and viral meningitis is the CSF lactate level before the antibiotic treatment with a sensitivity of 0·93 (95% CI 0·89–0·96) and specificity of 0·96 (0·93–0·98) [23]. Coupled with the CSF gram stain and culture to identify the causative pathogen and assess the antimicrobial susceptibility. With all these useful markers in the CSF, no studies have recorded any associated features with an increase of herniation risk after lumbar puncture [3]. The classical features of CSF are summarized in Table.2 with correlation to causative organisms.

Also, the most commonly method used is the PCR, which is able to detect organisms in bloodstream or CSF for several days after antibiotics have been given [24]. The PCR has high sensitivity (87–100%) and specificity (98–100%) [25].

Another diagnostic method to consider is the loop-mediated isothermal amplification, a DNA amplification, and detection method. It is quick – results in less than 2 hours – with positive results which can be detected by the naked eye. This technique has evident sensitivity and detection for N meningitidis, S pneumoniae, H influenzae, and Mycobacterium tuberculosis [26]. In the UK, this method assessed bedside test with a 100% positive value and 97% negative proactive value [27]. Thus, the speed and ease of this tool make it a very attractive tool, especially in poor resource settings [3].

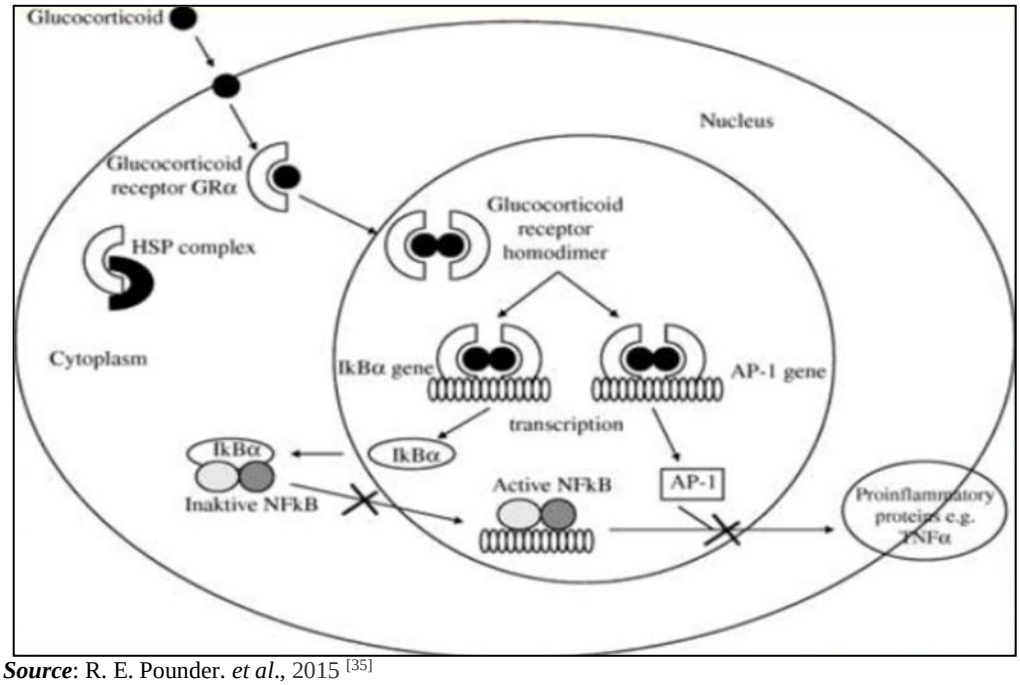
The management of bacterialmeningitis involves fast and appropriate diagnosis, antimicrobial therapy, adjunctive therapy, and chemoprophylaxis for contacts [4]. Despite the appropriate antibiotic selection, mortality is high and so consideration has focused on adjunctive therapies [3].

One of the adjunctive treatment agents is dexamethasone. DEXA is classified as glucocorticoid agonist. It is mostly indicated as an anti-inflammatory medication used specifically to decrease cerebral edema. The mechanism of action as follows: it crosses the cell membranes and binds with cytoplasmic glucocorticoid receptors. This complex binds to DNA resulting in a modification of transcription, thus inhibiting leukocyte infiltration at the site of inflammation, interfering with the function of mediators of inflammatory response, suppressing of humoral immune responses, and reducing edema or scar tissue [7]. The glucocorticoids mechanism of action is illustrated in Figure.1.

Table 2: Classic features of cerebrospinal fluid for the different causes of meningitis

	Appearance	Opening pressure (cm CSF)	White blood cell concentration (cells per µL)	Predominant cell type	CSF protein (g/L)	CSF glucose (mmol)	CSF:serum glucose ratio
Normal	Clear	10–20	<5	NA	<0·4	2·6–4·5	>0·66
Bacterial	Turbid, cloudy, purulent	Raised	Raised (normally >100)	Neutrophils	Raised (normally >1·0)	Low	Very low
Viral	Clear	Normal or mildly raised	Raised (normally <1000)	Lymphocytes	Mildly raised (normally 0·5–1)	Normal or slightly low	Normal or slightly low
Tuberculous	Clear, cloudy	Raised	Raised (normally <500)	Lymphocytes	Greatly raised	Low	Very low

***Source*:** McGill F. *et al*., 2017 [3].



Source: R. E. Pounder. *et al*., 2015 [35]

Fig 1: Glucocorticoid mechanism of action

2.6 Beneficial versus side effect of DEXA in bacterial meningitis

Adjunctive corticosteroid therapy for acute bacterial meningitis is one of the most widely discussed controversial issues in recent times [28]. Multiple studies have revealed the impact of adjunctive dexamethasone therapy on acute bacterial meningitis. Beginning with the suspected cases, the European guidelines state that DEXA administration should be together with or soon after the first antibiotic dosage [6]. Similarly, a review carried outby (Ogunlesi TA et.al.2015) reported that adjunctive corticosteroid administration reduced the risk of death among neonates with bacterial meningitis [8]. On the other hand, a retrospective study directed at four teaching hospitals across Ethiopia showed that nearly all patients treated for suspected bacterial meningitis did not receive an accurate diagnosis. Therefore, adjuvant dexamethasone used in clinically unproven cases of bacterial meningitis was correlated with an increased mortality and poor Glasgow outcome scale scores at discharge. These findings demonstrate that there are potential deleterious effects in unverified cases [1]. Another review by (Brouwer MC *et al*., 2015) [22] found that corticosteroid dexamethasone did not significantly decrease the death rate [9]. (Table.3)

A different aspect to compare is the adverse events of DEXA. Dexamethasone raises the recurrent fever rate (28% versus 22%) but is not associated with other side effects according to a 2015 Cochrane review carried out by (Brouwer MC *et al*., 2015) [9]. Moreover, comparing adjuvant dexamethasone or glycerol with a placebo in children aged from 2 months to 16 years through a prospective randomized double-blind trial in Latin America noted hematochezia, recurrent fever and hyperglycemia [10]. Conversely, no side effects are recorded according to the European guidelines [6].

Another aspect to be considered is the effect of DEXA on neurological damage, especially hearing loss. The European guidelines mentioned that DEXA decreases severe hearing loss and neurological damage associated with bacterial meningitis in high-income countries [10]. These findings were also supported by a prospective randomized double-blind trial in Latin America [11]. The same results appeared in the review carried out by (Brouwer MC *et al*. 2015) [22], which also stated that DEXA reduced the hearing loss of any degree and short-term neurological sequelae, but there were no beneficial effects found among low-income countries. In addition, in children with meningitis due to *H. influenzae*, it decreased the rate of hearing loss by (4% versus 12%). No effect was evident due to any other type of bacteria [9].

To specify the mechanism of DEXA as anti-inflammatory medication in bacterial meningitis, a study was carried out by (Ichiyama T et.al) in which 14 CSF samples obtained from bacterial meningitis affected children at Yamaguchi University Hospital. Then, the 14 patients were divided into two groups. One received DEXA adjunctive therapy and the other did not. The results revealed that among the patients with dexamethasone, the ratio of CSF2/CSF1 sTNFR1 was significantly lower than that without dexamethasone ($p = 0.0063$). In addition, DEXA reduced the increase of CSF tumor necrosis factor receptor 1 levels. However, the ratio of CSF2/CSF1 IL-6 showed no significant differences [29].

An experimental study analyzed dexamethasone effectiveness on gram- negative bacteria-derived lipopolysaccharide (LPS) which induced inflammation in astroglial/microglial co-cultures. This study provided a possible explanation for the benefits of DEXA in the treatment of acute bacterial meningitis in vivo by revealing the ability of DEXA to decrease microglial activation and to reconstitute astrocytic properties in vitro [30].

A retrospective analysis of consecutive adult (>18 years of age) patients treated for acute community-acquired bacterial meningitis from 1 Jan.1990 to 31 Dec. 2009 at the teaching

tertiary care Zagreb Hospital for Infectious Diseases, Croatia, was carried out using the Glasgow Outcome Scale (GOS) as a measurement of disease outcome. From 20-year experience, it was concluded that benefits of adjunctive dexamethasone in adult bacterial meningitis are not evident. Both socioeconomic and methodological factors do not explain the discrepancy. Also, empirical use of DEXA appears controversial [12].

A systematic review of randomized controlled trials comparing DEXA with a placebo in the management of pediatric patients with bacterial meningitis appeared that neither mortality (p = 0.86), nor the incidence of neurological (p = 0.41), and auditory (p = 0.48) sequelae recorded differences between the groups. As a conclusion, there are no benefits in combining corticosteroids with the antibiotic of bacterial meningitis pediatric patients [31].

Similarly, a 2016 systematic meta-analysis evaluated the therapeutic and side effect of adjunctive dexamethasone therapy in bacterial meningitis patients. It collected randomized, double-blind, placebo-controlled trials published between 2000 and 2016 of DEXA in the management of bacterial meningitis, resulting in 10 articles covering 2,459 bacterial meningitis patients. The data analysis confirmed neither significant reduction in mortality (OR =0.9, P=0.14) nor severe neurological sequelae (OR =0.84, P=0.42). On the other hand, DEXA seemed to decrease hearing loss among survivors (OR =0.76, P=0.03). For the adverse events, no significant difference was found between these two groups**.** According to the previous results, there are still doubts about adjunctive DEXA benefits in the treatment of bacterial meningitis [32].

Two studies considered the influence of dexamethasone on the antibiotic penetration into cerebrospinal fluid which is the main treatment of bacterial meningitis. First, a double-blind randomized study focused on determining whether the adjunctive corticosteroid therapy affects CSF concentration of ceftriaxone in adult patients with acute bacterial meningitis. It concluded that the concentration of ceftriaxone in CSF was adequate and ceftriaxone penetration into CSF was not significantly affected by adjunctive dexamethasone [33]. This is supported by an experimental Pneumococcal Meningitis study which compared theinfluence of DEXA on ceftriaxone and vancomycin. The result illustrated that no statistically significant differences were recorded between the group treated with DEXA and that without DEXA in the ceftriaxone-treated groups. Additionally, in the vancomycin-treated groups, statistically significant lower CSF vancomycin levels at 2 h were found in the DEXA-treated rabbits, and differences in bacterial killing [34].

3. Conclusion

Although, many studies have supported the beneficial effect of adjuvant dexamethasone in preventing cerebral edema and/or hearing loss in acute bacterial meningitis, it has been reported that dexamethasone has major side effects such as recurrent fever, hyperglycemia and hematochezia, and there was no significant evident effect in decreasing mortality rates. In addition, it has a marked effect on limiting the penetration of antibiotics into the CSF. All these results support the stance against using dexamethasone in acute bacterial meningitis. Moreover, further research studies are needed to study the efficacy of DEXA versus other adjuvant medications in decreasing morbidity and mortality rates in acute bacterial meningitis in KSA.

4. Acknowledgment

The completion of this literature review could not have been possible without the participation and assistance of my supervisor Dr. Amal Youssef. Her contributions are appreciated and gratefully acknowledged.

5. References

1. Gudina EK, Tesfaye M, Adane A, Lemma K, Shibiru T, Wieser A, *et al*. Adjunctive dexamethasone therapy in unconfirmed bacterial meningitis in resource limited settings: is it a risk worth taking? BMC neurology. 2016; 16(1):153.
2. Kumar P, Clark M. Clinical Medicine Textbook, Ninth Edition. Elsevier Ltd. 2017, 1126-1128.
3. McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. The Lancet. 2017; 388(10063):3036-47.
4. Al Bekairy AM, Al Harbi S, Alkatheri AM, Al Dekhail S, Al Swaidan L, Khalidi N. Bacterial meningitis: An update review. African Journal of Pharmacy and Pharmacology. 2014; 8(18):469-78.
5. Rosto E, editor. Pathophysiology Made Incredibly Easy! Lippincott Williams & Wilkins; 2009:143-148.
6. Chaudhuri A, Martin PM, Kennedy PG, Andrew Seaton R, Portegies P, Bojar M, *et al*. EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults. European Journal of Neurology. 2008; 15(7):649-59.
7. Harvey R, Champe P, Howland R, Mycek M. Pharmacology Textbook Sixth Edition. Lippincott Williams & Wilkins. 2014, 279-282.
8. Ogunlesi TA, Odigwe CC, Oladapo OT. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. The Cochrane Library, 2015.
9. Brouwer M C, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. The Cochrane Library, 2015.
10. Peltola H, Roine I, Fernández J, Zavala I, Ayala SG, Mata AG, *et al*. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clinical Infectious Diseases. 2007; 45(10):1277-86.
11. Van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, *et al*. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clinical Microbiology and Infection. 2016; 22(3):S37-62.
12. Peterković V, Trkulja V, Kutleša M, Krajinović V, Lepur D. Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice. Journal of Neurology. 2012; 259(2):225-36.
13. Du KX, Dong Y, Zhang Y, Hou LW, Fan DX, Luo Y, *et al*. Effects of dexamethasone on aquaporin-4 expression in brain tissue of rat with bacterial meningitis. International Journal of Clinical and Experimental Pathology. 2015; 8(3):3090.

14. McIntyre PB, O'Brien KL, Greenwood B, Van De Beek D. Effect of vaccines on bacterial meningitis worldwide. The Lancet. 2012; 380(9854):1703-11.
15. Netherlands Reference Laboratory for Bacterial Meningitis (AMC/ RIVM). Bacterial meningitis in the Netherlands Annual Report 2010. Amsterdam: University of Amsterdam, 2011.
16. Garges HP, Moody MA, Cotten CM, Smith PB, Tiffany KF, Lenfestey R, *et al*. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters? Pediatrics. 2006; 117(4):1094-100.
17. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clinical Microbiology Reviews. 2010; 23(3):467-92.
18. Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960–2012: an analysis of national surveillance data. The Lancet: Infectious Diseases. 2014; 14(9):805-12.
19. Martin NG, Sadarangani M, Pollard AJ, Goldacre MJ. Hospital admission rates for meningitis and septicaemia caused by Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae in children in England over five decades: a population-based observational study. The Lancet: Infectious Diseases. 2014; 14(5):397-405.
20. Ardanuy C, Tubau F, Pallares R, Calatayud L, Domínguez MA, Rolo D, *et al*. Epidemiology of invasive pneumococcal disease among adult patients in Barcelona before and after pediatric 7-valent pneumococcal conjugate vaccine introduction, 1997–2007. Clinical Infectious Diseases. 2009; 48(1):57-64.
21. Koopmans MM, Brouwer MC, Bijlsma MW, Bovenkerk S, Keijzers W, van der Ende A, *et al*. Listeria monocytogenes sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study. Clinical Infectious Diseases. 2013; 57(2):247-53.
22. Adriani K, Brouwer M, Beek D. Risk factors for community-acquired bacterial meningitis in adults. The Netherlands Journal of Medicine. 2015; 73(2):53-60.
23. Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. Journal of Infection. 2011; 62(4):255-62.
24. Bronska E, Kalmusova J, Dzupova O, Maresova V, Kriz P, Benes J. Dynamics of PCR-based diagnosis in patients with invasive meningococcal disease. Clinical Microbiology and Infection. 2006; 12(2):137-41.
25. Poppert S, Essig A, Stoehr B, Steingruber A, Wirths B, Juretschko S, *et al*. Rapid diagnosis of bacterial meningitis by real-time PCR and fluorescence in situ hybridization. Journal of Clinical microbiology. 2005; 43(7):3390-7.
26. Nagdev KJ, Kashyap RS, Parida MM, Kapgate RC, Purohit HJ, Taori GM, *et al*. Loop-mediated isothermal amplification for rapid and reliable diagnosis of tuberculous meningitis. Journal of Clinical Microbiology. 2011; 49(5):1861-5.
27. Bourke TW, McKenna JP, Coyle PV, Shields MD, Fairley DJ. Diagnostic accuracy of loop-mediated isothermal amplification as a near-patient test for meningococcal disease in children: an observational cohort study. The Lancet: Infectious Diseases. 2015; 15(5):552-8.
28. Peterković V, Trkulja V, Kutleša M, Krajinović V, Lepur D. Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice. Journal of Neurology. 2012; 259(2):225-36.
29. Ichiyama T, Matsushige T, Kajimoto M, Tomochika K, Matsubara T, Furukawa S. Dexamethasone decreases cerebrospinal fluid soluble tumor necrosis factor receptor 1 levels in bacterial meningitis. Brain and Development. 2008; 30(2):95-9.
30. Hinkerohe D, Smikalla D, Schoebel A, Haghikia A, Zoidl G, Haase CG, *et al*. Dexamethasone prevents LPS-induced microglial activation and astroglial impairment in an experimental bacterial meningitis co-culture model. Brain Research. 2010; 1329:45-54.
31. Bernardo WM, Aires FT, de Sá FP. Effectiveness of the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis. Revista da Associação Médica Brasileira (English Edition). 2012; 58(3):319-22.
32. Shao M, Xu P, Liu J, Liu W, Wu X. The role of adjunctive dexamethasone in the treatment of bacterial meningitis: an updated systematic meta-analysis. Patient preference and adherence. 2016; 10:1243.
33. Buke AC, Cavusoglu C, Karasulu E, Karakartal G. Does dexamethasone affect ceftriazone penetration into cerebrospinal fluid in adult bacterial meningitis. International Journal of Antimicrobial Agents. 2003; 21(5):452-6.
34. Cabellos C, Martinez-Lacasa J, Martos A, Tubau FE, Fernandez A, Viladrich PF, *et al*. Influence of dexamethasone on efficacy of ceftriaxone and vancomycin therapy in experimental pneumococcal meningitis. Antimicrobial Agents and Chemotherapy. 1995; 39(9):2158-60.
35. Pounder RE, *et al*. (eds). Alimentary Pharmacology & Therapeutics, 2015.