Int J Clin Exp Med 2019;12(5):4505-4516
www.ijcem.com /ISSN:1940-5901/IJCEM0089236

Review Article

Anti-cytokine and anti-endotoxin therapies for meningococcal disease: a systematic review and meta-analysis

Li Zhou[1], Xiaohong Xu[1], Hui Yu[2], Chengpeng Jiang[1], Bin Yi[3], Haoyu Chen[1]

[1]Department of Digestive Infection, Gansu Provincial Maternity and Child-care Hospital, Lanzhou 730050, Gansu, China; [2]Department of Infection, Children's Hospital of Fudan University, Shanghai 200032, China; [3]Department of Neonatology, Gansu Provincial Maternity and Child-care Hospital, Lanzhou 730050, China

Received December 1, 2018; Accepted January 9, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: The benefits and harms of anti-cytokine and anti-endotoxin for treating patients with meningococcal disease remain unclear. The goal of this study was to compare the effectiveness and toxicity of anti-cytokine and anti-endotoxin for meningococcal disease. This meta-analysis was performed according to the PRISMA guidelines. Randomized controlled trials (RCTs) and quasi-RCTs reporting comparisons of toxicity of anti-cytokine and anti-endotoxin for meningococcal disease were selected for inclusion irrespective of publication status or language. Results are expressed as risk ratios (RR) with 95% confidence intervals (CI) or number needed to treat to benefit (NNTB) for dichotomous outcomes and mean difference (MD) with 95% CI. Two trials (660 participants) met our inclusion criteria. Most of the outcomes had a moderate level of bias. There were no significant differences in mortality from meningococcal disease (RR 0.71, 95% CI 0.49 to 1.03), NNTB 20; number of participants with any complications (RR 0.68, 95% CI 0.43 to 1.08), NNTB 12; and long-term complications (RR 0.76, 95% CI 0.57 to 1.01), NNTB 17 between anti-endotoxin versus placebo. The evidence does not support the use of anti-endotoxin in the treatment of meningococcal disease. Outcomes from large parallel RCTs are needed to better inform clinicians regarding the use of anti-endotoxin or anti-cytokine for meningococcal disease. Patient-centered outcomes should be considered for inclusion in future studies.

Keywords: Meningococcal disease, Neisseria meningitides, anti-cytokine, anti-endotoxin therapies, LPS

Introduction

Meningococcal disease is a contagious, bacterial infection caused by Neisseria meningitides (N. meningitides). The most common presentations of the disease are meningococcal septicemia and meningitis and symptoms including fever, headache, fatigue, myalgia, vomiting and tachycardia [1]. Cases of meningococcal disease tend to cause considerable public anxiety. Onset of symptoms can progress rapidly and result in death within hours. Despite advances in antibiotic therapy and intensive care facilities, 3% to 34% of children with severe meningococcaemia still die [2, 3]. In as many as 10% to 15% of survivors there is significant resultant morbidity. Meningococcal disease can cause neurological defects including hearing loss, speech disorders, and loss of limbs, mental retardation and paralysis [4].

The pathophysiology of meningococcal disease consists of a complex interaction of bacterial and host factors. It initiates the inflammatory cascade which is triggered by the release of endotoxin, resulting in multi-organ failure, coagulopathy, capillary leak, metabolic derangement and eventually death. Rapid recognition and aggressive management are essential in reducing mortality. High concentrations of endotoxin have been shown to correlate with disease severity and fatal outcome [5-7]. LPS triggers an inflammatory cascade resulting in myocardial dysfunction, altered immune response and disseminated intravascular coagulation (DIC). Anti-endotoxins are aimed at correcting coagulopathy, blood purification, and anti-inflammatory cytokines. The lipooligosaccharide (LOS) coat of N. meningitidis, released into serum in high concentrations, is a potent stimulator of inflammatory pathways. Important mediators

include cytokines (pro-inflammatory and anti-inflammatory), chemokines and prostaglandins [8].

Although anti-cytokine and anti-endotoxin are used for meningococcal disease, it is not clear whether they are appropriate treatments for this infection. The disordered physiology in MCD results from a complex interaction of several mediators, therefore, attempts to correct this by altering just one step represents a gross oversimplification of the process. In addition, the experimental model of endotoxemia, which is often used, is a poor representation of an acutely ill patient with rapidly progressive shock. In order to yield conclusive results any future trials must be multi-center, random, controlled trials, but these are expensive and, in practice, difficult to conduct. The current study aimed to review available randomized controlled trials (RCTs) or quasi-RCTs of anti-cytokine and anti-endotoxin for meningococcal disease to provide more reliable evidence for clinicians.

Methods

Data sources and search strategy

The Cochrane Central Register of Controlled Trials CENTRAL (2017, issue 7), MEDLINE (1948 to July, 2017), EMBASE (2010 to July, 2017) and the Chinese Biomedical literature database (1978 to July, 2017) were searched. The reference lists of identified studies, key textbooks, review articles, and relevant studies to identify additional relevant studies. The search strategy of MEDLINE and EMBASE is showed in **Appendix 1**. All searches were updated on July 2016. There were no language or publication restrictions.

Selection of studies

Eight review authors undertook this review. The above search strategy was used to obtain relevant titles and abstracts of studies. Three review authors (LZ, XHX, HY) independently screened titles and abstracts and discarded studies that were not applicable. Studies and reviews were initially retained that might include relevant data or trial information. Five review authors (CPJ, BY, DHL, HYC, BLW) independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies met the inclusion criteria.

RCTs and quasi-RCTs addressing the effectiveness and safety of anti-cytokine and anti-endotoxin for meningococcal disease were selected. Inclusion criteria were as follows: (1) children and adults with a clinical diagnosis of probable or microbiologically-proven meningococcal disease or participants with septicemia or meningitis, (2) anti-cytokine versus placebo, (3) anti-cytokine versus another treatment, (4) anti-endotoxin versus placebo, (5) anti-endotoxin versus another treatment, (6) anti-cytokine versus anti-endotoxin. Studies that met the following criteria were further excluded: (1) immunocompromised participants; (2) irrelevant study design; (3) no access to either the full-text or abstracts for quality assessment and data extraction; (4) indeterminate title/abstract.

Types of outcome measures

The primary outcomes included: mortality from meningococcal disease, morbidity from meningococcal infection, number of participants with any morbidity. Secondary outcomes included: burden of disease on the family and the caregivers; important long-term complications such as amputations, skin grafts or persistent neurological defects including hearing loss, speech disorders, mental retardation and paralysis; adverse effects from anti-endotoxin or anti-cytokine treatment; frequency and distribution of early complications; recurrence of meningococcal disease.

Data extraction and management

Five review authors (CPJ, BY, DHL, HYC, BLW) independently extracted data using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial existed, reports were grouped together and the most recent or most complete data set was used. Any discrepancies between published versions were highlighted. We requested by written correspondence any further information required from the original trial author(s) and included any relevant information we obtained in this manner in the review. A fourth review author (HYC) resolved disagreements.

Assessment of risk of bias in included studies

Three review authors (LZ, HY, BY), a content expert and a methodologist, who were not blinded to the authorship of the studies or the journals in which they were published, independently assessed the risk of bias of the included studies. Another review author (XHX) resolved any disagreements among the review authors by discussion or by asking the study authors open-ended questions, if possible. The following items were assessed using the risk of bias assessment tool [9]: random sequence generation (selection bias), allocation concealment (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias).

Statistical analysis

Results for dichotomous variables are expressed as risk ratios (RR) and continuous variables as mean differences (MD), both with 95% confidence intervals (CI). Dichotomous outcomes are presented as RR with 95% confidence intervals (CI) for individual trials. The findings of each study were discussed and, if possible, feasible data were pooled. The number needed to treat to benefit (NNTB) were calculated if the results are significant. Clinical heterogeneity was evaluated by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. Statistical heterogeneity was assessed using the Chi^2 test and by calculating the I^2 statistic [10]. I^2 statistic values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. If heterogeneity existed, reasons were investigated and caution was advised in the interpretation of the results. Publication bias was addressed by conducting a comprehensive literature search that encompasses published and unpublished studies and trial registries. As there were only three included trials, a funnel plot was used to detect reporting biases and use a statistical test to check for any plot asymmetry.

Review Manager [11] software was used to conduct the statistical analysis. A fixed-effect model was used for calculating summary estimates in the absence of significant heterogeneity, otherwise a random-effects model was used. Descriptive techniques were used when clinical heterogeneity existed or when there were no suitable data for analysis.

A subgroup analysis was used to explore possible sources of heterogeneity including dose and duration of therapy. A sensitivity analysis was performed to explore the influence of low methodological quality studies (i.e. quasi-RCTs) and different designs (i.e. parallel versus crossover trials).

Results

Results of the search and basic characteristics

The electronic searches identified 1652 records. After screening titles and abstracts, we identified 27 potential citations for further review. Finally, two randomized, double-blind, placebo-controlled multicenter trials [12, 13] were included. The literature selection process is shown in **Figure 1**.

A total of 660 participants were enrolled in the two included studies. Sample sizes ranged from 267 to 393 participants. One study was conducted in 22 centers in the UK and the USA [13]. One study was conducted in 26 centers in the Netherlands, the UK, France, Spain and Norway [12]. No trials studied anti-cytokine versus other treatments, anti-endotoxin versus other treatments, and anti-cytokine versus anti-endotoxin for meningococcal disease. Included studies only compared the effectiveness and toxicity of anti-endotoxin versus no intervention [12, 13] for meningococcal disease.

Risk of bias in included studies

The included studies all mentioned randomization. One study was randomized by center in blocks of two or four to receive the intervention [12]. One study was randomized using the Statistical Analysis System [13]. The included studies all mentioned double-blinding but did not describe the method in detail. One study reported that a participant died [13]. One study reported that all patients were randomized and analyzed [12]. The details of risk of bias of included studies are shown in **Figures 2** and **3**.

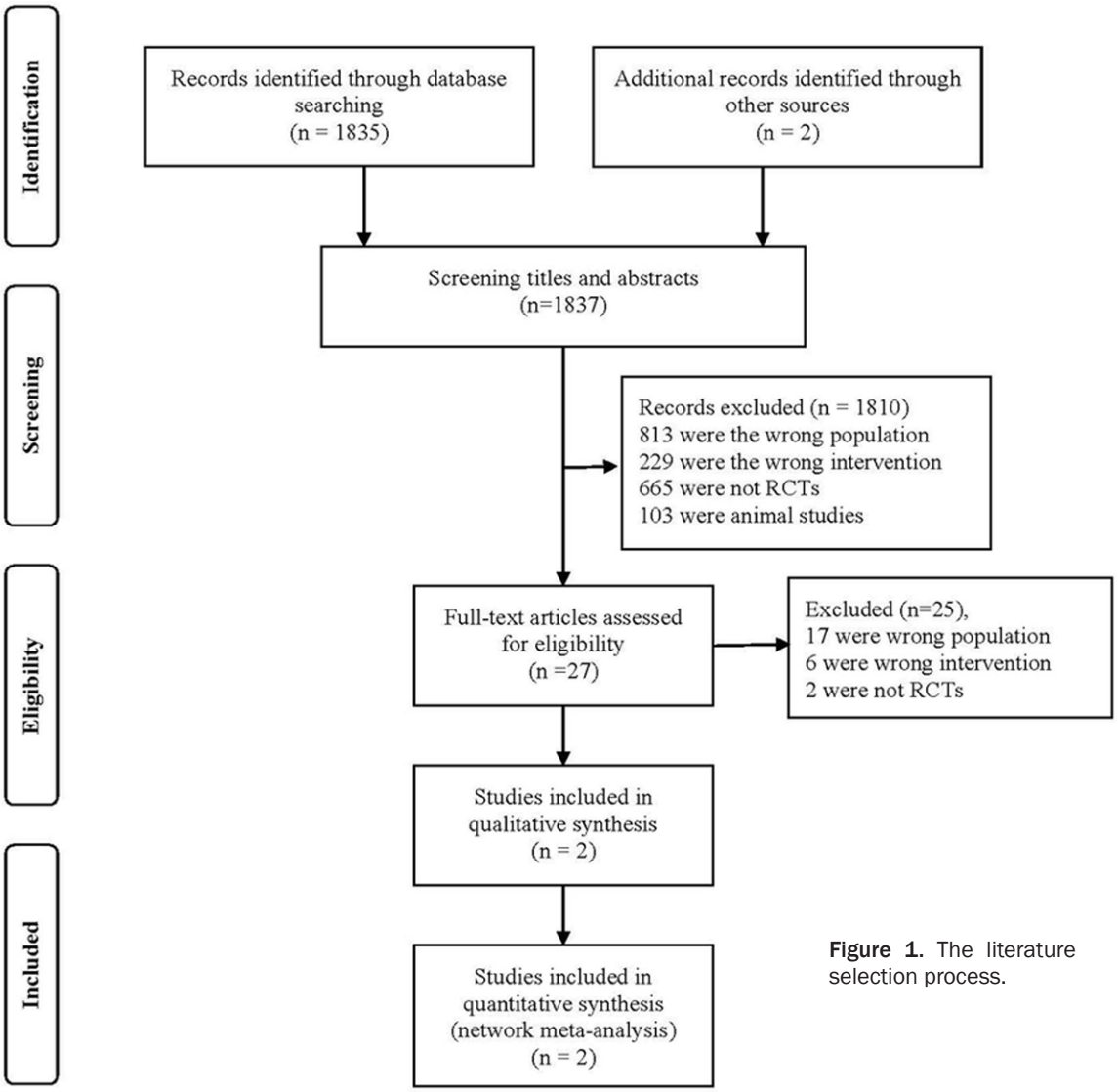

Figure 1. The literature selection process.

Analysis of mortality, morbidity and long-term complications

Two studies [12, 13] reported mortality from meningococcal disease. There was no significant difference of mortality from meningococcal disease between the anti-endotoxin and no intervention groups (**Figure 4**) (RR 0.71, 95% CI 0.49 to 1.03). One study [12] reported the number of participants with any morbidity. There were no significant differences of the number of participants with any morbidity between the anti-endotoxin and no intervention groups (**Figure 5**) (RR 0.68, 95% CI 0.43 to 1.08). Two studies [12, 13] reported important long-term complications. There was no significant difference of important long-term complications between anti-endotoxin and the no intervention groups (**Figure 6**) (RR 0.76, 95% CI 0.57 to 1.01). Morbidity from meningococcal infection, burden of disease on the family and the caregivers, adverse effects from anti-endotoxin, frequency and distribution of early complications, recurrence of meningococcal disease were not reported in any of the included studies.

Quality of the evidence

Figure 7 presents the results of the quality of evidence. Most of the outcomes had a moderate level of quality (**Figure 7**).

Discussion

Meningococcal disease is important because it is a significant cause of mortality and morbidi-

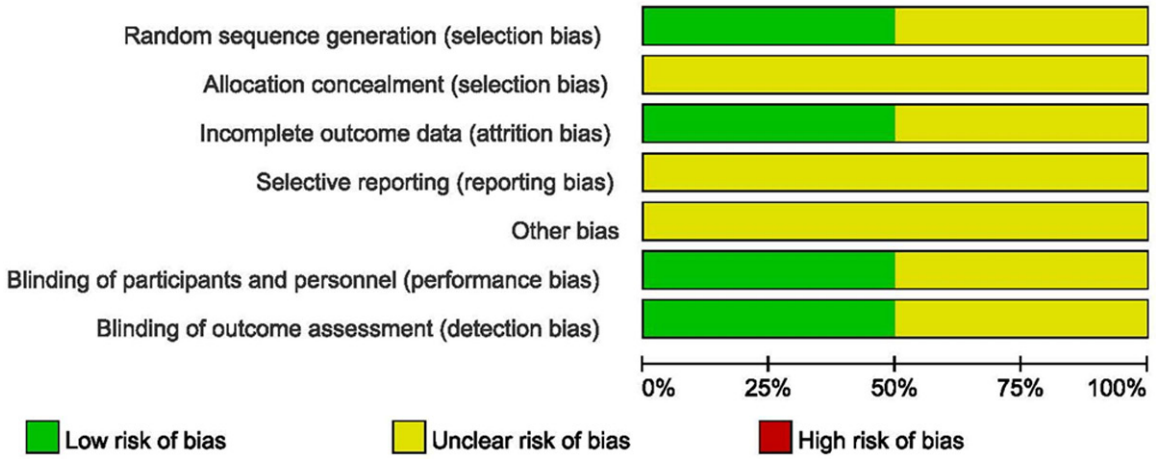

Figure 2. Bias risk.

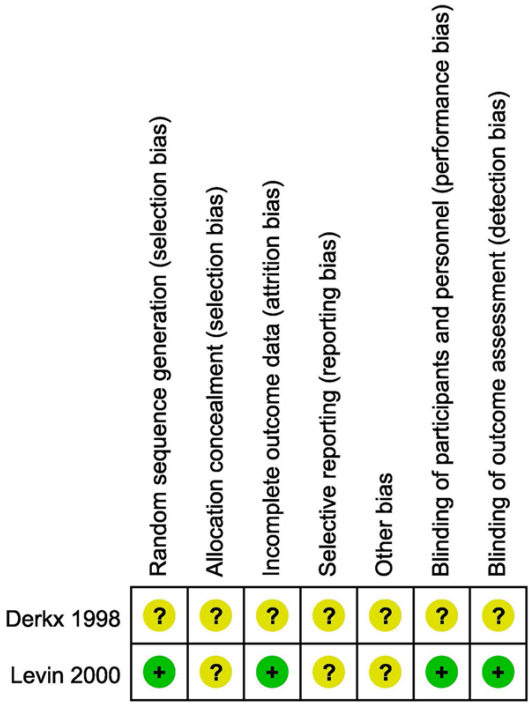

Figure 3. Risk of bias of the selected studies.

ty. The annual notified incidence is currently about 5/100,000 each year, the highest rate recorded since World War II. Despite the recent introduction of the meningococcal C vaccine, there is no immediate prospect of disease eradication [14]. Our current study indicates that compared with no treatment, anti-endotoxin and anti-cytokine does not reduce mortality of meningococcal disease. Also, anti-endotoxin does not reduce the number of participants with any morbidity and important long-term complications. Two small RCTs comparing anti-endotoxin and anti-cytokine versus placebo for meningococcal disease were identified after checking approximately 1383 abstracts. As a result, the effects of longer-term therapy cannot be ascertained. Anti-endotoxin and anti-cytokine were associated with adverse events. Such adverse events are of importance to patients and these adverse events might influence patients to stop taking anti-endotoxin and anti-cytokine. Therefore, even though anti-endotoxin and anti-cytokine showed beneficial effects for meningococcal disease in some patient groups, there are limitations to applying the results to other patient groups.

Randomized, double-blind, placebo-controlled trials were included. The random allocation sequence was implemented using centers in blocks of two or four to receive the intervention [12], the Statistical Analysis System [13]. These studies did not mention allocation concealment. Both of two studies [12, 13] mentioned double-blinding but they did not describe the method in detail. In addition, there was no indirectness of evidence (indirect population, intervention, control, and outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).

The overwhelming evidence is that many of the new therapies have failed to show any benefit [14]. The pre-clinical data from many trials often point clearly to the fact that blocking or neutralizing mediators or supplementing low levels of clotting factors might reduce morbidity and mortality. It may be that the regulatory

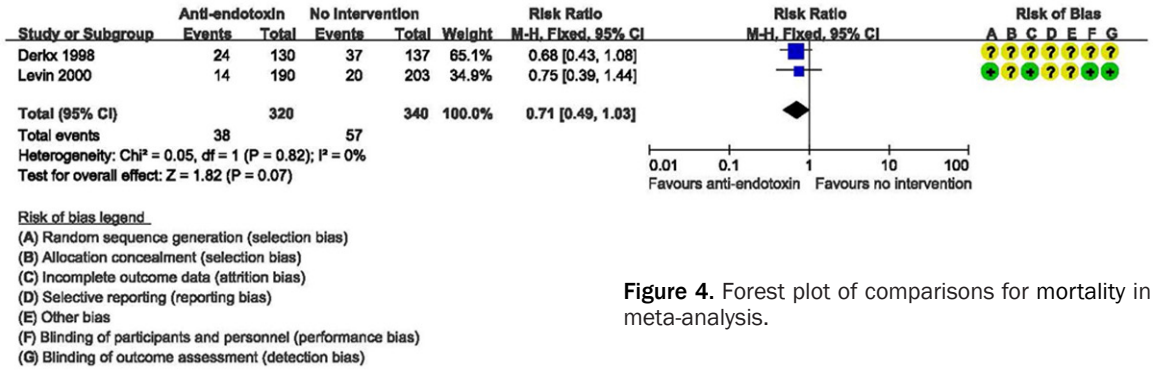

Figure 4. Forest plot of comparisons for mortality in meta-analysis.

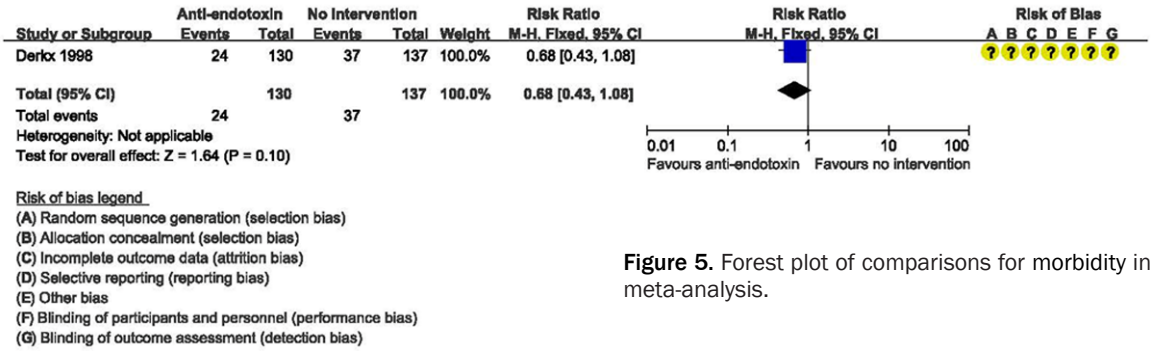

Figure 5. Forest plot of comparisons for morbidity in meta-analysis.

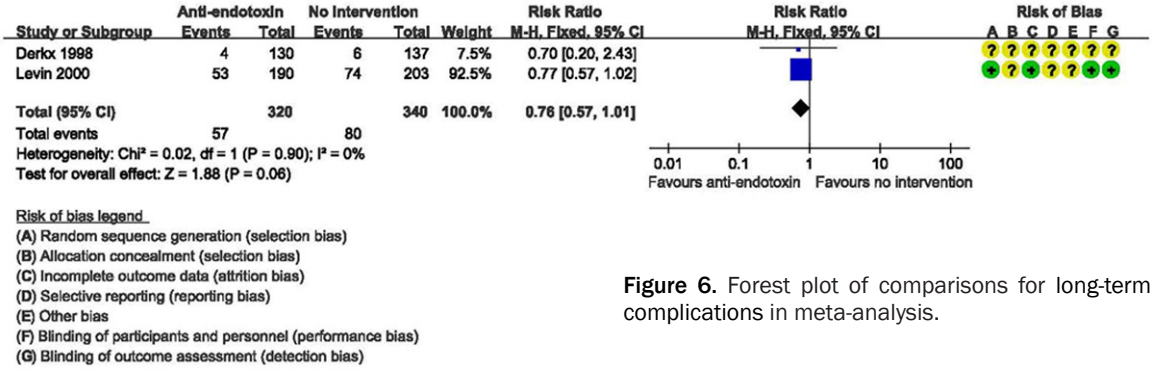

Figure 6. Forest plot of comparisons for long-term complications in meta-analysis.

mechanisms are far more complex than we suppose, or that different sub-groups of patients respond differently [14]. It may be that the drugs administered do not act *in vivo* in the manner in which they are expected to. As an example, HA-1A was meant to bind to and specifically neutralize the lipid A moiety of endotoxin but it was later shown that this binding was non-specific [14]. It could be that a multi-targeted approach using combination therapy, rather than single agents, is the way forward. The issue of timing of therapy is crucial in a rapidly progressive disease such as meningococcal disease. The window of opportunity in which the inflammatory cascade can be modified is small and it may be that by the time a patient presents with meningococcal septic shock, any immunomodulatory strategies, regardless of how effective they are, will be too late.

The few limitations in the design and implementation of the studies therefore suggest a low likelihood of bias. However, for some outcomes the total number of events was less than 300, so imprecision of results might exist. Electronic, online trial and manual searches were conducted to search for relevant articles but there may have been papers that were not identified. This review only includes published data. Unpublished data of anti-endotoxin and

A

Anti-endotoxin versus placebo for meningococcal disease

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Anti-endotoxin versus placebo (95% CI)
Mortality from meningococcal disease	660 (2 studies)	⊕⊕⊕⊕ **HIGH**	**RR 0.71** (0.49 to 1.03)	**Study population**	
				168 per 1000	**49 fewer per 1000** (from 86 fewer to 5 more)
				Moderate	
				184 per 1000	**53 fewer per 1000** (from 94 fewer to 6 more)
Number of participants with any morbidity	267 (1 study)	⊕⊕⊕⊖ **MODERATE**[1] due to imprecision	**RR 0.68** (0.43 to 1.08)	**Study population**	
				270 per 1000	**86 fewer per 1000** (from 154 fewer to 22 more)
				Moderate	
				270 per 1000	**86 fewer per 1000** (from 154 fewer to 22 more)
Important long-term complications	660 (2 studies)	⊕⊕⊕⊖ **MODERATE**[1]	**RR 0.76** (0.57 to 1.01)	**Study population**	
				235 per 1000	**56 fewer per 1000** (from 101 fewer to 2 more)
				Moderate	

B

	due to imprecision	204 per 1000	49 fewer per 1000 (from 88 fewer to 2 more)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed ris in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] total number of events is less than 400

Figure 7. Quality of evidence.

anti-cytokine were not included (although we requested it from study authors). As a result, selective biases may exist in our review.

Double-blind RCTs of anti-cytokine versus another treatment, anti-endotoxin versus another treatment and anti-cytokine versus anti-endotoxin for meningococcal disease are required. Trials evaluating these outcomes as primary endpoints should be large and of reasonable duration to confirm the conclusions from the included studies. This systematic review only evaluated the efficacy of anti-cytokine and anti-endotoxin versus no intervention for meningococcal disease. Anti-cytokine versus anti-endotoxin have not been tested in RCTs and future trials should attempt to determine the efficacy of anti-cytokine versus anti-endotoxin for meningococcal disease, whether the effect is dose-dependent. In addition, future prospective studies that carefully investigate the underlying mechanisms of the effects of anti-cytokine and anti-endotoxin in the treatment of meningococcal disease are strongly encouraged.

In conclusion, this systematic review showed that anti-endotoxin and anti-cytokine does not reduce mortality from meningococcal disease. Anti-endotoxin did not reduce the number of participants with any morbidity and important long-term complications. The participants were from the UK, USA, The Netherlands, France, Spain, Norway and Germany. High quality RCTs of anti-endotoxin and anti-cytokine are warranted. RCTs of other anti-endotoxin versus anti-cytokine are also needed. Based on the paucity of evidence, a recommendation for the use of anti-endotoxin and anti-cytokine cannot be made in the treatment of meningococcal disease.

Acknowledgements

We thank Scott Hackett, Paul Baines, Sarah Thorning, and Alistair Thomson, authors of the original Cochrane protocol [15]. We are also grateful for the support of Clare Dooley and Liz Dooley, Assistant Managing Editor, and Managing Editor, respectively, of the Cochrane Acute Respiratory Infections Group. We thank the following people for commenting on our draft protocol: Karl Gallegos, Elaine Beller and Peter Morris.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li Zhou, Department of Digestive Infection, Gansu Provincial Maternity and Child-Care Hospital, No. 143 Qilihe North Street, Qilihe District, Lanzhou, Gansu, China. E-mail: lizhou2018@yandex.ru

References

[1] Marzouk O, Thomson AP, Sills JA, Hart CA, Harris F. Features and outcome in meningococcal disease presenting with maculopapular rash. Arch Dis Child 1991; 66: 485-7.

[2] Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. Pediatr Infect Dis J 1996; 15: 967-78.

[3] Thorburn K, Baines P, Thomson APJ, Hart CA. Mortality in severe meningococcal disease. Arch Dis Child 2001; 85: 382-5.

[4] Fergusion LE, Hormann MD. Neisseria meningitidis: presentation, treatment and prevention. J Pediatr Health Care 2002; 16: 119-24.

[5] Brandtzaeg P, Kierulf P, Gaustad P, Skulberg A, Bruun JN, Halvorsen S, Sørensen E. Plasma endotoxin as a predictor of multiple organ failure and death in systemic meningococcal disease. J Infect Dis 1989; 159: 195-204.

[6] Brandtzaeg P, Mollnes TE, Kierulf P. Complement activation and endotoxin levels in systemic meningococcal disease. J Infect Dis 1989; 160: 58-65.

[7] Brandtzaeg P, Ovstebøo R, Kierulf P. Compartmentalization of lipopolysaccharide production correlates with clinical presentation in meningococcal disease. J Infect Dis 1992; 166: 650-2.

[8] Hackett SJ, Thomson AP, Hart CA. Cytokines, chemokines and other effector molecules involved in meningococcal disease. J Med Microbiol 2001; 50: 847-59.

[9] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org 2011.

[10] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.

[11] Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2012.

[12] Derkx B, Wittes J, McCloskey R. Randomized, placebo-controlled trial of HA-1A, a human monoclonal antibody to endotoxin, in children with meningococcal septic shock. European Pediatric Meningococcal Septic Shock Trial Study Group. Clin Infect Dis 1999; 28: 770-7.

[13] Levin M, Quint PA, Goldstein B, Barton P, Bradley JS, Shemie SD, Yeh T, Kim SS, Cafaro DP,

Scannon PJ, Giroir BP. Recombinant bactericidal/permeability-increasing protein (rBPI21) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. rBPI21 Meningococcal Sepsis Study Group. Lancet 2000; 356: 961-7.

[14] Carrol ED, Thomson AP, Hart CA. New therapies and vaccines for meningococcal disease. Expert Opin Investig Drugs 2001; 10: 1487-500.

[15] Hackett S, Baines P, Thomson A. Anti-cytokine and anti-endotoxin therapies in meningococcal disease. Cochrane Database Syst Rev 2003; CD004420.

Appendix 1

MEDLINE (Ovid)

1 exp Meningitis, Meningococcal/
2 Meningitis, Bacterial/
3 exp Meningococcal Infections/
4 meningit*.tw.
5 meningococc*.tw.
6 exp Neisseria meningitidis/
7 neisseria meningit*.tw.
8 (n adj1 mening*).tw.
9 exp Sepsis/
10 sepsis.tw.
11 septicemia.tw.
12 septic shock.tw.
13 or/1-12
14 exp Endotoxins/
15 endotoxin*.tw,nm.
16 (anti-endotoxin* or antiendotoxin*).tw,nm.
17 (J5 or E5 or MAB-T88 or HA-1A or E5531 or “BPI (rBPI21)”).tw,nm.
18 cytokines/ or interleukin 1 receptor antagonist protein/ or exp tumor necrosis factors/
19 cytokine*.tw,nm.
20 (anti-cytokine* or anticytokine*).tw,nm.
21 tumour necrosis factor.tw,nm.
22 tnf*.tw,nm.
23 anti-tnf*.tw,nm.
24 (mak195F or mak-195F or mak 195F or afelimomab).tw,nm.
25 (bay 1351 or bay-1351 or bay1351).tw,nm.
26 (interleukin* or anti-il* or anti il*).tw,nm.
27 (tnfr55* or lenercept*).tw,nm.
28 “recombinant human il-1 receptor antagonist”.tw,nm.
29 or/14-28
30 13 and 29

EMBASE (ELSEVIER)

#27. #23 AND #26
#26. #24 OR #25
#25. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR ‘cross over’:ab,ti OR ‘cross-over’:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
#24. ‘randomized controlled trial’/exp OR ‘single blind procedure’/exp OR ‘double blind procedure’/exp OR ‘crossover procedure’/exp
#23. #9 AND #22
#22. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#21. ‘recombinant human il-1 receptor antagonist’:ab,ti OR ‘recombinant human il-1 receptor antagonists’:ab,ti
#20. tnfr55*:ab,ti OR lenercept*:ab,ti
#19. interleukin*:ab,ti OR ‘anti-il’:ab,ti OR ‘anti il’:ab,ti
#18. bay1351:ab,ti OR ‘bay-1351’:ab,ti OR ‘bay 31 1351’:ab,ti
#17. mak195f:ab,ti OR ‘mak-195f’:ab,ti OR ‘mak 195f’:ab,ti OR afelimomab:ab,ti
#16. ‘tumour necrosis factor’:ab,ti OR ‘tumor necrosis factor’:ab,ti OR tnf:ab,ti
#15. cytokine*:ab,ti OR anticytokine*:ab,ti OR ‘anti cytokine’:ab,ti OR ‘anti-cytokine’:ab,ti
#14. ‘cytokine’/de OR ‘tumor necrosis factor’/de OR ‘interleukin 1 receptor blocking agent’/exp

#13. j5:ab,ti OR e5:ab,ti OR 'mab-t88':ab,ti OR 'ha-1a':ab,ti OR e5531:ab,ti OR rbpi:ab,ti OR 'bpi rbpi21':ab,ti
#12. 'anti endotoxin':ab,ti OR 'anti-endotoxin':ab,ti OR antiendotoxin*:ab,ti
#11. endotoxin*:ab,ti
#10. 'endotoxin'/exp
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#8. sepsis:ab,ti OR septicem*:ab,ti OR 'septic shock':ab,ti
#7. 'sepsis'/de OR 'septicemia'/de OR 'septic shock'/de
#6. ((neisseria OR n) NEAR/1 mening*):ab,ti
#5. 'neisseria meningitidis'/de
#4. meningit*:ab,ti OR meningococc*:ab,ti
#3. 'meningococcosis'/de OR 'meningococcemia'/de
#2. 'epidemic meningitis'/de
#1. 'bacterial meningitis'/de