

Bacterial meningitis and meningococcal septicaemia: Evidence Update January 2012

A summary of selected new evidence relevant to NICE clinical guideline 102 'Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care' (2010)



Evidence Update 4

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE teams. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/meningitis). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Introduction


This Evidence Update identifies new evidence that might generate future change to the practice laid out in the following accredited reference guidance:

 ¹**Bacterial meningitis and meningococcal septicaemia. NICE clinical guideline 102 (2010).** Available from www.nice.org.uk/guidance/CG102

More than 2000 pieces of evidence were identified and assessed of which 12 were selected for the Evidence Update. An Evidence Update Advisory Group, comprised of subject experts, reviewed and commented on the prioritised evidence.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. Meningitis associated with tuberculosis (TB) is not included in the scope, because tuberculous meningitis (or meningeal TB) is covered in the following guidance:

 ¹Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE clinical guideline 117 (2011). Available from www.nice.org.uk/guidance/CG117

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

¹ NICE-accredited guidance is denoted by the accreditation symbol 

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages to be taken from the Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update has the potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

Key message	Effect on guidance	
	Potential change	No change
<p>Bacterial meningitis and meningococcal septicaemia in children and young people – symptoms, signs and initial assessment</p> <ul style="list-style-type: none"> Evidence from recent systematic reviews and a case comparison study appears to support the current guidance on signs and symptoms indicative of bacterial meningitis. 		✓
<p>Diagnosis in secondary care</p> <ul style="list-style-type: none"> Evidence from a recent systematic review and other studies appears to support the current guidance on laboratory investigations indicative of bacterial meningitis. 		✓
<p>Management in secondary care</p> <ul style="list-style-type: none"> In high-income countries, the use of corticosteroids as adjunctive therapy to reduce the risk of hearing loss appears to be supported by recent evidence, and they should continue to be administered in accordance with current recommendations. Intravenous immunoglobulins are not currently recommended by guidance, and recent studies do not appear to provide sufficient evidence to warrant their inclusion in the management of meningitis. Evidence suggests that activated protein C is not associated with any survival benefit, consistent with the recommendation in current guidance that it should not be used. The manufacturer has now withdrawn this treatment. 		✓ ✓ ✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text.

1.1 Bacterial meningitis and meningococcal septicaemia in children and young people – symptoms, signs and initial assessment

A systematic review by [Van den Bruel et al. \(2010\)](#), which assessed the clinical features of serious infections (not just meningitis) in children aged 1 month to 18 years in ambulatory care in the developed world (30 studies; 14,453 patients), found 'red flag' symptoms that were in agreement with those identified in [NICE clinical guideline \(CG\) 102](#).

The diagnostic accuracy of 'red flag' symptoms of children with meningococcal disease in primary care were studied further by the same group ([Haj-Hassan et al. 2011](#)) in a two sample comparison study of children aged 1 month to 16 years. Parents of children with an acute self-limiting infection (n = 407) were asked about symptoms experienced by their child, and the findings compared with the symptoms reported by parents of children with meningococcal disease (n = 345) in a previous study. The authors noted that the reducing incidence of bacterial meningitis and meningococcal disease makes further studies of the diagnostic accuracy of clinical features in non-hospitalised children and young people extremely challenging and unlikely to be conducted. The findings of significant symptoms of meningococcal disease in this study were generally in accordance with those identified in [NICE CG102](#). However, the presence of pallor did not appear to be a 'red flag' symptom in this study, which the authors speculated could have been due to differences in parental and GP interpretation of this clinical feature.

A systematic review by [de Jonge et al. \(2010\)](#) considered 31 studies involving approximately 6000 patients and gave a narrative report of the number of studies identifying specific prognostic factors for sequelae of bacterial meningitis. No relevant clinical features beyond those identified in [NICE CG102](#) were noted.

Key references

de Jonge RCJ, van Furth AM, Wassenaar M et al. (2010) Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infectious Diseases* 10: 232
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC2921388/pdf/1471-2334-10-232.pdf

Haj-Hassan T, Thompson M, Mayon-White RT et al. (2011) Which early 'red flag' symptoms identify children with meningococcal disease in primary care? *British Journal of General Practice* 61: e97–104
Abstract: www.ingentaconnect.com/content/rcgp/bjgp/2011/00000061/00000584/art00001

Van den Bruel A, Haj-Hassan T, Thompson M et al. (2010) Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. *Lancet* 375: 834–45
Abstract: [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(09\)62000-6](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)62000-6)

1.2 Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia

No new key evidence was found in this section.

1.3 Diagnosis in secondary care

A systematic review by [Van den Bruel et al. \(2011\)](#) of 14 studies (3981 patients) assessed the diagnostic value of laboratory tests in identifying serious infections (not just meningitis) in febrile children. Measuring inflammatory markers was shown to be diagnostically useful in an emergency department setting, in line with the recommendations in [NICE CG102](#). This study did not demonstrate any advantage for the use of procalcitonin over serum C-reactive protein (CRP) in this setting for serious infections in general, in line with recommendations in NICE CG102.

A predictive model by [Close et al. \(2011\)](#) based on a case control study of suspected meningitis and meningococcal septicaemia in 719 patients admitted to hospitals in London, the South West and West Midlands found 385 confirmed cases for analysis, including 191 children and young people aged 19 years and below with bacterial meningitis/meningococcal septicaemia and 39 with viral meningitis. The model confirmed the diagnostic value of peripheral blood polymorphonuclear (PMN) cell count, CRP and presence of haemorrhagic rash, supporting [NICE CG102](#), and also provided a threshold level for PMN ($> 16 \times 10^9 /L$) and CRP ($> 100 \text{ mg/L}$). The probability of a diagnosis of meningitis or meningococcal septicaemia was $> 95\%$ if any of these factors were present, which increased to $> 99\%$ if two or more factors were present.

[Dubos et al. \(2010\)](#) provided validation of two clinical decision rules for distinguishing between bacterial and aseptic meningitis in children in the paediatric emergency room or intensive care setting, based on data from 198 children under 18 years (mean age 5 years; 96 cases of bacterial meningitis) from six centres in five European tertiary care centres. Both the Bacterial Meningitis Score (BMS) and the Meningitest showed 100% sensitivity. Specificity was poor, though significantly higher with the BMS (BMS: 52% specificity; 95% confidence interval [CI] 42% to 62%; Meningitest: 36% specificity; 95% CI 27% to 46%; $p < 10^{-8}$). Procalcitonin levels did not appear to contribute additional specificity. This high level validation study used appropriate methods, and the findings support the current recommendations of [NICE CG102](#).

Key references

Close RM, Ejidokun OO, Verlander NQ et al. (2011) Early diagnosis model for meningitis supports public health decision making. *Journal of Infection* 63: 32–8
Abstract: www.sciencedirect.com/science/article/pii/S0163445311003604

Dubos F, Korczowski B, Aygun DA et al. (2010) Distinguishing between bacterial and aseptic meningitis in children: European comparison of two clinical decision rules. *Archives of Disease in Childhood* 95: 963–7
Abstract: www.adc.bmj.com/content/95/12/963.abstract

Van den Bruel A, Thompson MJ, Haj-Hassan T et al. (2011) Diagnostic value of laboratory tests in identifying serious infections in febrile children: a systematic review. *British Medical Journal* 342: d3082
Full text: www.bmj.com/highwire/filestream/340425/field_highwire_article_pdf/0.pdf

1.4 Management in secondary care

Corticosteroids

A Cochrane review by [Brouwer et al. \(2010\)](#) (24 studies; 4041 patients) examined the effect of adjuvant corticosteroid therapy compared with controls on mortality, hearing loss and neurological sequelae in children and adults with acute bacterial meningitis. Subgroup analysis of the children found no impact of corticosteroid therapy on mortality (risk ratio [RR] = 0.95; 95% confidence interval [CI] 0.78 to 1.14). However corticosteroids did appear to reduce risk of any hearing loss (RR = 0.74; 95% CI 0.62 to 0.89) and severe hearing loss (RR = 0.67; 95% CI 0.49 to 0.91). Analysis by country income also showed that in

high-income countries there was a decreased risk of severe hearing loss (RR = 0.54; 95% CI 0.35 to 0.78) and short-term neurological sequelae (RR = 0.67; 95% CI 0.46 to 0.97) with corticosteroid, but no difference was observed in low-income countries.

A randomised controlled trial (RCT) by [Peltola et al. \(2010\)](#) was not included in the Cochrane review. This study conducted in Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela examined the effect of adjuvant intravenous dexamethasone, oral glycerol, both or neither in 383 children aged 2 months to 16 years with meningitis caused by a range of bacteria (mostly *Haemophilus influenzae* type b or *Streptococcus pneumoniae*). Neither dexamethasone nor glycerol prevented hearing loss. These publications are unlikely to affect the current recommendations for steroid administration in bacterial meningitis in [NICE CG102](#).

Key references

Brouwer MC, McIntyre P, de Gans J et al. (2010) Corticosteroids for acute bacterial meningitis. Cochrane Database of Systematic Reviews issue 9: CD004405
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004405.pub3

Peltola H, Roine I, Fernandez J et al. (2010) Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol. *Pediatrics* 125(1): e1-e8
Full text: www.pediatrics.aappublications.org/content/125/1/e1.full.pdf+html

Intravenous immunoglobulin

[NICE CG102](#) does not currently include recommendations for the use of intravenous immunoglobulin (IVIG) in meningococcal septicaemia. This treatment is currently undergoing active research evaluation and the use of polyclonal and/or monoclonal IVIG compared with control has been considered in three recent publications ([Alejandria et al. 2010](#), [Ohlsson et al. 2010](#) and [INIS Collaborative Group 2011](#)).

In a Cochrane review, Alejandria et al. (2010) assessed 24 studies on polyclonal IVIG and 18 studies on monoclonal IVIG in sepsis, severe sepsis and septic shock. Although there was some evidence of an effect on mortality of polyclonal IVIG in adults, in the seven studies of polyclonal IVIG in neonates, ranging in size from 31 to 60 participants, no reduction in mortality was found; most of the neonates were already in intensive care, which is outside the scope of [NICE CG102](#) and this Evidence Update.

For various monoclonal IVIGs, no significant survival benefit was seen in a subgroup analysis of anti-endotoxin IVIG, however pooled subgroup analysis of the nine studies which looked specifically at anti-cytokine IVIG did show a small but significant reduction in mortality (RR = 0.92; 95% CI 0.86 to 0.97; n = 7893). The one study conducted in children (anti-endotoxin HA-1A in meningococcal septic shock) found no significant survival benefit. Adjunctive therapy with monoclonal IVIG may warrant further research.

The effect of polyclonal IVIG in neonates with suspected or subsequently proven infection was the focus of a Cochrane review by Ohlsson et al. (2010), which included the seven neonatal studies assessed in the Alejandria et al. (2010) review summarised above, and three additional studies. Mortality appeared to be reduced with IVIG compared with placebo in both clinically suspected infection (RR = 0.58; 95% CI 0.38 to 0.89; n = 378) and subsequently proven infection (RR = 0.55; 95% CI 0.31 to 0.98; n = 262). However, the authors expressed concern about the quality of the studies included and considered the evidence insufficient to support the routine administration of IVIG to prevent mortality in infants with suspected or proven infection. Any conclusions with respect to meningitis may be limited as the review was designed to evaluate sepsis.

The authors of both Cochrane reviews considered that large multicentre studies were needed to assess the value of IVIG in sepsis. One such study, the International Neonatal

Immunotherapy Study (INIS) has now been published (INIS Collaborative Group 2011). This study involved 113 hospitals in nine countries and included 3493 infants receiving antibiotics for suspected or proven serious infection; there was evidence of infection in cerebrospinal fluid (CSF) in 91 infants in the active treatment group and 72 control subjects (i.e. approximately 5% of patients may have had meningitis). Patients were randomised to receive two doses of polyclonal IVIG 500 mg/kg or placebo, 48 hours apart. There were no significant differences in primary outcome (death or major disability at age 2 years) or secondary outcomes, including the incidence of subsequent sepsis. Subgroup analysis looking specifically at patients with proven infection in CSF was not conducted.

Although the Cochrane review by Ohlsson et al. (2010) was suggestive of an effect of polyclonal IVIG on mortality (within the limitations of the included evidence), the subsequent INIS trial now seems to indicate that IVIG may have no effect on death or major disability in neonatal sepsis. [NICE CG102](#) is unlikely to be affected by these results. It should however be noted that none of the evidence considered meningitis specifically as a subset of infection.

Key references

Alejandria MM, Lansang MAD, Dans LF et al. (2010) Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database of Systematic Reviews: issue 2: CD001090
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD001090

INIS Collaborative Group (2011) Treatment of neonatal sepsis with intravenous immune globulin. New England Journal of Medicine 365: 1201–11
Full text: <http://www.nejm.org/doi/full/10.1056/NEJMoa1100441>

Ohlsson A, Lacy J. (2010) Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database of Systematic Reviews issue 3: CD001239
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD001239.pub3

Activated protein C

A Cochrane review by [Martí-Carvajal et al. \(2011\)](#) of five RCTs (5101 patients), one of which included neonates and children, did not provide evidence to support the use of activated protein C in children and young people with meningococcal septicaemia, confirming the current recommendations of [NICE CG102](#). The US Food and Drug Administration has announced that the manufacturer of activated protein C has withdrawn the product, following failure to show a survival benefit; see www.fda.gov/Drugs/DrugSafety/ucm277114.htm for details.

Key reference

Martí-Carvajal AJ, Solà I, Lathyris D et al. (2011) Human recombinant activated protein C for severe sepsis. Cochrane Database of Systematic Reviews issue 4: CD004388
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD004388.pub4

1.5 Long-term management

No new key evidence was found in this section.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Management in secondary care: corticosteroids

- Corticosteroids for acute bacterial meningitis
www.library.nhs.uk/duets/ViewResource.aspx?resID=411735

Management in secondary care: intravenous immunoglobulin

- Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock
www.library.nhs.uk/duets/ViewResource.aspx?resID=411733
- Intravenous immunoglobulin for suspected or subsequently proven infection in neonates
www.library.nhs.uk/duets/ViewResource.aspx?resID=411734

Further evidence uncertainties for meningitis can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Bacterial Meningitis and Meningococcal Septicaemia. NICE clinical guideline 102 (2010). Available from www.nice.org.uk/guidance/CG102

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 January 2008 to 31 July 2011:

- Medline
- Embase
- CINAHL
- DARE
- CDSR
- Cochrane Central Register of Controlled Trials

Although the end of the search period of the most recent Clinical Guideline was July 2009, an earlier search date was used for the Evidence Update to confirm that all relevant information was previously included in the clinical guideline.

Table 1 provides details of the search strategy used. The clinical guideline used 29 separate search strategies to answer 29 clinical questions. This Evidence Update used more general terms to identify significant evidence published for bacterial meningitis and meningococcal septicaemia in relation to children and young people aged 16 years and under. Terminology for the Evidence Update search strategy was taken from the clinical guideline but is indicative of one general search. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

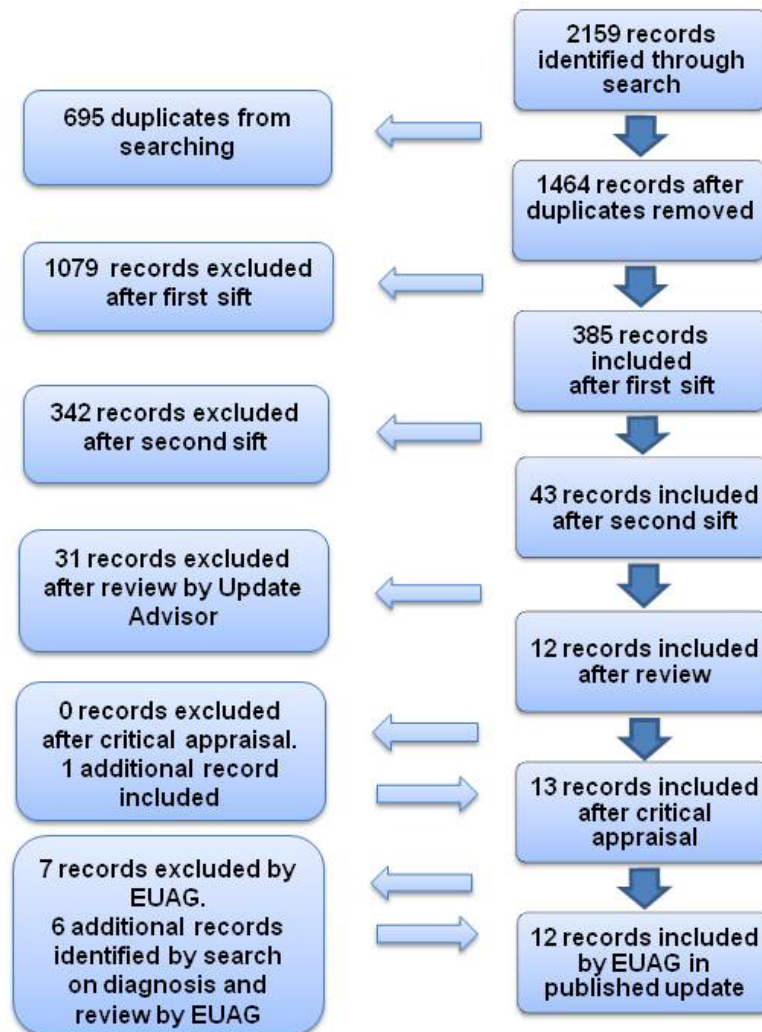
To ensure appropriate coverage of diagnostic evidence, additional searches were conducted refining the original population and subject headings and terms using the SIGN diagnostic filter (www.sign.ac.uk/methodology/filters.html), and applying the major focus limiter and diagnosis subheading to the exploded subject headings MENINGITIS, MENIGOCOCCAL INFECTIONS and MENINGOENCEPHALITIS.

Figure 1 provides details of the evidence selection process.

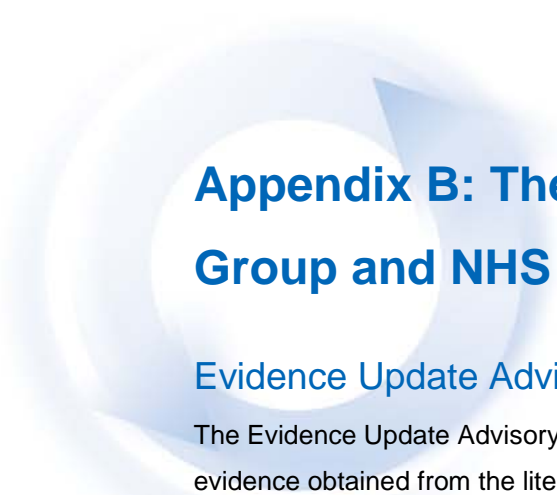
Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp CHILD/
2	child\$.ti,ab.
3	(pediatric? or paediatric?).ti,ab.
4	exp INFANT/
5	(neonat\$ or newborn?).ti,ab.
6	infan\$.ti,ab.
7	(baby or babies).ti,ab.
8	toddler?.ti,ab.
9	exp ADOLESCENT/
10	teen\$.ti,ab.
11	adolescen\$.ti,ab.
12	exp SCHOOLS/
13	school\$.ti,ab.
14	exp PUBERTY/
15	pubescen\$.ti,ab.
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	meningoencephalitis.ti,ab.
18	MENINGOENCEPHALITIS/
19	meningitis.ti,ab.
20	exp MENINGITIS/
21	((bacterial\$ or infect\$) adj3 meninges).ti,ab.
22	17 or 18 or 19 or 20 or 21
23	exp MENINGOCOCCAL INFECTIONS/
24	meningococc\$.tw.
25	septic?emia.tw.
26	SHOCK, SEPTIC/
27	(septic adj shock).ti,ab.
28	(sepsis adj5 hypotension).ti,ab.
29	BACTEREMIA/
30	(severe adj2 sepsis).ti,ab.
31	(septic?emi? or bacter?emi?).ti,ab.
32	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	22 or 32
34	16 and 33

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group



Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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