SIGN
Scottish Intercollegiate Guidelines Network

NHS
Quality Improvement Scotland

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Management of invasive meningococcal disease in children and young people

A national clinical guideline

May 2008

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group.

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1 Introduction

1.1 BACKGROUND

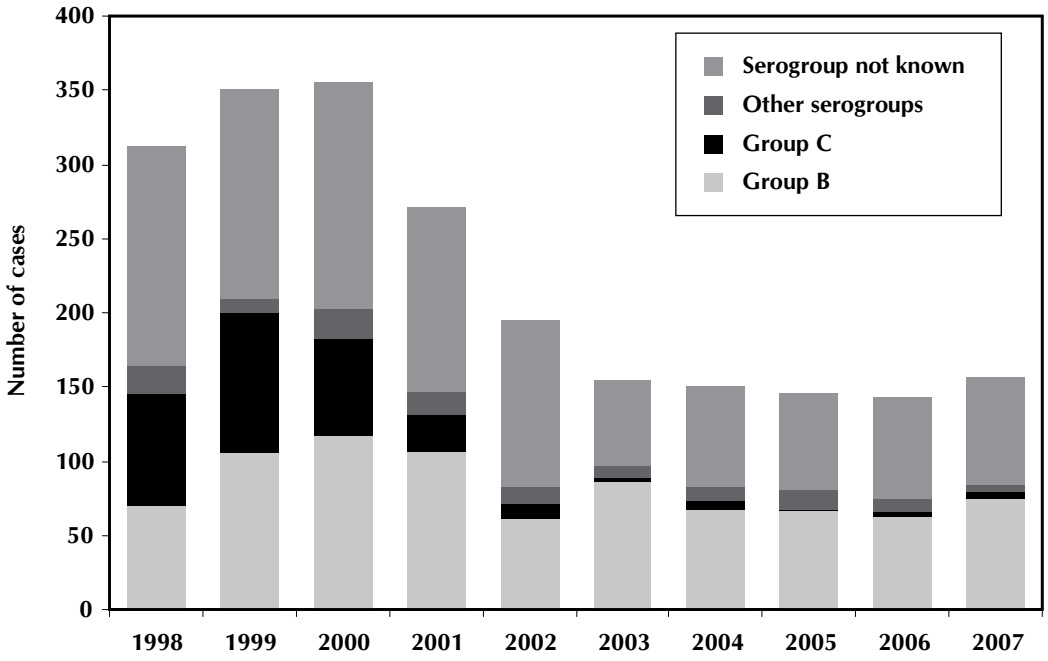
Invasive Meningococcal Disease (IMD) is a significant cause of morbidity and mortality in children and young people, caused by infection with the bacterium *Neisseria meningitidis*. There are at least 13 meningococcal serogroups of this bacterium. Historically, serogroups B and C were responsible for the majority of invasive disease in the United Kingdom, but the introduction of the Men C vaccine in 1999 reduced the disease incidence by approximately 50%, and IMD due to group C infection is now very rare.[1]

There is currently no licensed vaccine against group B disease in the UK, although specific vaccines have been developed in response to single strain epidemics in other countries (eg vaccine against meningococcal group B infection in New Zealand). Tetravalent vaccines are being developed to prevent serogroup A, C, Y and W135 disease.

The number of cases of IMD is monitored by the Health Protection Scotland (HPS) Meningococcal Invasive Disease Augmented Surveillance (MIDAS) scheme (Figure 1). Since 2000 the incidence of IMD has reduced to 140 -160 new IMD cases each year.

Despite the success of the Men C programme the youngest members of society continue to bear a disproportionate burden in terms of incidence of, and mortality from, IMD. The recorded case fatality rate (CFR) for meningococcal disease varies between 2.6-10% each year *(see table accompanying Figure 1)*, similar to the 5.6% observed in England and Wales.[2] A number of factors including increased awareness, public health measures, early resuscitation, improved resuscitation techniques, advances in critical care, surgical interventions and investment in rehabilitation may have contributed to improvements in outcome.[3] There is, however, a persistent mortality, particularly in the early hours of rapidly progressive septicaemia, emphasising the need for increased awareness, disease recognition and experienced assessment of the sick child, with an understanding of the potential for rapid disease progression, and the need for urgent and escalating intervention.

Figure 1: Meningococcal disease cases reported to Health Protection Scotland by serotype and case fatality rate (CFR) from 1998 to 2007



Recorded case fatality rate (CFR) for meningococcal disease by year

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
CFR (%)	5.8	6.6	7.3	4.8	6.7	2.6	10.0	6.9	4.9	6.4

The trigger for invasive disease is unknown, but there is marked seasonal variation, with higher incidence in the winter months and during outbreaks of viral respiratory tract infection. The disease is transmitted by droplet spread or by respiratory secretions, with an increased incidence in close personal contacts of index cases. The peak incidence of invasive disease occurs in pre-school children, and for survivors of acute infection there may be significant morbidity, including skin loss, limb loss, deafness and neurological impairment.

The most common clinical manifestation of invasive disease is meningitis, but up to 20% of patients will develop meningococcal septicaemia, associated with the highest mortality.

1.2 THE NEED FOR A GUIDELINE

The challenge for healthcare practitioners is to identify those patients who will progress from a non-specific early presentation to severe disease, particularly since the early symptoms and signs may be indistinguishable from intercurrent and self limiting viral infection.[4] The majority of deaths continue to occur in the first 24 hours, frequently before the institution of specialised care.[3]

The particular geography and population distribution in Scotland, combined with the rapid onset and progression of invasive disease, require the development of a guideline to ensure that the most effective treatment can be delivered within the context of a Scottish Health Service where "services are delivered as locally as possible, when that can be done safely and sustainably, but with prompt access to specialised services when necessary".[5]

Over the past 40 years there has been dramatic improvement in outcome from septic shock in children, with mortality reducing from 97% in the 1960s, 60% in the 1980s, to 9% in 1999. Changes in clinical practice have been based on case series, cohort studies and physiological experiments, rather than on evidence from randomised controlled trials.[6] There have also been significant changes to the organisation and delivery of health care, particularly in the provision of resuscitation and intensive care that have been associated with reduced mortality.

The paucity of high quality randomised controlled trial (RCT) evidence for the protocols and practices that underpin the clinical management of IMD has been a particular challenge in drafting this guideline. The guideline group was aware of pragmatic improvements that have had a positive effect on outcomes,[7] and have included good practice points to cover such issues as appropriate.

1.3 REMIT OF THE GUIDELINE

This guideline makes recommendations on best practice in the recognition and management of meningococcal disease in children and young people up to 16 years of age. It addresses the patient journey through pre-hospital care, referral, diagnostic testing, disease management, follow-up care and rehabilitation and considers public health issues. The guideline will be of interest to healthcare professionals, parents and carers who are involved in the diagnosis and management of children and young people with suspected or confirmed meningococcal disease. The guideline is based on a systematic review of the literature *(see section 12.1)*, including relevant studies in adult populations. This guideline is specifically directed at children with IMD, although many of the clinical symptoms and signs are features of systemic sepsis in infants, children and young people.

1.4 DEFINITION

Invasive Meningococcal Disease results from bacterial infection with *Neisseria meningitidis*, a gram-negative aerobic organism that is usually a commensal in humans; 5-25% of adults are asymptomatic carriers.[8] Meningococci that cause invasive disease develop a capsule that protects the organism from host defence mechanisms. IMD may present with a clinical spectrum that ranges from acute meningitis, with neck stiffness, photophobia and a bulging fontanelle (all symptoms may not be present), to rapidly progressive meningococcal septicaemia with a non-blanching rash, reduced conscious level, shock and multiorgan failure. Less common manifestations of IMD include pneumonia, conjunctivitis, otitis media, epiglottitis, arthritis, and pericarditis.[9]

1.5 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

2 Early assessment

Initial assessment may take place in primary care or in the emergency department (ED).

2.1 SIGNS AND SYMPTOMS

The diagnosis of meningococcal disease in its initial stages is often difficult because many of the early features are non-specific.[3] The classical presentations of IMD are uncommon in primary care. Presentation of an unwell child with fever is very common, and while only a small number will develop meningococcal disease, clinical judgement is required to best manage the small risk that a child presenting with non-specific symptoms and signs might have meningococcal disease at an early stage.

Invasive meningococcal disease generally presents in three illness patterns:[10]

- **Meningococcal septicaemia** (~20%) characterised by fever, petechiae, purpura and toxicity. This presentation is associated with a significantly poorer outcome.
- **Clinical meningitis**, with fever, lethargy, vomiting, headache, photophobia, neck stiffness, and positive Kernig's and Brudzinski's signs. These are the classic features of established bacterial meningitis of any cause. There may also be associated petechiae/purpura. Some infants and young children may have less specific features, such as poor feeding, irritability, a high-pitched cry, and a full fontanelle.
- **A mixed picture** of septicaemia and meningitis.

2.1.1 INITIAL ASSESSMENT

No community based studies were identified describing the frequency of symptoms and signs suggestive of meningococcal disease. From observational data in secondary care particular signs and symptoms have been associated with meningococcal disease and could be used in primary care to identify children who may be developing IMD.

Infants and young children present with non-specific symptoms such as fever, lethargy, poor feeding, nausea and vomiting and irritability within the first four to six hours. Meningococcal disease can rarely be excluded within the first four to six hours.[4]

3
2+

In children with meningococcal disease, non-specific symptoms of cold hands or feet, skin mottling or leg pain, pre-date classical symptoms or signs by several hours.[4] Two retrospective cohort studies have highlighted these symptoms. A study of 448 cases of meningococcal disease in children under the age of 16 suggested that 36.7% had experienced leg pain, 43.2% had cold hands and feet and 18.6% had abnormal skin colour.[4] A US-based study of 274 children between the ages of three and 20 reported that 16% had extremity pain at admission to hospital.[11] Although both of these studies support an association between non-specific symptoms and the subsequent development of meningococcal disease, both lack data on the predictive value of these non-specific symptoms within the general population.[12]

2+
3

The presence of a generalised petechial-pupural rash, beyond the distribution of the superior vena cava (SVC), with significant delay in capillary return, in a child who is unwell should raise suspicion of invasive meningococcal disease.[13] Petechiae in the distribution of the SVC may have other, more innocent causes such as coughing, but IMD should always be considered as a possible cause.[3]

3

D **A generalised petechial rash, beyond the distribution of the superior vena cava, or a purpuric rash in any location, in an ill child, are strongly suggestive of meningococcal septicaemia and should lead to urgent treatment and referral to secondary care.**

D **The following features in an ill child should prompt consideration of a diagnosis of IMD:**

- **petechial rash**
- **altered mental state**
- **cold hands and feet**
- **extremity pain**
- **fever**
- **headache**
- **neck stiffness**
- **skin mottling.**

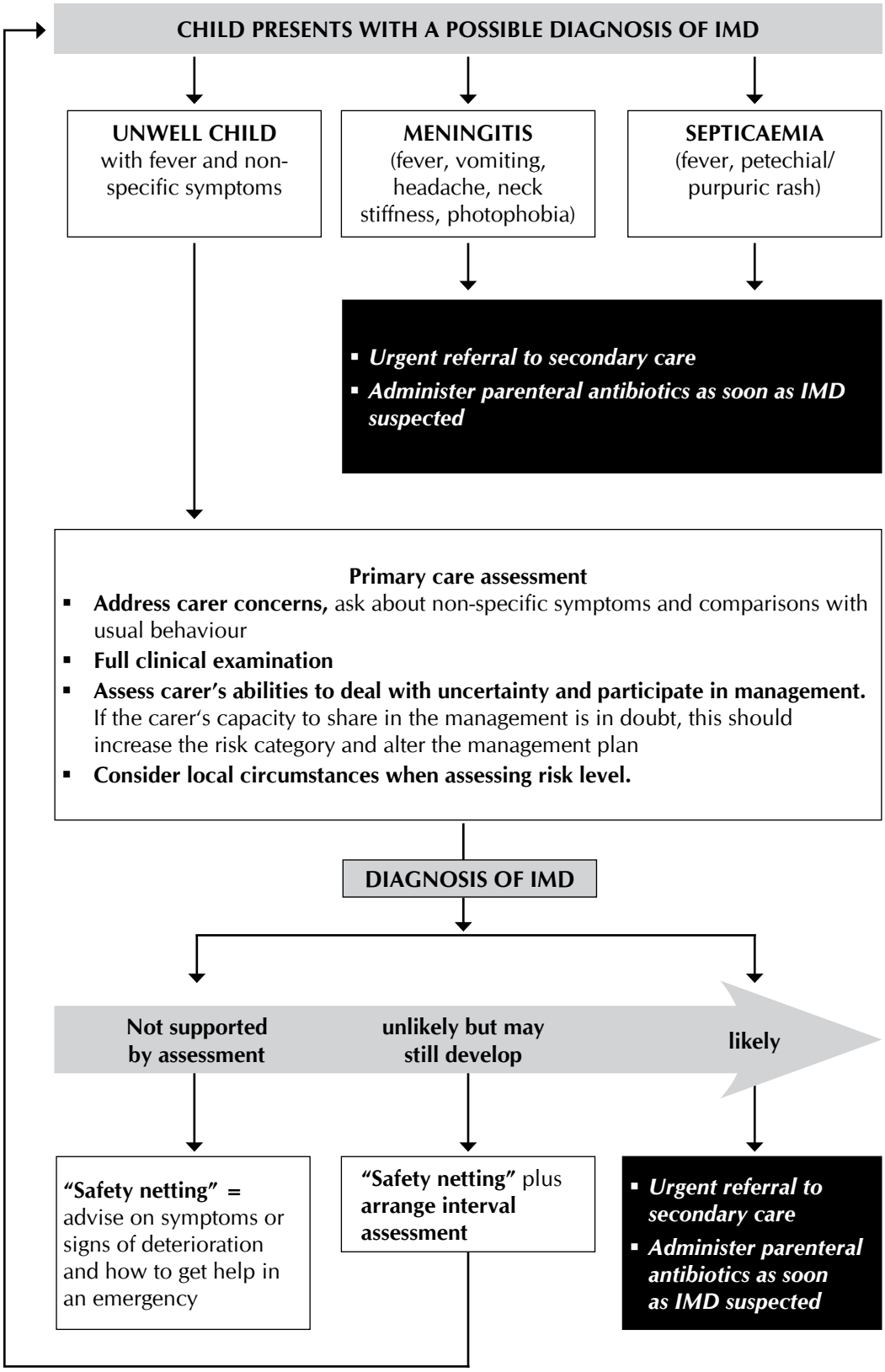
D
- **Meningococcal disease should not be automatically excluded as a potential diagnosis if young children present with non-specific symptoms such as fever, lethargy, poor feeding, nausea, vomiting and irritability or a non-blanching rash, within the first four to six hours of illness.**
- **If there is sufficient clinical suspicion, appropriate treatment should be commenced and assessment in secondary care should be arranged.**

2.1.2 MANAGING CHILDREN WITH NON-SPECIFIC SYMPTOMS

In practice the early assessment and management of the severely unwell child with or without a rash involves urgent referral to secondary care for further investigation and treatment. The most challenging group to manage is children with fever and non-specific symptoms who may be displaying the early symptoms and signs of meningococcal disease, but for whom the diagnosis is still uncertain.

A possible approach to managing the risk of a child with non-specific symptoms and signs having meningitis is to categorise the child and their carer depending on the apparent risk of IMD. This model of early assessment is shown in figure 2.

Figure 2


CHILD PRESENTS WITH A POSSIBLE DIAGNOSIS OF IMD
UNWELL CHILD with fever and non-specific symptoms
MENINGITIS (fever, vomiting, headache, neck stiffness, photophobia)
SEPTICAEMIA (fever, petechial/ purpuric rash)
Urgent referral to secondary care
Administer parenteral antibiotics as soon as IMD suspected
Primary care assessment
Address carer concerns, ask about non-specific symptoms and comparisons with usual behaviour
Full clinical examination
Assess carer's abilities to deal with uncertainty and participate in management. If the carer's capacity to share in the management is in doubt, this should increase the risk category and alter the management plan
Consider local circumstances when assessing risk level.
DIAGNOSIS OF IMD
Not supported by assessment
unlikely but may still develop
likely
"Safety netting" = advise on symptoms or signs of deterioration and how to get help in an emergency
"Safety netting" plus arrange interval assessment
Urgent referral to secondary care
Administer parenteral antibiotics as soon as IMD suspected

The success of this model is critically dependent upon an assessment of the parent/carer's capacity to manage uncertainty and work with the clinician to manage the child in the most effective manner. Geography, transport and access issues are also factors that influence the decision making process.

- Patients and their carers in the high-risk group should be urgently referred for assessment by secondary care staff who will have access to additional diagnostic tests.
- Children with low-risk presentations should be clinically assessed and treated by the clinician. Carers should be made aware that they should seek further help if their child's condition deteriorates.[14]
- Children at intermediate risk are often the most difficult to manage. Good practice suggests that they should be reassessed within four hours to seek evidence of any clinical deterioration (*see section 2.2*). Carers should be strongly advised to seek advice if their child deteriorates before the planned review.

☑ Parents or carers of children with non-specific symptoms who are unlikely to have meningococcal disease should be advised to call back if the child's condition deteriorates. This advice should take account of local access to health care.

2.2 INTERVAL ASSESSMENT

No studies were identified which specifically addressed the practice of interval assessment or alternatives such as telephone assessment.

For children where diagnosis of meningococcal disease is likely, urgent treatment is required and should not be delayed by interval assessment.[15] 4

D **Children with symptoms or signs which are highly suggestive of meningococcal disease should not have their treatment delayed by interval assessment.**

☑ Children with non-specific symptoms at initial presentation, in whom meningococcal disease cannot be excluded, should be reassessed within four to six hours.

☑ Carers should seek further clinical advice if the child's condition deteriorates prior to planned reassessment, eg rash changes. This advice should take account of local arrangements for health care.

2.3 AWARENESS CAMPAIGNS

There have been a number of high profile awareness campaigns such as the 'glass test' in recent years. There is widespread belief that these campaigns have raised the profile of meningococcal disease and contributed to control of the disease. Despite this, no quantitative evidence was identified to demonstrate the effectiveness of awareness campaigns or educational interventions to improve the recognition, diagnosis or treatment of meningococcal disease by parents or other members of the public.

3 Early treatment

3.1 ANTIBIOTIC THERAPY

The evidence on pre-hospital administration of intravenous antibiotics in children with suspected meningococcal disease is inconclusive.[144] One case control study suggested penicillin treatment in the community increased mortality, but the study only administered treatment to children with severe disease.[16] Other studies, one of which is based in an emergency department rather than the community, support the use of antibiotics to reduce the risk of mortality.[17,18] 2+ 3

Expert opinion advises starting antibiotic treatment before admission to hospital, due to the speed with which children with meningococcal disease can deteriorate, and because it is unlikely to cause harm unless the child is allergic to penicillin.[15] 4

No specific evidence comparing different antibiotic agents was identified but benzylpenicillin and ceftriaxone are widely used and have been shown to be effective in the treatment of meningococcal disease.[19,20] The US Food and Drug Administration (FDA) has issued an alert regarding the interaction between ceftriaxone and calcium containing solutions. Cefotaxime should be the first line antibiotic in meningococcal sepsis.[21] Public health guidance supports the administration of benzylpenicillin prior to admission to hospital.[15] 1+ 1++ 4

D **Parenteral antibiotics** *(either benzylpenicillin or cefotaxime)* **should be administered in children as soon as IMD is suspected, and not delayed pending investigations.**

3.2 OUT-OF-HOSPITAL CARE

Specific guidance has been produced by the Joint Royal Colleges Ambulance Liaison Committee and the Meningitis Research Foundation for the recognition and treatment of suspected IMD by primary care practitioners, which recommends:[22,23]

On scene:

- appropriate airway management
- oxygen therapy (with assisted ventilation if required)
- rapid transportation to the nearest appropriate hospital. 4

En route:

- administer intravenous or intramuscular benzylpenicillin
- treat shock with boluses of intravenous crystalloid
- identify and treat hypoglycaemia
- provide hospital alert message including age of patient.

Repeat assessment en route.

D **Pre-hospital practitioners should follow guidance produced by the Joint Royal Colleges Ambulance Liaison Committee and the Meningitis Research Foundation when treating children and young people with suspected IMD.**

3.3 SERVICE DELIVERY

There are no studies that provide definitive evidence that earlier diagnosis and treatment improve outcome from IMD, but swifter recognition and institution of appropriate therapy have been associated with reduced mortality in recent years.[24]

A single retrospective study has suggested potential risk factors for death in the management of children with meningococcal disease to include:[24]

- the absence of specialist paediatric care in the emergency, anaesthetic and intensive care departments
- inadequate fluid resuscitation
- the absence of consultant supervision within the first 24 hours
- failure to recognise disease severity, progression or complications.

D **Following arrival at hospital, children with suspected IMD should be reviewed and treated promptly by a senior and experienced clinician.**

D **Management of children with progressive IMD should be discussed with intensive care at an early stage.**

☑ Robust local protocols should ensure that children with IMD have rapid access to appropriate levels of supervision and care that take into account local services and geography.

3.3.1 REFERRAL TO PUBLIC HEALTH

Local protocols should include a process for referral.

4 Confirming the diagnosis

Sections 4, 5 and 6 relate to secondary care and focus on confirming the diagnosis and the treatment phase, primarily the first 48 hours of care. This takes account of the child's pre-hospital history, assessment and treatment, including signs and symptoms discussed in section 2.1.

4.1 LABORATORY DIAGNOSIS

4.1.1 BLOOD CULTURE

Blood culture has been the gold standard for the definitive diagnosis of IMD, and should be collected as soon as possible after admission to hospital, but should not delay treatment.[15] | 4

Blood polymerase chain reaction (PCR) for meningococcal DNA has high sensitivity (88%, 95% CI 68 to 97) and specificity (100%, 95% CI 84 to 100), likelihood ratio (LR) for positive blood, PCR = 0.89, LR for negative blood, PCR = 0.87.[25] The range of increased diagnosis attributed to PCR has been as much as 30-45%.[26,27] PCR can remain positive for up to nine days in patients given antibiotic therapy.[25] | 2^{++} 3

Recent research suggests that measuring the level of serum procalcitonin can be helpful in assessing patients who present with febrile illness to distinguish between those who are unlikely to have an invasive bacterial infection and those who do.[28] The role of this test in routine clinical practice is still to be established. The test is not widely available in NHSScotland at present. | 3

To confirm the diagnosis in all children with suspected IMD, blood should be taken for:

C ▪ **bacterial culture**

D ▪ **meningococcal PCR.**

4.1.2 LUMBAR PUNCTURE

The role of lumbar puncture (LP) in cases of suspected IMD without signs of clinical meningitis remains controversial.[29,30] Early lumbar puncture adds little to the diagnosis in clear cut cases with fever and generalised purpura, may lead to significant deterioration in those already seriously ill, and may delay treatment.

In patients with clinical meningitis without purpura, lumbar puncture carried out early, preferably before antibiotics are given, can help to establish diagnosis and ensure that appropriate therapy is given for the correct duration.[26,31-34] | 2^{+} 3

Examination of cerebrospinal fluid (CSF) by microscopy, culture and PCR is important in yielding information about the aetiology of meningitis, especially in patients without the typical features of IMD. PCR on CSF has been shown to be more sensitive than culture in samples taken before and after the start of antimicrobial therapy.[25,35] | 3

The collection of CSF should not delay institution of empirical antimicrobial therapy. PCR on CSF can still yield a positive result in samples collected after the start of antimicrobial therapy. In one study, PCR on CSF was positive after 13 days of therapy.[35]

Table 1: Contraindications to lumbar puncture[30]

Cardiorespiratory decompensation	
Raised intracranial pressure (ICP)	Signs include fluctuating or impaired levels of consciousness, focal neurological signs or abnormal posturing, dilated or poorly reactive pupils, relative bradycardia and/or hypertension, papilloedema (although this may not be present initially despite significantly raised ICP)
Coagulopathy	
Purpura/petechial rash	

☑ Lumbar puncture is not recommended in the initial assessment of suspected IMD with features of septicaemia. LP may be considered later if there is diagnostic uncertainty or unsatisfactory clinical progress, and there are no contraindications.

C **Lumbar puncture should be performed in patients with clinical meningitis without features of septicaemia** *(purpura)* **where there are no contraindications.**

D **Cerebrospinal fluid should be submitted for microscopy, culture and PCR.**

4.1.3 OTHER TESTS

In three studies, examination of aspirates or scrapings from skin lesions was useful in providing rapid diagnosis of IMD.[36-38] The studies showed variation in results due to the lack of a consistent gold standard and differences in the nature of lesions and procedures for the obtaining and examination of specimens. It is not possible to demonstrate if examination of skin lesions is more effective in diagnosing IMD than other tests. 2-

Insufficient evidence was identified to form recommendations on the use of throat swabs, urine antigen testing or routine blood antibody testing in confirming diagnosis of IMD.

5 Illness severity and outcome

5.1 CLINICAL VARIABLES

A combination of initial clinical features, laboratory results, sequential monitoring and repeated assessment over time provide a foundation for predicating progress and informing care planning and treatment. If there are features of serious illness or deterioration, early aggressive therapy is likely to offer the best chance of a good outcome.[24] 2-

Numerous studies explore the relationship between clinical and laboratory variables and risk of death but because of the relatively low number of deaths in recent studies from the developed world, many are underpowered to detect significant differences in mortality.

Indices of poor outcome include:[39-41] 2+ 3

- short duration of symptoms (< 24 hours)[39]
- signs of sepsis in the absence of meningitis
- acidosis
- coma
- poor perfusion
- hypotension
- admission between 0700 and 1100
- the presence of > 50 petechiae.[41]

Low platelet count, low absolute neutrophil count or a procalcitonin level of > 150 x 10^9/l have been associated with risk of death.[39-41] The arithmetic product of initial platelet and neutrophil count may be a superior indicator to any of the above, with a product of < 40 x 10^9/l having a positive predictive value of 66%.[42] One study identified a fibrinogen of < 2.5g/l as an additional factor.[40] 2+ 3

Although C-reactive protein is a frequently measured acute phase protein and may be useful diagnostically in helping to distinguish bacterial from viral infection, it has poor sensitivity and specificity in predicting outcome.[43,44] A high procalcitonin level at admission has been demonstrated to be a superior predictor of outcome in studies within and outwith the paediatric intensive care unit (PICU) setting.[43-46] In addition, a poor outcome is seen in patients with a high microbial load, as measured by PCR[47] or who have a unique sequence type.[48] Procalcitonin is not routinely measured in Scottish practice. 2+

Studies of plasma lipids[49] and vasopressin,[50] have failed to show an association, and the presence of adrenal insufficiency does not predict mortality.[51] 3

Mortality from meningococcal meningitis is low, so most studies of bacterial meningitis focus on neurological outcome. Meningococcal meningitis carries a lower risk of adverse neurological outcome than meningitis due to other bacteria such as pneumococcus.[52,53] Series looking at outcome for all-cause bacterial meningitis have identified seizures during the acute illness,[54] cranial nerve neuropathy,[53,55] low cerebrospinal fluid (CSF) glucose[56,57] and high CSF protein[57] as predictive factors. Although these studies included cases of meningococcal meningitis, they were the minority of total cases. In a study analysing a subgroup of 60 cases of meningococcal meningitis, none of these parameters was significantly associated with hearing loss.[53] Hearing loss is the most common morbidity of meningococcal disease. 3

C **Clinicians should be aware that the following are associated with high mortality;**

- **a platelet times neutrophil product of < 40 x 10^9/l**
- **a procalcitonin level of > 150ng/l**

D **Clinicians should be aware that meningococcal meningitis carries a lower risk of adverse neurological outcome than meningitis due to other bacteria.**

5.2 SCORING SYSTEMS

A number of illness severity scoring systems have been developed to monitor critical illness in children. A prospective study comparing nine severity scores showed the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) to be an easy to perform, repeatable scoring system on admission to hospital, before intensive care. A GMSPS ≥ 8 had 100% sensitivity, 75% specificity and a positive predictive value for death of 29%, which correlated significantly with laboratory markers.[58] A retrospective study also validated its use to identify children with poor prognosis who would benefit from early intensive care.[59]

2^{++}
3

Within the PICU setting studies have shown GMSPS to be useful for assessing severity of illness (*see Annex 1)*.[60, 61] GMSPS performed well compared to the PRISM III, Leclerc and Gedde-Dahl's MOC score in children on admission to intensive care.[60]

2^{+}
2^{-}

D **Children diagnosed with IMD should have sequential GMSPS performed and any deterioration should be discussed with intensive care.**

6 Treatment

6.1 RESUSCITATION

Initial resuscitation should follow the standard UK Resuscitation guidelines with an expectation that prompt and adequate fluid resuscitation may be required.[62] In view of the known risk for rapid deterioration in IMD, any standby time can allow allocation of responsibility for ensuring a secure airway, adequate ventilation and preparation for rapid intravascular or intraosseous access. Ensuring appropriately skilled and experienced personnel are in attendance may improve the outcome.[24] 2-

Both the immediate clinical assessment and the trend of all objective observations should be used to support decisions on resuscitation interventions.

Features of shock include:[63] 4

- Tachycardia
- Cool peripheries/pallor
- Capillary refill time (> 4 sec)
- Tachypnoea/oxygen saturation < 95%
- Hypoxia on arterial gases
- Base deficit > -5 mmol/l
- Confusion/ drowsiness/ decreased conscious level
- Poor urine output (< 1 ml kg^{-1} hr^{-1})
- Hypotension (late sign).

6.2 INTRAVENOUS FLUIDS

Meningococcal sepsis can cause early deterioration in organ perfusion and there is a risk of higher mortality if there is inadequate fluid resuscitation in children.[24] There is consensus, in adult and paediatric populations, that supports the use of early, aggressive intravenous (IV) fluid therapy once the diagnosis of invasive meningococcal disease has been made and there are signs of compensated shock.[64,65] Evidence for choice of fluid and optimal volumes for children is limited. 2- 4 2+

Systematic reviews of sepsis in adult patients demonstrate the use of isotonic crystalloids or colloids for fluid resuscitation.[66-68] There is no evidence at the present time that colloid is superior to crystalloid for the initial fluid although higher volumes of crystalloid may be required to sustain circulating volume.[67] 1+

The advanced paediatric life support approach of 20 ml/kg bolus fluids repeated if indicated after reassessment is appropriate till 60 ml/kg has been administered.[62] 1+

Studies in paediatric and adult patients demonstrated that in severe septic shock, fluid resuscitation in excess of 60 ml/kg is often required.[69,70] In these cases expert opinion advises to start inotropes early.[6,64,65,69,71] 1- 1+ 4

A randomised evaluation of fluid resuscitation in septic shock concluded that volumes in excess of 60 ml/kg are needed to restore plasma volume.[70] The response to initial IV fluid therapy, assessed by clinical signs and severity scoring, will guide the need for further fluid boluses. A poor response to repeated fluid boluses suggests rapidly progressive disease and the need for early discussion with intensive care, institution of inotropes and consideration of ventilatory support. 1+

In meningococcal meningitis without signs of shock or compensated shock, fluids can be administered at maintenance rates. There is insufficient evidence to support fluid restriction on the basis of a diagnosis of meningococcal meningitis alone.[72] 1++

B **If there are signs of shock, administer a rapid infusion of IV fluids as isotonic crystalloid or colloid solution up to 60 ml/kg given as three boluses of 20 ml/kg, with reassessment after each bolus.**

☑ Fluid resuscitation in excess of 60 ml/kg and inotropic support are often required.

☑ Evidence of circulatory failure and the need for repeated IV fluid boluses should prompt early consultation with intensive care as inotropic support and ventilation may be required.

6.3 ANTIBIOTICS

6.3.1 INITIAL ANTIBIOTIC THERAPY

Early antibiotic therapy is a fundamental aspect of care in patients with suspected IMD, whether as septicaemia or meningitis. Initial antibiotic treatment is empirical, taking account of likely causative organisms in different age groups, and knowledge of local antibiotic resistance patterns.

In the UK, cephalosporin resistance remains at very low levels and monotherapy with third generation cephalosporins (cefotaxime or ceftriaxone) has usually been an appropriate initial antibiotic choice in children over three months old with suspected IMD.[19,73,74] 1++ 2- 2+

There are concerns about the interaction of ceftriaxone with parenteral calcium containing products which is likely to be an issue in seriously ill children in the early period of care (http://www.fda.gov/cder/drug/infosheets/hcp/ceftriaxone.htm).

A switch to once daily ceftriaxone may be appropriate following the early intensive care period, simplifying care delivery and offering some degree of ambulatory care in the recovery phase.

Children with fever under three months pose particular clinical challenges. There is a significantly higher incidence of serious bacterial infection in this age group. IMD infection in very young infants is relatively uncommon, but is associated with a poorer outcome. In infants under three months, empirical antibiotic therapy should reflect the spectrum of causative organisms in this age group.[75] 4

The use of ceftriaxone facilitates elimination of carriage from the nasopharynx of infected patients. Patients treated with benzylpenicillin will require rifampicin or other antibiotics at the end of therapy for elimination of carriage.[15] 4

B **Parenteral cefotaxime should be used as initial treatment of previously well children over three months with a diagnosis of IMD.**

☑ Once daily ceftriaxone monotherapy may be substituted if calcium containing parenteral agents have not been used in the preceding 48 hours.

☑ When parenteral antibiotics are indicated for infants less than three months of age, cefotaxime plus an antibiotic active against listeria *(eg ampicillin or amoxicillin*) should be given.

6.3.2 DURATION OF ANTIBIOTIC TREATMENT

Evidence to guide the optimal duration of antibiotic treatment in IMD is limited.

There has been a trend to consider shorter duration of treatment in bacterial meningitis in children who show early clinical improvement.[76] A Chilean study compared outcomes in 100 young children over three months old with confirmed bacterial meningitis (*Neisseria meningitidis*, 34 cases) who showed early clinical recovery. They were randomised to four or seven days of ceftriaxone treatment. This small study suggested that ceftriaxone for four days is as effective as seven days, with no difference in complications.[77] 1+ 1-

A recent retrospective study from New Zealand explored the time and cumulative antibiotic dose required to produce sterile CSF in 48 children (mean age 4.4y; range 0-14) with a confirmed diagnosis of meningococcal meningitis. All had a sterile CSF by six hours after antibiotic therapy began.[78] The authors suggest this supports previous recommendations that antibiotic therapy in meningococcal meningitis is only required for four days. 3

Most studies excluded children under three months, since this age group may be particularly at risk of an adverse outcome.

While the evidence tends to support the safety of fewer than seven days' antibiotic therapy in children with uncomplicated IMD, the studies have involved relatively small numbers of children. At present there is insufficient evidence to recommend short treatment courses.

No evidence to support a differential duration in antibiotic therapy in children with septicaemia compared to meningitis was identified. This is not surprising given the overlap between the two clinical syndromes, and central nervous system infection commonly coexists with septicaemia.[79]

Current UK practice favours seven days' antibiotic therapy.

If ceftriaxone has been used, rifampicin chemoprophylaxis for the index case is not necessary *(see section 8.1)*.

☑ In children with invasive meningococcal disease the duration of antibiotic therapy should be seven days.

6.4 CORTICOSTEROID THERAPY

6.4.1 MENINGOCOCCAL SEPTICAEMIA

No randomised controlled trials (RCTs) were identified that specifically explored the use of adjunctive systemic corticosteroid therapy on outcome in children with meningococcal septicaemia. No applicable RCTs were identified on the use of systemic steroids in children with severe sepsis or septic shock.[80]

In adults with sepsis, treatment with high-dose steroids over several days is associated with adverse outcome, and steroids should not be given to children with meningococcal septicaemia.[81] 1++

In adult sepsis, RCTs using low (physiological replacement) doses of steroids (200-300 mg hydrocortisone per day for at least five days) reported reduced mortality in patients with inotrope-dependent septic shock.[82-86] A more recent, very large RCT did not confirm improved outcome, with adverse effects such as superinfection, hyperglycaemia and hypernatraemia in the treatment group.[87] 1++ 1- 2-

B **Steroids are not recommended for the treatment of children with meningococcal septicaemia** *(see section 7.1.3 for an exception to this in the case of inotrope-resistant shock)*.

Some children with meningococcal septic shock show signs of adrenal dysfunction.[51,88] A small subgroup of these children show signs of absolute adrenal insufficiency (profound and progressive hypotension despite maximum inotropic support, possibly associated with hypoglycaemia and hyponatraemia). For this subgroup a trial of hydrocortisone (starting at 2 mg/kg and titrating up to effect) may be considered.

6.4.2 MENINGOCOCCAL MENINGITIS

In bacterial meningitis, children treated with high (anti-inflammatory) doses of steroids (dexamethasone 0.15 mg/kg 6 hourly for four days) at an early stage (within 24 hours) of infection have a significantly reduced risk of developing severe hearing loss. The number needed to treat (NNT) to prevent one child developing severe hearing loss is 20.[89] Adult patients with meningococcal meningitis show a trend towards reduction in other neurological sequelae (relative risk (RR) 0.5 (0.1 to 1.7)).[90] Children with meningococcal meningitis show a trend towards reduced hearing loss and other neurological sequelae, which does not reach statistical significance. This is interpreted as due to limited power from low event rate rather than from no benefit from treatment.[91] 1+

At presentation, meningitis due to *Neisseria meningitidis* may be impossible to differentiate from other types of meningitis, and initial treatment must begin before definitive microbiological diagnosis. Empirical treatment with an antibiotic with effective central nervous system (CNS) penetration should be based on age and underlying disease status, since delay in treatment is associated with adverse clinical outcome. This includes administration of systemic corticosteroid therapy.[92] 4

A **In children beginning empirical antibiotic treatment for bacterial meningitis of unknown aetiology, parenteral dexamethasone therapy** *(0.15 mg/kg six hourly)* **should be commenced with, or within 24 hours of, the first antibiotic dose, and be continued for four days.**

B **In children with meningococcal meningitis, parenteral dexamethasone therapy** *(0.15 mg/kg six hourly)* **should be commenced with, or within 24 hours of, the first antibiotic dose, and be continued for four days.**

7 Intensive care

Healthcare professionals should access paediatric intensive care units (PICU) in accordance with local policies. For further information see www.snprs.scot.nhs.uk

Seriously ill children managed in a centralised paediatric intensive care unit have a lower overall mortality, and have a shorter duration of stay, than children admitted to a non-specialist centre, OR increased risk of death 2.09 (1.37-3.19) in non-specialist centre, mean duration of stay 3.93 versus 2.14 days.[93] This is probably due to the presence of full-time specialist staff, who are experienced in the care of critically ill children. 2+

Children with meningococcal disease have an improved chance of survival if looked after in a PICU (59% reduction in mortality per year, OR of yearly trend 0.41, 95% CI 0.27 to 0.62).[7] Discussion between local physicians and the paediatric intensive care team at an early stage was felt to contribute to improved outcome. 3

D **Transfer to PICU should be arranged for patients who continue to deteriorate despite appropriate supportive therapy** *(oxygen, fluids and antibiotics).*

7.1 INTENSIVE CARE MANAGEMENT

7.1.1 VENTILATION AND AIRWAY MANAGEMENT

Expert opinion, in a review which reported that little scientific evidence is available, supports current practice that airway and breathing should be rigorously monitored and maintained.[6] The decision to intubate and ventilate should be made on clinical diagnosis of increased work of breathing, hypoventilation, impaired mental status or presence of a moribund state. Volume loading may be required before and during intubation. Anaesthetic induction agents that maintain cardiovascular stability should be used. 4

Due to low functional residual capacity young infants and neonates with severe sepsis may require early intubation.[65] The principles of lung-protective strategies for adults can also be applied to children. 4

D **In patients with progressive meningococcal disease:**

- **airway and breathing should be rigorously monitored and maintained**
- **the decision to intubate and ventilate should be made if there is increased work of breathing, hypoventilation, low level of consciousness or presence of a moribund state**
- **volume loading should be considered before and during intubation, and anaesthetic induction agents that maintain cardiovascular stability should be used**
- **lung-protective ventilation strategies should be instituted.**

☑

- High frequency oscillation ventilation should be considered for patients when conventional ventilation is failing.
- Early ventilatory support should be considered for children with fluid resistant shock, after institution of inotrope therapy.

7.1.2 FLUIDS

Fluid management in intensive care follows the principles for early fluid therapy as outlined in section 6.2.

Colloids or isotonic crystalloids should be used for IV fluid resuscitation.[66-68]

Early goal-directed fluid resuscitation aiming to achieve a high central venous pressure (8-12mmHg), a mean arterial pressure of at least 65 mmHg, urine output of at least 0.5 ml/kg/hr and central venous oxygen saturation of at least 70% has been correlated with decreased mortality in adult patients with septic shock.[69] Although no paediatric data exist to further support such goals, many PICUs aim to achieve comparable, age-adjusted parameters in clinical practice. 1+

7.1.3 INOTROPES

Expert opinion advises that inotropes should be commenced early in children with IMD and fluid resistant shock.[6,64,65,69,71] Inotropes can be commenced peripherally. Treatment may include inotropic support, vasoconstrictor support or vasodilators, depending on the specific clinical derangement. 4 1+ 3

Dopamine can be used as a first line treatment. In children with preserved blood pressure and high systemic vascular resistance, the addition of vasodilators such as sodium nitroprusside, glycerine trinitrate or milrinone, may be useful. Falling blood pressure, indicating dopamine-resistant shock, should be quickly recognised, and adrenaline added for cold shock, and noradrenaline for warm shock, to restore normal perfusion and blood pressure.

In refractory hypotension (inotrope-resistant shock), an additional infusion of IV vasopressin (0.02-0.06 units/kg/hr) or vasopressin analogues has been used successfully in a small number of patients.[94] Absolute adrenal insufficiency should also be considered, particularly if refractory hypotension is associated with hypoglycaemia and hyponatraemia. For this subgroup, a trial of hydrocortisone (starting at 2 mg/kg and titrating up to effect) may be helpful.[95]

D **Children with fluid resistant shock should receive early inotropic therapy, and ventilatory support should be considered.**

☑ In children with refactory hypotension (inotrope-resistant septic shock), IV vasopressin and steroid dose titration are appropriate rescue strategies.

7.1.4 MONITORING

There is expert opinion that non-invasive monitoring (electrocardiogram, blood pressure, temperature, $Sa0^2$) should be applied in all children with fluid sensitive shock.[6] Central venous and arterial access should be considered in those with fluid resistant septic shock. 4

There was insufficient evidence identified for or against echocardiography, gastric tonometry, femoral artery thermodilution, pulmonary arterial catheters or intracranial pressure monitoring to direct therapy in septic shock in children.

D **Non-invasive monitoring should be applied in all children with fluid sensitive shock.**

D **Central venous and arterial access should be considered in children with fluid resistant septic shock.**

7.1.5 RENAL REPLACEMENT THERAPY

Whilst there is evidence from an adult study in septic shock that high volume venovenous haemofiltration is associated with improved haemodynamic stability, reduced inotropic requirement (statistically significant) and reduced mortality (not statistically significant), there are no controlled studies that demonstrate renal replacement therapy improves outcome in children with sepsis.[96] It is still common practice to use renal replacement therapy in the most severely affected children particularly for the management of fluid balance, metabolic acidosis and acute or impending renal failure. 3

☑ Continuous venovenous haemofiltration may be considered in children with inotrope -dependent septic shock, severe metabolic acidosis, acute or impending renal failure and complex or problematic fluid balance.

7.1.6 EXTRA CORPOREAL MEMBRANE OXYGENATION

A single study, in a small number of patients, has demonstrated that a subgroup of the most severely affected children, in whom the primary pathophysiological disturbance is acute lung injury or acute respiratory distress syndrome (ARDS), may benefit from extra corporeal membrane oxygenation (ECMO), but this reduction in mortality did not extend to those patients with refractory shock.[97] 2-

☑ ECMO should not be used as a standard therapy for refractory shock in children with IMD.

☑ ECMO may be considered in patients with ARDS secondary to IMD who have failed to respond to conventional intensive care management.

7.1.7 PLASMAFILTRATION

One small randomised controlled trial, in five patients failed to demonstrate that plasmafiltration improved outcome.[98] In the absence of benefit, the use of plasmafiltration should be restricted to controlled clinical trials, rather than standard therapy. 1-

7.1.8 STEROIDS

For use of steroids, see section 6.4.

7.1.9 HAEMATOLOGICAL AND IMMUNOLOGICAL SUPPORT

Activated protein C (APC) improves outcome in the management of severe sepsis in adults,[99] but this is not the case in children. An open-label phase two trial, and a phase three RCT of APC in children, have shown a higher incidence of serious adverse events compared to adult studies.[100,101] In particular, there was a higher incidence of serious bleeding events (30% in paediatric patients vs 6.9% in adults).[101] The paediatric RCT of APC was terminated early because of this, and failure to achieve outcome.[100]

A meta-analysis of different anticoagulant therapies (Antithrombin-III, APC and TFPI) for adult patients with sepsis, showed a marginal decrease in mortality (OR 0.869, CI 0.75 to 1) but a substantially increased risk of bleeding (OR 1.7, CI 1.4 to 2.07).[102] A general review of adult and paediatric data suggested there was no evidence of benefit of any anticoagulant therapy other than APC in adults.[103] Two randomised controlled trials on the use of Antithrombin-III in the management of adults with severe sepsis failed to show it to be of any benefit.[104,105] No paediatric data were found. 1++ 4 1++

No evidence was identified to support the use of heparin, fresh frozen plasma or PG12 in the management of coagulation abnormalities associated with invasive meningococcal disease.

There is conflicting evidence on the benefits of IV immunoglobulin in the management of patients with sepsis.[106,107] Analysis of the highest quality studies identified in one systematic review does not support its use.[107] There is no evidence to support the use of IV immunoglobulin in children with IMD. 1++

☑ Activated protein C should not be used in the treatment of meningococcal sepsis in children.

7.2 SURGICAL MANAGEMENT

Consensus would suggest that early compartment pressure monitoring (within the first 24 hours) may be of value in reducing the incidence of muscle necrosis in children with extensive limb involvement *(peripheral limb oedema or confluent purpuric rash)*. Fasciotomies in limbs in which the compartment pressure is raised may reduce the requirement for proximal amputation.[108-111] 4

Evidence taken from adult orthopaedic trauma literature suggests that fasciotomy is indicated if the differential pressure (the difference between diastolic blood pressure and the measured compartment pressure) is less than 30mmHg.[112] No research was identified to provide information on the normal compartment pressures in children. 3

D **Compartment pressure monitoring should be considered in children with extensive limb involvement.**

☑ Urgent specialist referral is necessary for assessment and interpretation of compartment pressure monitoring.

There is no consensus on the optimal timing of surgical debridement. Some authors recommend early debridement and others argue that leaving the tissues to demarcate can allow for some recovery.[113-115] No evidence was identified to support an early aggressive versus conservative approach. Expert opinion suggests that secondary infection should provoke urgent debridement.[109,113,116] 4

In the absence of super-added infection it is difficult to make recommendations on the timing of debridement.

D **Urgent surgical debridement should be performed in the presence of secondary wound infection if the child's condition allows.**

☑ Orthopaedic and plastic surgery teams should be consulted early for needs assessment.

8 Prevention of secondary transmission

8.1 PROPHYLACTIC ANTIBIOTICS

A Cochrane review identified 24 randomised or quasi-randomised trials addressing the effectiveness of different antibiotic treatments for prophylaxis against meningococcal disease and eradication of *Neisseria meningitidis*.[117] No cases of meningococcal disease occurred during follow up, so the effectiveness regarding prevention of disease could not be directly assessed. Chemoprophylaxis with a range of antibiotics (ciprofloxacin, rifampicin, minocycline, ampicillin) was effective at eradication of *Neisseria meningitidis* one week after treatment. Based on a median prevalence of carriers of 230 per 1,000 the absolute risk reduction (rifampicin vs placebo) after one week was 190 per 1,000 (95%CI 177-203) and the NNT to eradicate carriage from the carrier was six (95% CI 5-20). As the risk of invasive disease following acquisition of the organism varies, no NNT can be calculated for the prevention of a case of meningococcal disease. 1++

A systematic review of retrospective cohort studies, including meta-analysis of three studies addressing cases of meningococcal disease one to 30 days after onset in the index case (1,249 cases and 4,271 household contacts) showed a summary risk ratio of 0.11 (0.02-0.58), demonstrating that chemoprophylaxis for household contacts reduced the risk of subsequent cases by 89%.[118] The absolute risk reduction was 46/10,000 (95%CI 9/10,000-83/10,000) and the NNT to prevent a case was estimated at 218 (95% CI 121-1,135). 1++

Without prophylaxis the absolute risk to an individual in the same household one to 30 days after an index case is one in 300. The absolute risk to a pupil in an institution becoming a case in a four week period is 1:1,500 (preschool), 1:18,000 (primary school) and 1:33,000 (secondary school).[15] 4

One retrospective study of healthcare workers who had spent at least 0.5 hours with an infected patient estimated the risk of secondary infection at a rate of 0.8 per 100,000 healthcare workers.[119] The Health Protection Agency Meningococcal Forum recommends that chemoprophylaxis is offered to healthcare workers whose mouth or nose has been exposed to droplets or secretions from the respiratory tract of a patient during the acute illness phase of meningococcal disease.[15] 3 4

Clinicians should liaise closely with the health protection teams of the public health departments of NHS Boards to ensure appropriate public health actions. See "Guidance on the Public Health management of meningococcal Disease in the UK" for a summary of the issues to be considered. www.hpa.org.uk/infections/topics_az/meningo/meningococcalguidelines.pdf

C **Chemoprophylaxis should be offered to those who have prolonged close contact in a household setting with a child with meningococcal disease during the seven days before onset of illness.**

D **In isolated cases of meningococcal disease, prophylaxis is not indicated for pupils in the same nursery, school or class as a child diagnosed with meningococcal disease, unless they are a close contact.**

D **Chemoprophylaxis should be offered to healthcare workers whose mouth or nose is directly exposed to droplets or respiratory secretions from a child with meningococcal disease during the acute illness prior to completion of 24 hours of antibiotics.**

Full guidance on public health issues for meningococcal disease in the UK is available from www.hpa.org.uk/infections/topics_az/meningo/menu.htm

1.Prolonged close contact is defined as those living and/or sleeping in the same household (including extended household), pupils in the same dormitory, boy/girlfriends or university students sharing a kitchen in a hall of residence. NB Unless already identified as a close contact, staff and children attending the same nursery, crèche, school, class tutor are not normally offered chemoprophylaxis.[15]

Health Protection Agency Meningococcus Forum. Guidance for public health management of meningococcal disease in the UK. London: Health Protection Agency; 2006. [cited 7 Mar 2008]. Available from URL: http://www.hpa.org.uk infections/topics_AZ meningo/meningococcalguidelines.pdf.

8.2 VACCINATION

No studies were identified to confirm whether administration of meningococcal vaccination to patients with IMD decreases the risk of reoccurrence. Expert opinion advises that the Men C vaccine should be offered to patients prior to discharge from hospital.[15] | 4

D **Prior to discharge from hospital, Men C vaccine should be offered to:**

- **any patient who has not been immunised, whatever the serogroup**
- **patients with confirmed serogroup C disease who have previously been immunised with Men C.**

Expert advice should be sought from the health protection team about who will be responsible for the vaccination of contacts. See "Guidance on the Public Health management of meningococcal Disease in the UK" for a summary of the issues to be considered. www.hpa.org.uk/infections/topics_az/meningo/meningococcalguidelines.pdf

8.3 INFECTION CONTROL

Meningococci micro-organisms are transmitted through large particle droplets (> 5μm in size).[120] Patients are considered to be non-infectious after 24 hours of IV treatment with ceftriaxone.[15] | 4

Children with conditions where there is a risk of droplet transmission should be admitted to a single room in hospital and standard infection control procedures should be followed.[121] This should not compromise clinical care and the need for frequent observation. The greatest risk of transmission is to healthcare staff exposed to respiratory secretions when carrying out procedures such as endotracheal tube management, intubation, mouth to mouth resuscitation or close examination of the oropharynx.[15] Personal protective equipment (mask, goggles, visor, plastic apron and gloves) should be used during these procedures.[122] | 4

Staff carrying out postmortems of patients with meningococcal disease are not considered to be at risk of infection.[15] | 4

D **Children with suspected meningococcal infection should be admitted to a single room in hospital, where practical.**

D **Infection control measures for droplet infection should be implemented when a child with suspected meningococcal infection is admitted to hospital. These can be discontinued after 24 hours of effective treatment.**

D **Healthcare staff at high risk of exposure to respiratory secretions should use appropriate personal protective equipment.**

9 Follow-up care

9.1 LONG TERM COMPLICATIONS

There is a wide range of potential long term complications for children following infection with meningococcal disease.[52,113,123-129] Not all children develop morbidities and it is difficult to predict which children, and precisely how many, are at risk of some of these complications. 2+ 3

9.1.1 HEARING LOSS

Hearing loss is the most common morbidity of meningococcal disease and meningitis with reported incidence rates ranging from 1.9% to 25%.[57,123,125,127-132] The incidence of hearing loss appears to be higher in underdeveloped countries (9.4-25%)[57,130,132] compared with developed countries (1.9-4.2%).[123,125,127,131] 3

A Canadian study found an incidence of moderate to severe hearing impairment in 5/21 (23%) of patients.[129] Only 72% of survivors had been tested. An American study found 9/42 patients had mild to severe hearing loss. Only 48% of this cohort was tested. No explanations were given to the reasons for lack of follow up in either of these studies. If the numbers were looked at as a part of the whole cohort rather than just those tested then the incidences would be lower at 17% and 10.3% respectively. 3

☑ All children who have had a diagnosis of meningitis should have their hearing tested to allow any therapies required to be started as early as possible.

9.1.2 NEUROLOGICAL MORBIDITIES

Neurological morbidities, including epilepsy, motor deficits, learning disabilities and neurodevelopmental delay, may occur in children who have survived meningococcal disease.[52,124,125,127-130,133,134] 3

9.1.3 PSYCHIATRIC, PSYCHOSOCIAL AND BEHAVIOURAL DEVELOPMENT

Child and adult survivors of IMD have reported a reduction in their quality of life, such as reduced energy, increased anxiety, reduction of leisure activities and reduced ability to work.[123] 15% of survivors had confirmed physical sequelae, and for those with no physical sequelae,19% reported an adverse impact on their quality of life. 3

A study comparing neurodevelopmental outcome in meningococcal disease found significant differences between the survivors and the control group when assessing motor function, cognitive ability and behaviour. Survivors of meningococcal disease scored less well on visual-motor integration, verbal performance and IQ testing, and higher for cognitive and global problems and for measures of attention deficit hyperactivity disorder.[124] A Brazilian study reported a small increased risk of developing psychosis in adulthood and schizophrenia.[130] 2+ 3

A retrospective study on the psychiatric adjustment of children aged four to 17 in the year following meningococcal disease showed that psychiatric disorders were present in 23/40 children over six years of age.[135] The most common primary disorders were depressive, oppositional defiant and anxiety disorders. At 12 month follow up psychiatric disorders were present in 13/40 children over the age of six and 7/26 under the age of six. Two children had post-traumatic stress disorder. Illness severity score, clinical shock on admission and impairing pre-morbid emotional and behavioural problems were independent predictors of psychiatric disorder at 12 month follow up. 3

9.1.4 ORTHOPAEDIC COMPLICATIONS

Children who have survived severe invasive meningococcal disease may be at risk of bone and joint complications, particularly injury to growth plates.[113,136,137] Some of these complications may not be apparent until many years after the initial illness. 3

9.1.5 SKIN AND LIMB COMPLICATIONS

Post necrotic scarring can lead to difficulties for children who have survived meningococcal disease. Some children with extensive soft tissue necrosis may require skin grafting, more complex reconstructive surgery or digit, limb or other amputations. In the longer term further scar revisions, contracture release or amputation stump revision may be required.[114,115,123,125,128] 3

9.1.6 RENAL DYSFUNCTION

Renal impairment can be a morbidity of IMD in children.[123,125] Incidence may be increased in children who required renal replacement therapy during their acute illness.[134] 3

9.1.7 RECOMMENDATIONS ON MORBIDITIES

D **Children and families or carers of children who have survived invasive meningococcal disease should be made aware of potential long term complications of the disease.**

C **When assessing the follow-up needs of children with meningococcal disease healthcare professionals should consider the following potential morbidities:**

- **hearing loss**
- **neurological complications**
- **psychiatric, psychosocial and behavioural problems**
- **bone and joint complications, with awareness that these may not be apparent for many years after illness**
- **post necrotic scarring with possible requirements for amputations and skin grafting. Long term follow up may be needed for children for scar revision, surgical repair of deformities, leg length discrepancy, angular deformities and poorly fitting prosthesis**
- **renal impairment, particularly in those who required renal replacement therapy during their acute illness.**

☑ All children who have had meningococcal sepsis or meningitis should have a follow-up appointment and be carefully assessed for evidence of any immediate or potential long term complications.

☑ An individual care plan should be developed for each patient on leaving hospital.

9.2 IMPACT ON FAMILY AND CARERS

PICU admission for invasive meningococcal disease can result in the development of a post-traumatic stress disorder in patients and immediate carers.[138-142] This is correlated with the length of stay in the PICU.[141] Mothers, as the more common primary carers, have a higher risk of developing post-traumatic stress disorder than fathers. 2^+

C **Healthcare professionals involved in the follow up of children with meningococcal disease need to be aware of the potential for post-traumatic stress disorder in both the children and their families and carers.**

10 Provision of information

10.1 FREQUENTLY ASKED QUESTIONS

This section presents questions and concerns that patients, parents and carers may express during their experience of meningococcal disease. They are derived from enquiries commonly received on the Meningitis Trust and Meningitis Research Foundation telephone help lines. Possible answers are suggested, reflecting the evidence reported within the guideline. This section is not intended to be used as a patient information leaflet, but as an aid to health professionals when discussing these issues with patients and their carers. It could be used alongside leaflets produced by the organisations listed in section 10.2, which provide more detailed information.

Meningococcal disease can be very traumatic for patients and their families, both in terms of the acute illness and the potential for long term complications. There are many issues with which families may have to cope and they need support and reassurance from healthcare professionals throughout the patient journey.

What is Meningococcal disease?

Parents and carers should be given an explanation of what meningococcal disease is, as well as other terms that are commonly used, such as meningococcal organism, meningitis and septicaemia. Healthcare professionals should explain that it is an infection which can develop so quickly that a child can change from being healthy and active to seriously ill within a few hours. It is important to emphasise that while the disease can be life threatening, most children make a full and complete recovery.

Why my child?

Parents often feel angry and want to understand why their child has been affected. Although the risk of developing meningococcal disease is low, the bacteria, *Neisseria meningitidis,* is fairly common with a significant number of the population carrying the organism with no ill effect. It should be explained to parents and carers that for the majority of people this bacterium is harmless as most people develop a natural resistance. The reasons for invasive disease are not yet fully understood but the disease is most common in pre-school children.

What are the potential complications?

The majority of children make a good recovery but there may be complications which parents and carers may wish to be aware of as they can develop after the child has recovered from the acute illness:

- **Hearing impairment** is the most common after-effect from meningitis. Children should be given a hearing test soon after they have recovered from the acute illness and should be reassured that they will receive specialist care if a problem is identified.
- **Neurobehavioural problems and learning disabilities.** Advise parents and carers that there is a small risk that children may develop problems with learning and behaviour, or neurological complications, such as epilepsy. Parents and carers should be advised to inform their child's teacher that their child has had meningococcal disease, so that they can provide extra support and understanding if required.
- **Renal complications.** Explain that a very small number of children who receive renal replacement therapy during treatment of meningococcal septicaemia may be left with longer term renal impairment.
- **Skin, limbs, joints and bones.** Explain that septicaemia (purpura fulminans) can cause damage to the skin and the underlying tissue that may result in scarring to the legs, arms and body. Serious damage to large areas of tissue and muscle may need skin grafts to improve appearance and restore function to injured areas. Long term follow up with ongoing reconstructive surgery, may be required.

In severe cases of septicaemia, fingers, toes and limbs may need to be amputated, but fortunately this is not common. Children may also be at risk of bone and joint complications which sometimes affect the actual growth of the limb. Rehabilitation may take a long time.

How long is my child infectious and what about infection to others?

Advise parents and carers that a child who has had meningococcal disease will have received antibiotics and will not be infectious very soon after starting antibiotic therapy.

Can my child catch meningococcal disease again?

It is natural for parents to worry about the disease recurring. Explain that one episode of meningococcal disease does not mean that a child is immune in future as there are different groups. Men C vaccination is effective in reducing the risk against meningococcus C but does not protect against infection from groups A and B.

The risk of recurrent infection by the same group is usually only associated with children with compromised immunity. It is unlikely that a child will have more than one experience of meningococcal disease, but parents should be advised to continue to look out for the signs and symptoms of the disease and seek medical attention if they have any subsequent concerns.

What about public health involvement and preventive measures?

Let parents and carers know that a suspected case of meningococcal disease will be notified to the local NHS Board public health department by the attending clinician. The public health team will trace close contacts and arrange for appropriate preventive treatment as soon as possible. Although there is a very low risk of getting meningococcal disease, close contacts need to be given advice on early symptoms and signs, as early recognition and treatment give the best chance of making a good recovery. The incubation period is up to seven days. Possible side effects of any preventive therapies should be explained, such as treatment with rifampicin causing coloured urine.

It is important this is clearly explained and written information given to the immediate family as it is often administered at the hospital when their only focus is their child.

What should I expect when my child is discharged from hospital?

All children who have had meningococcal sepsis or meningitis should have a follow-up appointment and be carefully assessed for evidence of any immediate or potential long term complications, some of which may not be apparent initially. An individual care plan must be developed through consultation and agreement with the parents/carers for each patient prior to leaving hospital.

After receiving expert care during the hospital stay patients, parents and carers can feel isolated on leaving that environment behind. It is helpful to inform families of organisations that can offer further support and information during this difficult time. The large spectrum of potential after-effects may mean a broad selection of organisations would be of help to children and their families (*see section 10.2*).

10.2 SOURCES OF FURTHER INFORMATION AND SUPPORT FOR PATIENTS, PARENTS AND CARERS

Action for Sick Children (Scotland)
22 Laurie Street
Edinburgh EH6 5AB
Tel: 0131 553 6553
Email: enquiries@ascscotland.org.uk • Website: www.ascscotland.org.uk

Helps sick children and young people meet their healthcare needs in partnership with parents, carers and professionals

British Deaf Association
(Scottish Deaf Association)
Suite 222, The Pentagon
36 Washington Street
Glasgow G3 8AZ
Videophone IP: Glasgow.bda.bslphone.com, IP: 81.158.182.123
Text phone: 0141 248 5567 • Tel: 0141 248 5554
Email: scotland@signcommunity.org.uk • Website: www.bda.org.uk

An organisation run by people with hearing difficulties. Promotes sign language and campaigns for sign language users to have the same rights, responsibilities, opportunities and quality of life as others.

Child Brain Injury Trust (CBIT)
Princes House
5 Shandwick Place
Edinburgh EH2 4RG
Helpline: 0845 601 4939 (Mon, Tue, Wed, Fri 10.00am - 1.00pm) • Tel: 0131 229 1852
Email: jennyhill@cbituk.org
Email: helpline@cbituk.org • Website: www.cbituk.org

The Child Brain Injury Trust (CBIT) supports anyone in the United Kingdom affected by childhood acquired brain injury. They provide information, support and training to families and professionals.

Contact a Family
209 - 211 City Road
London EC1V 1JN
Tel: 020 7608 8700
Helpline: 0808 808 3555 or Text phone 0808 808 3556 Freephone for parents and families (Mon-Fri, 10am-4pm & Mon, 5.30-7.30pm)
Email: info@cafamily.org.uk • Website: www.cafamily.org.uk

Contact a Family is a UK-wide charity providing advice, information and support to the parents of all disabled children - no matter what their disability or health condition. They also enable parents to get in contact with other families, both on a local and national basis.

Cruse Bereavement Care
Riverview House
Friarton Road
Perth PH2 8DF
Tel: 01738 444 178 • Day by Day Helpline 0870 167 1677
Email: info@crusescotland.org.uk • Website: www.crusescotland.org.uk

Cruse Bereavement Care Scotland is a national organisation which offers a free confidential bereavement counselling service to people of all ages. Cruse volunteers are trained to listen and to help you to work through your grief. They have all undertaken a full training and are regularly supervised. Cruse Bereavement Care Scotland is not aligned with any religious group or political party, and follows an equal opportunities policy.

ENABLE Scotland
6th Floor
7 Buchanan Street
Glasgow G1 3HL
Tel: 0141 226 4541• Fax: 0141 204 4398
Email: enable@enable.org.uk • Website: www.enable.org.uk

ENABLE Scotland is a dynamic charitable organisation run by its members. It campaigns for a better life for children and adults with learning disabilities and supports them and their families to participate, work and live in their local communities.

Epilepsy Scotland
48 Govan Road
Glasgow G51 1JL
Tel: 0141 427 4911 • Helpline: 0808 800 2200
Email: enquiries@epilepsyscotland.org.uk • Website: www.epilepsyscotland.org.uk

Epilepsy Scotland directly involves people with epilepsy to campaign for better services to ensure people with epilepsy have high standards of care, easy access to information and support, and not experience prejudice.

Meningitis Association of Scotland
9 Edwin Street
Glasgow G51 1ND
Tel: 0141 427 6698 • Tel: 0141 554 6680
Website: www.menscot.org

The Association includes a Consultant Neuropsychologist for the treatment of long term side effects as a result of meningitis.

Meningitis Research Foundation
133 Gilmore Place
Edinburgh EH3 9PP
Freephone 24-hour helpline: 080 8800 3344
Website: www.meningitis.org

Offers support to people affected by meningitis and septicaemia, including in-depth information about the diseases and patterns of recovery, befriending by a trained volunteer befriender with similar experience and a listening ear. The Foundation also funds scientific research into meningitis and septicaemia, and provides education and support to the general public and healthcare professionals.

Meningitis Trust
Centrum Offices Ltd
38 Queen Street
Glasgow G1 3DX
Tel/fax: 0845 120 2123 • Freephone 24-hour helpline: 0800 028 1828
Website: www.meningitis-trust.org

Provides support through counselling, financial grants and home visits for individuals and families affected by meningitis/meningococcal septicaemia. The Trust also provides tailored disease information and education programmes for the general public and healthcare professionals.

Murray Foundation
1st Floor, Broomloan House
Ibrox Stadium
Glasgow G51 2XD
Tel: 0141 580 8564 • Fax: 0141 580 7241 • Helpline: 0800 028 2822
Email:info@murray-foundation.org.uk • Website: www.murray-foundation.org.uk

The Murray Foundation is a support service for those affected by limb loss or absence and their families in Scotland. The Foundation works closely with NHS and other professionals to supplement the service already offered.

NDCS Scotland
Tel: 0141 248 4457 • Minicom: 0141 222 4476
Email: ndcs.scotland@ndcs.org.uk

NDCS is an organisation of families, parents and carers, providing emotional and practical support through a freephone helpline and a network of trained Regional Officers, Family Support Workers and Family Officers.

National Deaf Children's Society
15 Dufferin Street
London EC1Y 8UR
Tel: 020 7490 8656 • Minicom: 020 7490 8656 • Helpline (voice and text): 0808 800 8880
Email: ndcs@ndcs.org.uk • Website: www.ndcs.org.uk

Neurological Alliance
Stroke House
240 City Road
London EC1V 2PR
Tel: 020 7566 1540
Email: admin@neural.org.uk • Website: www.neural.org.uk

The Neurological Alliance enables charities to work together to improve the quality of life of all those in the UK living with a neurological condition. The Neurological Alliance does not provide advice and information to individuals about services or specific neurological conditions.

Royal College of Speech and Language Therapists
Scotland Policy Officer - Kim Hartley
21 Queen Street
Edinburgh EH2 1JX
Tel: 0131 226 5250/4940
Email: kim.hartley@rcslt.org • Website: www.rcslt.org.uk

The RCSLT represents speech and language therapists and support workers, to promote excellence in practice and influence health, education and social care policies.

Social, Emotional and Behavioural Difficulties Association
SEBDA Head Office, Church House
1 St Andrew's View
Penrith, Cumbria CA10 7YF
Tel: 01768 210510
Website: www.sebda.org

SEBDA is a charitable organisation that exists to promote excellence in services for children and young people who have social, emotional and behavioural difficulties.

11 Implementation and audit

11.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

11.1.1 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

There is no relevant SMC advice.

11.2 KEY AUDIT POINT

- *Suspected meningococcal deaths should be notified and subject to audit*

12 The evidence base

12.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using a search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsychINFO, and the Cochrane Library. For most searches, the year range covered was 2000-2006. Internet searches were carried out on various websites including the New Zealand Guidelines Group, National Electronic Library for Health Guidelines Finder, and the US National Guidelines Clearinghouse. The search strategies can be requested from the SIGN Executive. The main searches were supplemented by material identified by individual members of the development group.

12.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research were identified by the guideline development group:

- evaluation of the effectiveness of health education campaigns aimed at increasing awareness and recognition of meningococcal disease
- a prospective validation of the predictive value of early symptoms in diagnosing meningococcal disease in a population of children presenting in the community with undifferentiated illness
- which signs and symptoms are definitive markers for referring a child to secondary care
- research to determine whether there are any pre-hospital interventions which are efficacious in reducing mortality and morbidity in children and young people with suspected invasive meningococcal disease
- procalcitonin assay as an indicator of severity and a predictor of outcome
- research to identify the normal compartment pressures in children
- evaluation of the capability of cefotaxime to eliminate carrier status
- an investigation of the role of vasopressin beyond rescue treatment in patients with inotrope resistant shock
- research into the role and importance of organisational changes to, and the interface between primary, secondary and intensive care.

12.3 REVIEW AND UPDATING

This guideline was published in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

13 Development of the guideline

13.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at **www.sign.ac.uk**

13.2 THE GUIDELINE DEVELOPMENT GROUP

Dr David Simpson *(Chair)*	*Consultant in Paediatric Anaesthesia and Intensive Care, Royal Hospital for Sick Children, Edinburgh*
Ms Lynsey Andrews	*Medical Information Officer, Meningitis Research Foundation, Edinburgh*
Dr Roland Armes	*Consultant in Emergency and Paediatric Emergency Medicine, Aberdeen Royal Infirmary and Royal Aberdeen Children's Hospital*
Dr Jack Beattie	*Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow*
Dr Tom Beattie	*Consultant in Paediatric Emergency Medicine, Royal Hospital for Sick Children, Edinburgh*
Dr Emma Breene	*General Practitioner, Garthdee Medical Practice, Aberdeen*
Dr Elizabeth Chalmers	*Consultant Haematologist, Royal Hospital for Sick Children, Glasgow*
Ms Joyce Coppola	*Health Protection Nurse Specialist, Fife NHS Board*
Ms Anne Currie	*Assistant Scotland Manager, Meningitis Trust, Glasgow*
Mrs Margaret Dolan	*Pharmaceutical Adviser, NHS National Services Scotland, Edinburgh*
Dr Rosie Hague	*Consultant in Paediatric Infectious Diseases and Immunology, Royal Hospital for Sick Children, Glasgow*
Dr Pota Kalima	*Consultant Clinical Microbiologist, Western General Hospital, Edinburgh*
Mrs Joanna Kelly	*Information Officer, SIGN*
Dr Una MacFadyen	*Consultant Paediatrician, Stirling Royal Infirmary*
Dr Graham MacKenzie	*Locum Consultant in Public Health Medicine, Fife NHS Board*
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Dr Jim McMenamin	*Consultant Epidemiologist, Health Protection Scotland, Glasgow*
Mr Daren Mochrie	*Head of Accident and Emergency Services, Scottish Ambulance Service, Ayr*
Dr John J M O'Dowd	*General Practitioner and Specialist Registrar in Public Health Medicine, Lanarkshire NHS Board*
Mrs Margaret Pelosi	*Lay representative, Glasgow*
Ms Jane Richardson	*Senior Nurse, Royal Hospital for Sick Children, Edinburgh*
Dr Jennifer Scarth	*Consultant in Paediatric Intensive Care, Royal Hospital for Sick Children, Glasgow*

Ms Ailsa Stein	*Programme Manager, SIGN*
Mr Ken Stewart	*Consultant Plastic Surgeon, Royal Hospital for Sick Children, Edinburgh*
Dr Ulf Theilen	*Consultant Intensivist, Royal Hospital for Sick Children, Edinburgh*
Dr Adam Watts	*Specialist Registrar in Orthopaedics, Royal Hospital for Sick Children, Edinburgh*
Dr Graham Wilson	*Consultant Anaesthetist, Royal Aberdeen Children's Hospital*
Dr Louise Wilson	*Specialist Registrar in Public Health, University of Glasgow*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

13.3 CONSULTATION AND PEER REVIEW

13.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 28 February 2007 and was attended by 92 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

13.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Alan Begg	*General Practitioner, Angus*
Ms Linda Glennie	*Head of Research and Medical Information, Meningitis Research Foundation*
Professor Colin A Graham	*Associate Professor in Emergency Medicine, The Chinese University of Hong Kong*
Ms Caroline Haines	*Nurse Consultant PIC/HDU, Bristol Royal Hospital for Sick Children*
Dr Jilly Hamilton	*General Practitioner, Glasgow*
Professor Simon Kroll	*Professor of Paediatrics and Molecular Infectious Diseases, Imperial College and St Mary's Hospital, London*
Dr Ian K MacOnochie	*Consultant in Paediatric Accident and Emergency, St Mary's Hospital, London*
Dr Tom Marshall	*Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh*
Dr Simon Nadel Lead	*Clinician for Peadiatric Intensive Care, St Mary's Hospital, London*
Dr Charles Saunders	*Consultant in Public Health Medicine, Fife NHS Board*
Dr Andrew Seaton	*Consultant Physician, Gartnavel Hospital, Glasgow*
Ms Joanna Shenfield	*Lay reviewer, Glenrothes*

Dr Charles Siderfin	*Acute Medicine Lead General Practitioner, Balfour Hospital, Kirkwall*
Dr James Stuart	*Regional Director South West, Health Protection Agency*
Dr Angela Thomas	*Consultant Paediatrician Haematologist, Royal Hospital for Sick Children, Edinburgh*
Mr James Wallace	*Director of Pharmacy Services, Royal Hospital for Sick Children, Glasgow*

13.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	*Chair of SIGN; Co-Editor*
Dr Emilia Crighton	*Faculty of Public Health Medicine*
Professor Chris Kelnar	*Royal College of Paediatrics and Child Health*
Professor John Kinsella	*Royal College of Anaesthetisits*
Dr Lorna Thompson	*Programme Manager, SIGN*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

13.3.4 ACKNOWLEDGMENTS

SIGN is grateful to the following former members of the guideline development group:

Dr James Beattie	*General Practitioner, Inverurie Medical Group*
Dr Luciana Brondi	*Medical Information Officer, Meningitis Research Foundation, Edinburgh*
Dr Hilary Connetta	*Specialist Registrar in Paediatric Medicine, Royal Hospital for Sick Children, Glasgow*
Dr Vincent Choudhery	*Specialist Registrar in Paediatric Emergency Medicine, Royal Hospital for Sick Children, Glasgow*
Ms Rili Craig	*Formerly Information and Education Officer, Meningitis Research Foundation, Edinburgh*
Ms Elaine Pritchett	*Infection Control Nurse, Edinburgh*
Dr Rosalie Wilkie	*Consultant Paediatrician, Ninewells Hospital, Dundee*

Abbreviations and glossary

APC	Activated protein C
ARDS	Acute respiratory distress syndrome
CFR	Case fatality rate
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
ECMO	Extra corporeal membrane oxygenation
ED	Emergency department
FDA	Food and Drug Administration
GMSPS	Glasgow Meningococcal Septicaemia Prognostic Score
GP	General practitioner
HPS	Health Protection Scotland
ICP	Intracranial pressure
IMD	Invasive meningococcal disease
IV	Intravenous
LP	Lumbar puncture
LR	Likelihood ratio
MIDAS	Meningococcal Invasive Disease Augmented Surveillance
MTA	Multiple technology appraisals
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
OR	Odds ratio
Petechiae	A non-blanching rash with lesions of less than 2mm in diameter
PCR	Polymerase chain reaction
PICU	Paediatric intensive care unit
Primary care	Out of hospital care, including out of hours services and ambulances
PRISM	Paediatric risk of mortality score
Purpura	A non-blanching rash with lesions of 2mm or more in diameter
RCT	Randomised controlled trial
RR	Relative risk
Secondary care	Care in hospital
SMC	Scottish Medicines Consortium
SVC	Superior vena cava
t-Pa	Tissue plasminogen activator
TFPI	Tissue factor pathway inhibitor

Annex 1

Glasgow Meningococcal Septicaemia Prognostic Scoring Tool[143,142]

	Points
BP < 75mm Hg systolic, age < 4y < 85 mm Hg systolic, age > 4y	3
Skin/rectal temperature difference > 3ºC	3
Modified coma scale score < 8 or 8a Deterioration of ≥ 3 points in 1 hour	3
Deterioration in hour before scoring	2
Absence of meningism	2
Extending purpuric rash or Widespread ecchymoses	1
Base deficit (capillary or arterial) > 8.0	1
Maximum score:	15
a Modified Coma Scale	
(i) Eyes open: Spontaneously To speech To pain None	 4 3 2 1
(ii) Best verbal response: Orientated Words Vocal sounds Cries None	 6 4 3 2 1
(iii) Best motor response: Obeys commands Localises to pain Moves to pain None	 6 4 1 0
Add scores (i) + (ii) + (iii) to give result. Score ≥ 8, or an escalating score is indicative of serious and rapidly progressing disease.	

Annex 2

Key questions used to develop the guideline

The guideline is based on a series of structured key questions that, where possible, define the *population* concerned, the *intervention* (or diagnostic test, etc) under investigation, the type of *control* used, and the *outcomes* used to measure the effectiveness of the interventions. These questions form the basis of the systematic literature search

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THE KEY QUESTIONS USED TO DEVELOP THE GUIDELINE	
PRE-HOSPITAL ISSUES	
Key question	**Notes**
1. In a child presenting in the community setting, which grouping of signs and symptoms should arouse suspicion of meningococcal disease? a. fever b. neck stiffness c. headache d. photophobia e. vomiting f. dizziness g. rapid breathing h. drowsiness i. less than 50% of usual fluid intake in 24 hours (children under 1) j. strange high-pitch crying (children under 1) k. abnormal skin colour l. collapse m. leg pain/refusal to walk n. rash o. heart rate p. cold hands/feet	
2. In a child presenting in the community setting with symptoms suggestive of meningococcal disease, what is the evidence that specific secondary assessment (after 4-6 hours), looking for disease progression, improves diagnosis?	include telephone assessment
3. In a child presenting in the community setting with symptoms suggestive of meningococcal disease, which key features indicate the need for immediate hospital assessment?	
4. In patients with suspected meningococcal disease, do pre-hospital antibiotics increase patient survival or affect morbidity (ITU admission, length of hospital stay, deafness, limb amputation)?	consider: penicillin, cefotaxime, cetriaxone
5. In patients with suspected meningococcal disease, which antibiotic is the most effective in increasing patient survival or decreasing morbidity (ITU admission, length of hospital stay, deafness, limb amputation).	consider: penicillin, cefotaxime, cetriaxone; dose, timing and route (intravenously, intramuscularly, non-parenteral)

6. Do educational programmes improve the speed of: a. recognition b. diagnosis c. treatment of meningococcal disease; increase survival or decrease disease severity (ITU admission, length of hospital stay, deafness, limb amputation)?	consider: public information campaigns; lay education programmes; professional education programme
7. Do 'process mapping programmes' for those with progressive symptoms increase survival or decrease disease severity (ITU admission, length of hospital stay, deafness, limb amputation)?	to do with time factors, door-to-needle times, promptness of treatment
8. In patients with suspected meningococcal disease, is there evidence that pre-hospital (ambulance) resuscitation increases survival or decreases disease severity (ITU admission, length of hospital stay, deafness, limb amputation)?	consider: oxygen, IV fluids (colloid/ crystalloid (Normal saline) Hartmanns, Ringer Lactate), intubation

PUBLIC HEALTH ISSUES

Key question	**Notes**
9. What is the evidence that the following groups who have had contact with a meningococcal patient within the last seven days should receive prophylactic antibiotics? a. 'kissing contact' b. household contact c. pupils in same class/school d. contact with bodily fluids (at resuscitation)	
10. What is the evidence that the following antibiotics are effective in preventing meningococcal disease occurring in the contact groups? a. Rifampicin b. Ciproflaxin c. Ceftriaxone	consider timing and dose
11. Does administration of meningococcal vaccination to cases of invasive meningococcal disease decrease the risk of further meningococcal disease?	

SECONDARY PAEDIATRIC CARE Starting point defined as the first point of contact with secondary paediatric care, and focusing on the early diagnostic and treatment phase (first 48h).	
Key question	**Notes**
12. In patients with suspected Invasive Meningococcal Disease (IMD), which clinical factors are useful in predicting disease severity/ risk of poor clinical outcome? a. Clinical signs: ▪ Tachycardia ▪ Tachypnoea ▪ hypotension ▪ poor peripheral perfusion (CRT) ▪ central/core temperature differential ▪ rash extent/severity ▪ progression of rash ▪ presence of fever (risk linked to fever level?) ▪ neck stiffness ▪ irritability/fussiness ▪ lethargy/lassitude/drowsiness ▪ level of consciousness (as measured by Glasgow Coma Scale) b. Lab studies: ▪ White cell count (high/low) – include neutrophil count ▪ coagulopathy (including FDPs) ▪ CRP ▪ Platelets ▪ blood gases (arterial, venous, capillary) ▪ renal function ▪ liver function ▪ cortisol ▪ blood sugar ▪ others eg CPK (rhabdomyolysis).	
13. In patients with suspected IMD, what is the evidence that using any of the following meningococcal scoring systems predict severe disease/risk of poor clinical outcome? a. Leclerc b. Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) c. Gedde-Dahl's MOC score	consider: timing and frequency of scoring

14. In patients with suspected IMD, which early investigations are useful in later confirmation of IMD? a. Blood culture b. Skin scraping (extended) c. Blood PCR d. Throat swab e. Urine rapid antigen testing f. Blood rapid antigen testing	
15. In patients with suspected IMD, does lumbar puncture (early/late) influence: a. early/late clinical management b. final diagnosis c. morbidity and mortality	
16. In patients with suspected IMD, what infection control procedures are effective during inpatient care in reducing secondary healthcare associated infection in clinical staff and visitors (Excludes laboratory workers)? a. Source isolation b. Protective clothing, including masks, gowns, aprons c. Chemoprophylaxis (rifampicin)	Includes staff and immediate family visitors and index case
17. In patients with suspected IMD, what treatments reduce mortality and morbidity? a. Antibiotics (consider route of administration) b. Corticosteroid therapy c. IV fluids [colloid/ crystalloid (Normal saline Hartmanns, Ringer Lactate) debate, FFP, artificial colloids] d. Resuscitation (oxygen, airway care, circulation)	consider: selection, timing, dose, duration
TERTIARY CARE, REHABILITATION ▪ Definition of tertiary care –relates to a facility capable of providing interventions as in Q20, ie ICU in a specialist paediatric hospital ▪ Outcome measure for all questions will primarily be mortality and residual disability.	

Key question	Notes
18. In meningococcal disease patients requiring ICU admission, is there evidence that the following influences outcome (as defined above)? a. a specialised/centralised retrieval team b. paediatric intensive care c. telephone remote support d. early referral and/or retrieval	
19. In meningococcal disease patients requiring ICU admission, is there evidence that the timing of a consultation with a specialist centre/PICU influences outcome (as defined above)?	
20. In the patients requiring intensive care management, what is the evidence that the following interventions influence mortality and morbidity? a. Ventilation/airways management b. Inotropes c. Invasive monitoring d. Renal replacement therapy (haemofiltration, CVVH, plasmapharesis) e. ECMO (extra corporeal membrane oxygenation) f. Mechanical circulatory support (hyper-osmolar fluids) f. Plasmafiltration g. Steroids – physiological replacement or higher dose (circulatory shock steroids) h. Invasive management of intracranial hypertension	consider: timing

21. In critically ill ITU patients with meningococcal disease, what is the evidence that hematological and immunological support reduce mortality and morbidity? a. Immunoglobulins b. Activated protein C and Protein C c. Heparin d. FFP e. PG12 f. t-Pa g. PAF h. Antithrombin-III	
22. What is the evidence that in patients with extensive skin involvement, compartmental pressure monitoring and fasciotomy improve outcome in terms of avoiding tissue necrosis and amputation and decrease residual disability?	
23. What is the evidence that the timing of early surgical debridement or conservative treatment is more effective in decreasing tissue necrosis, and avoiding amputation and secondary infection?	
24. What are the morbidities associated with meningococcal disease and what further support and information provision do patients need as a result? a. organ dysfunction (renal failure, visual impairment) b. hearing loss c. psychosocial/behavioural problems d. mobility e. post-traumatic stress disorder f. educational achievement g. speech h. ambulation i. cognition j. pain k. quality of life l. residual haematological disability m. hydrocephalus n. epilepsy o. cerebral palsy p. long term respiratory complications q. skin involvement	
25. What is the evidence that families/carers/siblings of those who have had meningococcal disease experience psychosocial problems and, if so, do psychosocial interventions and information provision improve their quality of life?	

References

1. Health Protection Scotland. Surveillance Systems: Meningococcal Invasive Disease Augmented Surveillance (MIDAS). [cited 15 Apr 2008]. Available from url: http://www.hps.scot.nhs.uk/resp/ssdetail.aspx?id=13
2. Health Protection Agency. Enhanced Surveillance of Meningococcal Disease National Annual Report: July 2002 - June 2003. London: Health Protection Agency; 2003. [cited 11 Mar 2008]. Available from URL: http://www.hpa.org.uk/infections/topics_az/meningo/ESMD_annual_report_0203.pdf
3. Tibby SM, Murdoch IA, Durward A. Mortality in meningococcal disease: please report the figures accurately. Arch Dis Child 2002;87(6):559.
4. Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, et al. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367(9508):397-403.
5. The Scottish Government. Delivering for Health. Edinburgh: The Scottish Government; 2005. [cited 7 Mar 2008]. Available from url: http://www.scotland.gov.uk/Publications/2005/11/02102635/26389
6. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 2002;30(6):1365-78.
7. Booy R, Habibi P, Nadel S, de Munter C, Britto J, Morrison A, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. Arch Dis Child 2001;85(5):386-90.
8. Cartwright KA, Stuart JM, Jones DM, Noah ND. The Stonehouse survey: nasopharyngeal carriage of meningococci and Neisseria lactamica. Epidemiol Infect 1987;99(3):591-601.
9. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med 2001;344(18):1378-88.
10. Riordan FA, Marzouk O, Thomson AP, Sills JA, Hart CA. The changing presentations of meningococcal disease. Eur J Pediatr 1995;154(6):472-4.
11. Inkelis SH, O'Leary D, Wang VJ, Malley R, Nicholson MK, Kuppermann N. Extremity pain and refusal to walk in children with invasive meningococcal disease. Pediatrics 2002;110(1 Pt 1):e3.
12. Nascimento-Carvalho CM, Moreno-Carvalho OA. Changing the diagnostic framework of meningococcal disease. Lancet 2006;367(9508):371-2.
13. Wells LC, Smith JC, Weston VC, Collier J, Rutter N. The child with a non-blanching rash: how likely is meningococcal disease? Arch Dis Child 2001;85(3):218-22.
14. Neighbour, R. The Inner Consultation: How to Develop an Effective and Intuitive Consulting Style. 2nd ed. Oxford: Radcliffe Publishing Ltd; 2004.
15. Health Protection Agency Meningococcus Forum. Guidance for public health management of meningococcal disease in the UK. London: Health Protection Agency; 2006. [cited 7 Mar 2008]. Available from URL: http://www.hpa.org.uk/infections/topics_AZ/meningo/meningococcalguidelines.pdf
16. Harnden A, Ninis N, Thompson M, Perera R, Levin M, Mant D, et al. Parenteral penicillin for children with meningococcal disease before hospital admission: case-control study. Br Med J 2006;332(7553):1295-8.
17. Miner JR, Heegaard W, Mapes A, Biros M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. J Emerg Med 2001;21(4):387-92.
18. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 2005;98(4):291-8.
19. Prasad K, Singhal T, Jain N, Gupta PK. Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis (Cochrane Review). In: The Cochrane Library, Issue 1, 2006. London: John Wiley & Sons Ltd.
20. Singhi P, Kaushal M, Singhi S, Ray P. Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis. J Trop Pediatr 2002;48(5):273-9.
21. Faust SN, Pollard AJ, Nadel S, Ninis N, Levin M. Ceftriaxone drug alert: no longer for first line use in meningococcal sepsis. Arch Dis Child 2008;93(2):184-5.
22. Fisher JD, Brown SN, Cooke MW, eds. UK Ambulance Service Clinical Practice Guidelines. London: Joint Royal Colleges Ambulance Liaison Committee and the Ambulance Service Association; 2006. [cited 7 Mar 2008]. Available from URL: http://www2.warwick.ac.uk/fac/med/research/hsri/emergencycare/jrcalc_2006/guidelines/clinical_guidelines_2006.pdf
23. Meningitis Research Foundation and Joint Royal Colleges Ambulance Liaison Committee. Meningococcal Septicaemia: Identificaton and Management for Ambulance Personnel. 2nd ed. Meningitis Research Foundation; 2003. [cited 7 Mar 2008]. Available from URL: http://www.meningitis.org.uk/assets/x/50114
24. Ninis N, Phillips C, Bailey L, Pollock JI, Simon N, Britto J, et al. The role of healthcare delivery in the outcome of meningococcal disease in children: Case-control study of fatal and non-fatal cases. Br Med J 2005;330(7506):1475-8.
25. Bryant PA, Li HY, Zaia A, Griffith J, Hogg G, Curtis N, et al. Prospective study of a real-time PCR that is highly sensitive, specific, and clinically useful for diagnosis of meningococcal disease in children. J Clin Microbiol 2004;42(7):2919-25.
26. Ragunathan L, Ramsay M, Borrow R, Guiver M, Gray S, Kaczmarski EB. Clinical features, laboratory findings and management of meningococcal meningitis in England and Wales: report of a 1997 survey. Meningococcal meningitis: 1997 survey report. J Infect 2000;40(1):74-9.
27. Tsolia MN, Theodoridou M, Tzanakaki G, Kalabalikis P, Urani E, Mostrou G, et al. The evolving epidemiology of invasive meningococcal disease: a two-year prospective, population-based study in children in the area of Athens. FEMS Immunol Med Microbiol 2003;36(1-2):87-94.
28. Mills GD, Lala HM, Oehley MR, Craig AB, Barratt K, Hood D, et al. Elevated procalcitonin as a diagnostic marker in meningococcal disease. Eur J Clin Microbiol Infect Dis 2006;25(8):501-9.
29. Pollard AJ, Britto J, Nadel S, DeMunter C, Habibi P, Levin M. Emergency management of meningococcal disease. Arch Dis Child 1999;80(3):290-6.
30. Riordan FA, Cant AJ. When to do a lumbar puncture. Arch Dis Child 2002;87(3):235-7.
31. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001;108(5):1169-74.
32. Kneen R, Solomon T, Appleton R. The role of lumbar puncture in children with suspected central nervous system infection. BMC Pediatr 2002;2:8.
33. Richardson DC, Louie L, Louie M, Simor AE. Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis. J Clin Microbiol 2003;41(8):3851-3.
34. Tzanakaki G, Tsolia M, Vlachou V, Theodoridou M, Pangalis A, Foustoukou M, et al. Evaluation of non-culture diagnosis of invasive meningococcal disease by polymerase chain reaction (PCR). FEMS Immunol Med Microbiol 2003;39(1):31-6.
35. Bronska E, Kalmusova J, Dzupova O, Maresova V, Kriz P, Benes J. Dynamics of PCR-based diagnosis in patients with invasive meningococcal disease. Clin Microbiol Infect 2006;12(2):137-41.
36. Arend SM, Lavrijsen AP, Kuijken I, van der Plas RN, Kuijper EJ. Prospective controlled study of the diagnostic value of skin biopsy in patients with presumed meningococcal disease. Eur J Clin Microbiol Infect Dis 2006;25(10):643-9.
37. Periappuram M, Taylor MR, Keane CT. Rapid detection of meningococci from petechiae in acute meningococcal infection. J Infect 1995;31(3):201-3.
38. van Deuren M, van Dijke BJ, Koopman RJ, Horrevorts AM, Meis JF, Santman FW, et al. Rapid diagnosis of acute meningococcal infections by needle aspiration or biopsy of skin lesions. Br Med J 1993;306(6887):1229-32.
39. Duarte MC, Amorim MR, Cuevas LE, Cabral-Filho JE, Correia JB. Risk factors for death from meningococcal infection in Recife, Brazil. J Trop Pediatr 2005;51(4):227-31.
40. Malley R, Huskins WC, Kuppermann N. Multivariable predictive models for adverse outcome of invasive meningococcal disease in children. J Pediatr 1996;129(5):702-10.
41. Smith I, Bjornevik AT, Augland IM, Berstad A, Wentzel-Larsen T, Halstensen A. Variations in case fatality and fatality risk factors of meningococcal disease in Western Norway, 1985-2002. Epidemiol Infect 2006;134(1):103-10.
42. Peters MJ, Ross-Russell RI, White D, Kerr SJ, Eaton FE, Keengwe IN, et al. Early severe neutropenia and thrombocytopenia identifies the highest risk cases of severe meningococcal disease. Pediatr Crit Care Med 2001;2(3):225-31.
43. Casado-Flores J, Blanco-Quiros A, Nieto M, Asensio J, Fernandez C. Prognostic utility of the semi-quantitative procalcitonin test, neutrophil count and C-reactive protein in meningococcal infection in children. Eur J Pediatr 2006;165(1):26-9.
44. Van der Kaay DC, De Kleijn ED, De Rijke YB, Hop WC, De Groot R, Hazelzet JA. Procalcitonin as a prognostic marker in meningococcal disease. Intensive Care Med 2002;28(11):1606-12.
45. Carrol ED, Newland P, Thomson APJ, Hart CA. Prognostic value of procalcitonin in children with meningococcal sepsis. Crit Care Med 2005;33(1):224-5.
46. Leclerc F, Leteurtre S, Noizet O, Dorkenoo A, Sadik A, Cremer R, et al. Procalcitonin as a prognostic marker in children with meningococcal septic shock. Arch Dis Child 2002;87(5):450.

47. Ovstebo R, Brandtzaeg P, Brusletto B, Haug KBF, Lande K, Hoiby EA, et al. Use of robotized DNA isolation and real-time PCR to quantify and identify close correlation between levels of Neisseria meningitidis DNA and lipopolysaccharides in plasma and cerebrospinal fluid from patients with systemic meningococcal disease. J Clin Microbiol 2004;42(7):2980-7.
48. Gottfredsson M, Diggle MA, Lawrie DI, Erlensdottir H, Hardardottir H, Kristinsson KG, et al. Neisseria meningitidis sequence type and risk for death, Iceland. Emerg Infect Dis 2006;12(7):1066-73.
49. Vermont CL, den Brinker M, Kakeci N, de Kleijn ED, de Rijke YB, Joosten DFM, et al. Serum lipids and disease severity in children with severe meningococcal sepsis. Crit Care Med 2005;33(7):1610-5.
50. Leclerc F, Walter-Nicolet E, Leteurtre S, Noizet O, Sadik A, Cremer R, et al. Admission plasma vasopressin levels in children with meningococcal septic shock. Intensive Care Med 2003;29(8):1339-44.
51. Bone M, Diver M, Selby A, Sharples A, Addison M, Clayton P. Assessment of adrenal function in the initial phase of meningococcal disease. Pediatrics 2002;110(3):563-9.
52. Bedford H, De Louvois J, Halket S, Peckham C, Hurley R, Harvey D. Meningitis in infancy in England and wales: Follow up at age 5 years. Br Med J 2001;323(7312):533-6.
53. Kutz JW, Simon LM, Chennupati SK, Giannoni CM, Manolidis S. Clinical predictors for hearing loss in children with bacterial meningitis. Arch Otolaryngol Head Neck Surg 2006;132(9):941-5.
54. Chang CJ, Chang HW, Chang WN, Huang LT, Huang SC, Chang YC, et al. Seizures complicating infantile and childhood bacterial meningitis. Pediatr Neurol 2004;31(3):165-71.
55. Lucena R, Fonseca N, Nunes L, Cardoso A, Goes J, Correia MC, et al. Intra-hospital lethality among infants with pyogenic meningitis. Pediatr Neurol 2005;32(3):180-3.
56. Eisenhut M, Meehan T, Batchelor L. Cerebrospinal fluid glucose levels and sensorineural hearing loss in bacterial meningitis. Infection 2003;31(4):247-50.
57. Forsyth H, Kalumbi F, Mphaka E, Tembo M, Mwenechanya J, Kayira K, et al. Hearing loss in Malawian children after bacterial meningitis: Incidence and risk factors. Audiol Med 2004;2(2):100-7.
58. Riordan FAI, Marzouk O, Thomson APJ, Sills JA, Hart CA. Prospective validation of the glasgow meningococcal septicaemia prognostic score. Comparison with other scoring methods. Eur J Pediatr 2002;161(10):531-7.
59. Thomson AP, Sills JA, Hart CA. Validation of the Glasgow Meningococcal Septicemia Prognostic Score: a 10-year retrospective survey. Crit Care Med 1991;19(1):26-30.
60. Castellanos-Ortega A, Delgado-Rodriguez M. Comparison of the performance of two general and three specific scoring systems for meningococcal septic shock in children. Crit Care Med 2000;28(8):2967-73.
61. Silva PS, Fonseca MC, Iglesias SB, Carvalho WB, Bussolan RM, Freitas IW. Comparison of two different severity scores (Paediatric Risk of Mortality [PRISM] and the Glasgow Meningococcal Sepsis Prognostic Score [GMSPS]) in meningococcal disease: preliminary analysis. Ann Trop Paediatr 2001;21(2):135-40.
62. Advanced Life Support Group. Advanced Paediatric Life Support: The Practical Approach. 3rd ed. London: BMJ Books; 2000.
63. Nadel S, Kroll JS. Diagnosis and management of meningococcal disease: the need for centralized care. FEMS Microbiol Rev 2007;31(1):71-83.
64. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32(3):858-73.
65. Parker MM, Hazelzet JA, Carcillo JA. Pediatric considerations. Crit Care Med 2004;32(11 Suppl):S591-4.
66. Alderson P, Bunn F, Li Wan Po A, Li L, Roberts I, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. London: John Wiley & Sons Ltd.
67. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients (Cochrane Review). In: The Cochrane Libray, Issue 2, 2004. London: John Wiley & Sons Ltd.
68. Bunn F, Alderson P, Hawkins V. Colloid solutions for fluid resuscitation (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. London: John Wiley & Sons Ltd.
69. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345(19):1368-77.
70. Upadhyay M, Singhi S, Murlidharan J, Kaur N, Majumdar S. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded Gelatin in saline) in pediatric septic shock. Indian Pediatr 2005;42(3):223-31.
71. Matok I, Vard A, Efrati O, Rubinshtein M, Vishne T, Leibovitch L, et al. Terlipressin as rescue therapy for intractable hypotension due to septic shock in children. Shock 2005;23(4):305-10.
72. Oates-Whitehead RM, Maconochie I, Baumer H, Stewart MER. Fluid therapy for acute bacterial meningitis (Cochrane Review). In: The Cochrane Library, Issue 4, 2005. London: John Wiley & Sons Ltd.
73. Lebel MH, Hoyt MJ, McCracken GH. Comparative efficacy of ceftriaxone and cefuroxime for treatment of bacterial meningitis. J Pediatr 1989;114(6):1049-54.
74. Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J, Auckenthaler R, Bernath O, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N Engl J Med 1990;322(3):141-7.
75. El Bashir H, Laundy M, Booy R. Diagnosis and treatment of bacterial meningitis. Arch Dis Child 2003;88(7):615-20.
76. Martin E, Hohl P, Guggi T, Kayser FH, Fernex M. Short course single daily ceftriaxone monotherapy for acute bacterial meningitis in children: results of a Swiss multicenter study. Part I: Clinical results Infection 1990;18(2):70-7.
77. Roine I, Ledermann W, Foncea LM, Banfi A, Cohen J, Peltola H. Randomized trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. Pediatr Infect Dis J 2000;19(3):219-22.
78. Crosswell JM, Nicholson WR, Lennon DR. Rapid sterilisation of cerebrospinal fluid in meningococcal meningitis: Implications for treatment duration J Paediatr Child Health 2006;42(4):170-3.
79. 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(4):485-7.
80. Grandgirard D, Leib SL. Strategies to prevent neuronal damage in paediatric bacterial meningitis. Curr Opin Pediatr 2006;18(2):112-8.
81. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit Care Med 1997;25(7):1095-100.
82. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. London: John Wiley & Sons Ltd.
83. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. Br Med J 2004;329(7464):480-4.
84. Burry LD, Wax RS. Role of corticosteroids in septic shock. Ann Pharmacother 2004;38(3):464-72.
85. Keh D, Sprung CL. Use of corticosteroid therapy in patients with sepsis and septic shock: an evidence-based review. Crit Care Med 2004;32(11 Suppl):S527-33.
86. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med 2004;141(1):47-56.
87. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358(2):111-24.
88. De Kleijn ED, Joosten KFM, Van Rijn B, Westerterp M, De Groot R, Hokken-Koelega ACS, et al. Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. Pediatr Infect Dis J 2002;21(4):330-6.
89. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis (Cochrane Review). In: The Cochrane Library, Issue 4, 2005. London: John Wiley & Sons.
90. van de Beek D, de Gans J, McIntyre P, Prasad K. Steroids in adults with acute bacterial meningitis: a systematic review. Lancet Infect Dis 2004;4(3):139-43.
91. McIntyre P. Should dexamethasone be part of routine therapy of bacterial meningitis in industrialised countries? Adv Exp Med Biol 2005;568:189-97.
92. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39(9):1267-84.
93. Pearson G, Shann F, Barry P, Vyas J, Thomas D, Powell C, et al. Should paediatric intensive care be centralised? Trent versus Victoria. Lancet 1997 349(9060):1213-7.
94. Rodríguez-Núñez A, Fernández-Sanmartín M, Martinón-Torres F, González-Alonso N, Martinón-Sánchez JM. Terlipressin for catecholamine-resistant septic shock in children. Intensive Care Med 2004;30(3):477-80.
95. Aneja R, Carcillo JA. What is the rationale for hydrocortisone treatment in children with infection-related adrenal insufficiency and septic shock? Arch Dis Child 2007;92(2):165-9.
96. Joannes-Boyau O, Rapaport S, Bazin R, Fleureau C, Janvier G. Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. ASAIO J 2004;50(1):102-9.
97. Luyt DK, Pridgeon J, Brown J, Peek G, Firmin R, Pandya HC. Extracorporeal life support for children with meningococcal septicaemia. Acta Paediatr 2004;93(12):1608-11.
98. Reeves JH, Butt WW, Shann F, Layton JE, Stewart A, Waring PM, et al. Continuous plasmafiltration in sepsis syndrome. Plasmafiltration in Sepsis Study Group. . Crit Care Med 1999;27(10):2096-104.

99. Green C, Dinnes J, Takeda I, Shepherd J, Hartwell D, Cave C et al. Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation. Health Technology Assess 2005; 9(11). [cited 7 Mar 2008]. Available from URL: http://www.ncchta.org/fullmono/mon911.pdf
100. Eisenberg P. Re: Discontinuation of Study F1K-MC-EVBP, Investigation of the Efficacy and Safety of Drotrecogin Alfa (Activated) in Pediatric Severe Sepsis [Open Letter to Healthcare Professionals]. 21 Apr 2005. [cited 11 Mar 2008]. Available from URL: http://www.fda.gov/medwaTCH/SAFETY/2005/Xigris_dearhcp_4-21-05.pdf
101. Goldstein B, Nadel S, Peters M, Barton R, Machado F, Levy H, et al. ENHANCE: results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. Pediatr Crit Care Med 2006;7(3):200-11.
102. Freeman BD, Zehnbauer BA, Buchman TG. A meta-analysis of controlled trials of anticoagulant therapies in patients with sepsis. Shock 2003;20(1):5-9.
103. Deans KJ, Haley M, Natanson C, Eichacker PQ, Minneci PC. Novel therapies for sepsis: a review. J Trauma 2005;58(4):867-74.
104. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, et al. High-dose antithrombin III in severe sepsis: A randomized controlled trial. JAMA 2001;286(15):1869-78.
105. Wiedermann CJ, Hoffmann JN, Juers M, Ostermann H, Kienast J, Briegel J, et al. High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: efficacy and safety. Crit Care Med 2006;34(2):285-92.
106. Alejandria MM, Lansang MA, Dans LF, Mantaring JBV. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). In: The Cochrane Library, Issue 4, 2005. London: John Wiley & Sons Ltd.
107. Pildal J, Gotzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis 2004;39(1):38-46.
108. Brown JC, Del Beccaro MA, Clausen CR. A Comparison of Time to Positive Culture and Time to Clinical Identification of Serious Bacterial Infection in Infants. Clin Pediatr (Phila) 2003;42(9):797-805.
109. Hunt DM. The orthopaedic management of purpura fulminans in meningococcal disease in children. Care Crit Ill 2001;17(4):118-20.
110. Potokar TS, Oliver DW, Ross Russell R, Hall PN. Meningococcal septicaemia and plastic surgery--a strategy for management. Br J Plast Surg 2000;53(2):142-8.
111. Warner PM, Kagan RJ, Yakuboff KP, Kemalyan N, Palmieri TL, Greenhalgh DG, et al. Current management of purpura fulminans: a multicenter study. J Burn Care Rehabil 2003;24(3):119-26.
112. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression J Bone Joint Surg Br 1996 78(1):99-104.
113. Bache CE, Torode IP. Orthopaedic sequelae of meningococcal septicemia. J Pediatr Orthop 2006;26(1):135-9.
114. Rode H, Millar AJW, Argent A, Hudson D, Davies J. Meningococcal septicaemia and purpura fulminans in children -- surgical management and outcome: a 22 year review of 68 patients. Prim Intention 2001;9(4):150-7.
115. Wheeler JS, Anderson BJ, De Chalain TM. Surgical interventions in children with meningococcal purpura fulminans--a review of 117 procedures in 21 children. J Pediatr Surg 2003;38(4):597-603.
116. Huang DB, Price M, Pokorny J, Gabriel KR, Lynch R, Paletta CE. Reconstructive surgery in children after meningococcal purpura fulminans. J Pediatr Surg 1999;34(4):595-601.
117. Fraser A, Gafter-Gvili A, Paul M, Leibovici L. Antibiotics for preventing meningococcal infections. Cochrane Database of Systematic Reviews 2005;1.
118. Purcell B, Samuelsson S, Hahne SJM, Ehrhard I, Heuberger S, Camaroni I, et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: Systematic review. Br Med J 2004;328(7452):1339-42.
119. Gilmore A, Stuart J, Andrews N. Risk of secondary meningococcal disease in health-care workers. Lancet 2000;356(9242):1654-5.
120. Tang JW, Li Y, Eames I, Chan PK, Ridgway GL. Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. J Hosp Infect 2006;64(2):100-14.
121. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007. Atlanta, GA: Centers for Disease Control and Prevention; 2007. [cited 11 Mar 2008]. Available from URL: http://www.cdc.gov/ncidod/dhqp/gl_isolation.html
122. Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SR, et al. epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect 2007;65(Suppl 1):S1-64.
123. Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. Clin Infect Dis 1998;26(5):1159-64.
124. Fellick JM, Sills JA, Marzouk O, Hart CA, Cooke RW, Thomson AP. Neurodevelopmental outcome in meningococcal disease: a case-control study. Arch Dis Child 2001;85(1):6-11.
125. Healy CM, Butler KM, Smith EB, Hensey OP, Bate T, Moloney AC, et al. Influence of serogroup on the presentation, course, and outcome of invasive meningococcal disease in children in the Republic of Ireland, 1995-2000. Clin Infect Dis 2002;34(10):1323-30.
126. Hussey G, Schaaf H, Hanslo D, Hitchcock J, Coetzee G, Pitout J, et al. Epidemiology of post-neonatal bacterial meningitis in Cape Town children. S Afr Med J 1997;87(1):51-6.
127. Oostenbrink R, Maas M, Moons KGM, Moll HA. Sequelae after bacterial meningitis in childhood. Scand J Infect Dis 2002;34(5):379-82.
128. Stovall SH, Schutze GE. Meningococcal infections in children from Arkansas. Pediatr Infect Dis J 2002;21(5):366-70.
129. Tucci M, Lebel MH, Gauthier M, Farrell CA, Lacroix J. Admission to a pediatric intensive care unit for bacterial meningitis: Review of 168 cases. J Intensive Care Med 1995;10(5):253-60.
130. Abrahao AL, Focaccia R, Gattaz WF. Childhood meningitis increases the risk for adult schizophrenia. World J Biol Psychiatry 2005;6(Suppl 2):44-8.
131. Drake R, Dravitski J, Voss L. Hearing in children after meningococcal meningitis. J Paediatr Child Health 2000;36(3):240-3.
132. Melaku A. Sensorineural hearing loss in children with epidemic meningococcal meningitis at Tikur Anbessa Hospital. Ethiop Med J 2003;41(2):113-21.
133. Madagame ET, Havens PL, Bresnahan JM, Babel KL, Splaingard ML. Survival and functional outcome of children requiring mechanical ventilation during therapy for acute bacterial meningitis. Crit Care Med 1995;23(7):1279-83.
134. Slack R, Hawkins KC, Gilhooley L, Addison GM, Lewis MA, Webb NJ. Long-term outcome of meningococcal sepsis-associated acute renal failure. Pediatr Crit Care Med 2005;6(4):477-9.
135. Shears D, Nadel S, Gledhill J, Gordon F, Garralda ME. Psychiatric Adjustment in the Year After Meningococcal Disease in Childhood. J Am Acad Child Adolesc Psychiatry 2007;46(1):76-82.
136. Appel M, Pauleto AC, Cunha LA. Osteochondral sequelae of meningococcemia: radiographic aspects. J Pediatr Orthop 2002;22(4):511-6.
137. Belthur MV, Bradish CF, Gibbons PJ. Late orthopaedic sequelae following meningococcal septicaemia. A multicentre study. J Bone Joint Surg Br 2005;87(2):236-40.
138. Balluffi A, Kassam-Adams N, Kazak A, Tucker M, Dominguez T, Helfaer M. Traumatic stress in parents of children admitted to the pediatric intensive care unit. Pediatr Crit Care Med 2004;5(6):547-53.
139. Ehrlich TR, Von Rosenstiel IA, Grootenhuis MA, Gerrits AI, Bos AP. Long-term psychological distress in parents of child survivors of severe meningococcal disease. Pediatr Rehabil 2005;8(3):220-4.
140. Judge D, Nadel S, Vergnaud S, Garralda ME. Psychiatric adjustment following meningococcal disease treated on a PICU. Intensive Care Med 2002;28(5):648-50.
141. Shears D, Nadel S, Gledhill J, Garralda ME. Short-term psychiatric adjustment of children and their parents following meningococcal disease. Pediatr Crit Care Med 2005;6(1):39-43.
142. Colville GA, Gracey D. Mothers' recollections of the Paediatric Intensive Care Unit: associations with psychopathology and views on follow up. Intensive Crit Care Nurs 2006;22(1):49-55.
143. Sinclair JF, Skeoch CH, Hallworth D. Prognosis of meningococcal septicaemia. Lancet 1987;2(8549):38.
144. Hahne SJ, Charlett A, Purcell B, Samuelsson S, Camaroni I, Ehrhard I, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. Bmj 2006;332(7553):1299-303.

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