Clinical Practice Guideline on the Management of Invasive Meningococcal Disease

NOTE:

It has been 5 years since the publication of this Clinical Practice Guideline and it is subject to updating.

The recommendations included should be considered with caution taking into account that it is pending evaluate its validity.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

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Instituto de Salud Carlos III
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This CPG is an aid to decision making in health care. The compliance of this guide is not mandatory, nor does it replace the clinical judgement of the health care personnel.

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Presentation

Initiatives to document the variability of clinical practice, analyse its causes and adopt strategies to eliminate it, have proven to be initiatives that promote effective and safe decision making, being patient oriented, by health care professionals. Such strategies include preparing clinical practice guidelines (CPG), a set of "systematically developed recommendations to help practitioners and patients make decisions about the most appropriate health care and to select the most appropriate diagnostic or therapeutic options when dealing with a health problem or a specific clinical condition."

The impetus for the development and use of CPGs reinforces and extends the GuíaSalud Project and including the completion of CPGs in the work plans of the Spanish Network of Agencies for Health Technology Assessment and NHS benefits.

The issue of this **CPG on the Management of Invasive Meningococcal Disease** (IMD) is within this context.

IMD is a process with high morbidity and mortality. Its management is affected by the lack of specificity of the symptoms and signs appearing, sometimes present in benign processes. The challenge for health professionals is to identify those patients who will progress rapidly to clinical deterioration.

Early diagnosis and immediate initiation of appropriate treatment greatly improves prognosis and the quality of life of patients. Appropriateness of care at every stage of the disease (acute, moderate and sequelae) is critical to achieve a favourable outcome.

Also in the case of children and adolescents, the impact of hospitalization, treatment, sequelae and deaths, is greater not only for the patients themselves, also for family members and caregivers.

It is essential to have common guidelines for both the diagnosis and the treatment, based on the best scientific knowledge available.

This is the main aim of this CPG, made specifically to be for the use by all health caregivers, primary care and hospital professionals involved in the care of children and adolescents affected by IMD.

This CPG is the result of the hard work carried out by a group of professionals from different fields and health disciplines belonging to diverse regions within in Spain.

The Directorate General of Public Health, Quality and Innovation is grateful to all these people for the work they have done and which will hopefully help professionals, patients, families and caregivers in decision-making, improving the adequacy of treatment and quality of life of those affected by this infectious process.

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Director General of Public Health, Quality and Innovation

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Cooperating Societies

Spanish Association of Paediatrics

Spanish Association of Primary Care Paediatrics

Irene Megías Foundation against Meningitis

Spanish Society of Clinical Microbiology and Infectious Diseases

Spanish Society of Epidemiology

Spanish Society of Community Pharmacy

Spanish Society of Paediatric Infectious Diseases

Spanish Society of Family and Community Medicine

Spanish Society of Paediatric Neurology

Spanish Society of Paediatric Emergency

The members of these societies have participated in the creation, expert collaboration, and external review of this CPG.

Declaration of interest: All members of the Working Group, as well as those who have participated in the expert collaboration and external review, have made the declaration of interest as appears in Appendix 4.

Public Exposure

This CPG has been subjected to a process of public exposure. The complete list of bodies and entities that participated in the process of public exposure is available on the website of GuíaSalud: www.guiasalud.es

Questions to be answered

Diagnosis of IMD

WARNING SIGNS AND SYMPTOMS OR RED FLAG

1. In paediatric patients who come to primary health care (or emergency), what set of signs and symptoms should arouse suspicion of IMD?

   – Fever

   – Neck Stiffness

   – Headache

   – Photophobia

   – Vomiting

   – Dizziness

   – Fast breathing

   – Drowsiness

   – Less than 50% of usual fluid intake in 24 hours (<1 year)

   – Strange pitched cry (<1 year)

   – Abnormal skin colour (pale, earthy, mottled, bluish)

   – Vascular collapse, hypotension, shock

   – Leg pain or refusal to walk

   – Rash

   – Changes in heart rate

   – Cold hands and feet

CLINICAL REASSESSMENT AS STRATEGY TO IMPROVE THE DIAGNOSIS

2. For a paediatric patient who goes to primary health care with symptoms suggestive of IMD, does a second specific clinical evaluation (after 4-6 hours) for disease progression improve the diagnosis?

3. For a paediatric patient who goes to primary health care with symptoms suggestive of IMD, does a telephone evaluation for disease progression improve the diagnosis?

NON-SPECIFIC LABORATORY TESTS

4. Among paediatric population with petechial rash, can non-specific laboratory tests (C-reactive protein, white cell count, blood gases), help to confirm or refute the diagnosis of IMD?

DIAGNOSIS OF INCREASED INTRACRANIAL PRESSURE

5. Among paediatric population with suspected or confirmed bacterial meningitis, can a cranial computed tomography reliably demonstrate an increase of intracranial pressure?

MICROBIOLOGICAL CONFIRMATION TESTS

6. In the case of patients with suspected IMD, what diagnostic tests done at an early stage are useful to confirm the diagnosis of IMD?
   – Blood culture
   – Skin scrapings
   – Blood Polymerase Chain Reaction (PCR)
   – Throat swab
   – Urine rapid antigen testing
   – Blood rapid antigen testing

Pre-hospital Management of IMD

PRE-HOSPITAL ADMINISTRATION OF ANTIBIOTICS

7. In patients with suspected IMD, does the pre-hospital administration of antibiotics reduce mortality?
8. In patients with suspected IMD, does the pre-hospital administration of antibiotics affect morbidity and influence the admission to the ICU, the duration of hospital stay, admission costs, the duration of school absence, etc.?
9. In patients with suspected IMD who come to primary health care, does the parenteral administration of antibiotics reduce mortality and morbidity more than the oral administration of antibiotics?
10. In patients with suspected IMD who come to primary health care, does the intramuscular administration of ceftriaxone, have a similar efficacy and safety to its intravenous administration?

PRE-HOSPITAL RESUSCITATION

11. In patients with suspected IMD, does resuscitation before reaching the hospital (in the ambulance) improve survival?, Can they reduce the severity of the disease and influence on the admission to the ICU, the duration of hospital stay, admission costs or the duration of school absence?

DEVELOPMENT AND IMPLEMENTATION OF PROTOCOLS

12. Do care processes (“process mapping programs”) for those patients with progressive symptoms improve survival or reduce the severity of the disease?; do these have any effect on the admission to the ICU or the duration of hospital stay, admission costs, the duration of school absence, etc.?

Hospital management of IMD

ANTIBIOTIC TREATMENT

13. What antibiotic regimen should be used to treat bacterial meningitis or confirmed meningococcal septicaemia?
14. In patients with IMD, is a short treatment (7 days) as effective or more and as safe as or more to than a prolonged treatment (> 7 days) to maintain or increase the cure rate of the disease and maintain or reduce the number of sequelae?

SAMPLING FOR MICROBIOLOGIC DIAGNOSIS

15. In patients with suspected IMD treated at a hospital emergency unit, should the antibiotic treatment start immediately or should it start after the realization of the lumbar puncture and blood culture?

INDICATIONS FOR LUMBAR PUNCTURE IN IMD

16. In patients with suspected IMD, does the lumbar puncture (early / late), affect the early/ late onset of the specific treatment, the final diagnose, as well as morbidity and mortality rates?
17. Among paediatric population less than three months of age with bacterial meningitis should a control lumbar puncture be done before stopping the antibiotic`s treatment?

EARLY SUPPORTIVE THERAPY

18. In patients with suspected IMD, do the following treatments reduce mortality and morbidity?
    - Corticosteroid Therapy
    - Intravenous fluids to debate: colloid-crystalloid (Hartmann normal saline, Ringer's lactate), fresh frozen plasma (FFP), artificial colloids.
    - Resuscitation (oxygen, airway care and circulatory system).

STABILIZATION AND TRANSPORTATION TO A PAEDIATRIC INTENSIVE CARE UNIT

19. Do specialized transport teams improve outcomes and reduce adverse incidents during the transport of patients with IMD at paediatric age?

Management of IMD in the ICU

CONSIDERATIONS BEFORE ADMISSION TO AN ICU

20. In patients with IMD requiring admission to the ICU, is there evidence that the time delays in consultation at a specialist centre or paediatric ICU affect the results (mortality and residual disability)?
21. In patients with IMD requiring admission to the ICU, is there any evidence that the following factors affect the results?
    - Stabilisation and transport by a specialized paediatric team
    - Paediatric Intensive Care
    - Remote telephone support
    - Early referral and / or recovery (or quick resolution of the process)

SUPPORTIVE THERAPY IN THE ICU

22. In patients requiring intensive care, is there evidence that the following interventions influence on mortality and morbidity?
    - Ventilation/airway management
    - Catecholamines
    - Invasive monitoring
    - Haemofiltration, continuous veno-venous haemofiltration, plasmapheresis
    - ECMO (extracorporeal membrane oxygenation)
    - Mechanical Circulatory Support (hyperosmolar fluids)
    - Plasmafiltration
    - Corticosteroids, high dose or physiological replacement
    - Invasive management of intracranial hypertension

ADJUVANT THERAPIES

23. In patients with IMD in the ICU, is there any evidence that the following hematologic and immunologic measures reduce mortality and morbidity?
    - Activated protein C and protein C
    - Immunoglobulins
    - Heparin
    - Fresh frozen plasma (FFP)
    - PG12
    - Tissue plasminogen activator (t-Pa) antagonists of the platelet-activating factor (PAF), antithrombin III

SURGICAL MANAGEMENT OF IMD

24. In patients with extensive skin affection, do compartmental pressure control and fasciotomy reduce the number and extension of tissue necrosis, amputations and degree of residual disability?
25. In patients with IMD and complications, what is more effective and safe to reduce tissue necrosis or prevent amputation or secondary infection: early surgical debridement or the conservative treatment?

Prognostic and severity factors of IMD

CLINICAL FACTORS AS SEVERITY INDICATORS

26. In patients with suspected invasive meningococcal disease, what clinical factors are useful to predict survival, mortality or sequelae
    - Clinical signs: tachycardia, tachypnoea, hypotension, poor peripheral perfusion, central and peripheral temperature difference, severity or extent of the eruption, eruption progression, presence of fever, stiff neck, irritability or nervousness, lethargy, fatigue, drowsiness, level of consciousness.
    - Laboratory study: white blood cell count, coagulopathy, CRP, platelets, blood gases, kidney function, liver function, cortisol, glucose, other (CPK, rhabdomyolysis).

SEVERITY AND MORTALITY RISK SCORING SYSTEMS

27. In patients with suspected IMD, is there any evidence that the use of any of the following prognostic scales can predict the severity of the disease or the risk of poor clinical results?
    - Leclerc
    - Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS)
    - Gedde-Dahl's MOC score

Prevention and control of IMD

INDICATIONS FOR ANTIBIOTIC PROPHYLAXIS

28. What evidence is there that the following groups, after having had contact with a patient with IMD in the past seven days, should receive antibiotic prophylaxis?

    – People who have had contact within the household

    – Students from the same class or school

    – People who have had contact with body fluids (after resuscitation)

    – People who have exchanged kisses

    – People who have shared drinks

    – People who have shared any means of transportation

ANTIBIOTICS OF CHOICE FOR THE PROPHYLAXIS OF IMD

29. What evidence is there that the following antibiotics are effective for the prevention of IMD in contact groups?

    – Rifampicin

    – Ciprofloxacin

    – Ceftriaxone

30. In people who have maintained close contact with a case of IMD, what is more effective in preventing secondary cases: oral rifampicin or intramuscular ceftriaxone?

31. In people who have maintained close contact with a case of IMD, what is more effective in preventing secondary cases: oral rifampicin or oral ciprofloxacin?

MENINGOCOCCAL VACCINATION OF PATIENTS WITH IMD

32. Can the meningococcal vaccination of cases of IMD, reduce the risk of a second IMD when compared to patients who have been diagnosed and treated by IMD and have not been vaccinated?

OTHER INFECTION CONTROL MEASURES

33. In patients with suspected IMD, are measures such as the isolation in an individual room, the use of individual protection equipment (non-sterile clean gloves, non-sterile clean gown, waterproof masks, eye or facial protection) and chemoprophylaxis effective in hospital care to reduce the risk of secondary infection associated to health care by clinical staff (except laboratory staff), family or people living with the index case?

Follow-up after IMD

SEQUELAE ASSOCIATED TO IMD AND SUPPORT TO PATIENTS, FAMILY AND CAREGIVERS

34. What are the sequelae associated to IMD and what aspects need greater support and information for patients, their families and caregivers?
35. What proportion of the paediatric population with bacterial meningitis develops physical or psychological morbidity?
36. What proportion of the paediatric population with meningococcal septicaemia develops physical or psychological morbidity?

IMPACT ON FAMILIES AND CAREGIVERS

37. Do families and caregivers of those who have suffered IMD suffer any psychosocial problems? And, if so, do the psychosocial interventions and supply of information improve their quality of life?

Awareness and information campaigns on IMD

38. Do the educational programs aimed at health professionals and the population in general improve the speed of recognition, diagnosis, and treatment of IMD? Do they increase survival or decrease the severity of the disease and its complications? Do they have any effect on the admission to the ICU or the duration of hospital stay, admission costs, the duration of school absence, etc.?

Levels of evidence and grades of recommendation

Table 1. SIGN[1] levels of evidence and grades of recommendation for intervention studies

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of clinical trials or well-conducted clinical trials with low risk of bias
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias
2++	High quality systematic reviews with cohort or case-control studies; Cohort or case-control studies with very low risk of bias and a high probability of establishing a causal relationship
2+	Well-conducted cohort or case-control well conducted studies with low risk of bias and a moderate probability of establishing a causal relationship
2-	Cohort or case-control studies with high risk of bias and a significant risk that the relationship is not causal
3	Non-analytic studies, such as case reports and case series
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1 + + and directly applicable to the target population of the guide, or a body of evidence including studies rated as 1 + and good agreement between them.
B	A body of evidence including studies rated as 2 + +, directly applicable to the target population and demonstrating the good agreement between them, or extrapolated scientific 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 scientific evidence from studies rated as 2 + +.
D	Scientific evidence levels 3 or 4, or extrapolated scientific evidence from studies rated as 2 +.

Studies classified as 1 - and 2 - should not be used for making recommendations due to their high potential for bias.

Good clinical practice *

√	Recommended practice based on clinical experience and consensus of the development group.

** Sometimes the development group realizes some important practical aspect which may want to be emphasized and for which there is probably no supporting evidence. In general, these cases have to do with some aspect of the treatment considered good clinical practice and that no one would normally question. These aspects are considered good clinical practice points. These messages are not an alternative to evidence-based recommendations, but should be considered only when there is no other way to highlight this aspect.*

Q	Evidence obtained from relevant and high quality studies. This category is not contemplated by SIGN.

Table 2. Levels of evidence and grades of recommendation for diagnostic questions[1].

Levels of scientific evidence	Type of evidence
Ia	Systematic review with homogeneity of level 1 studies.
Ib	Level 1 studies.
II	Level 2 studies. Systematic review of studies rated as 2.
III	Level 3 studies. Systematic review of studies of level 3.
IV	Consensus, expert opinions without explicit critical appraisal.
Level 1 Studies	Meet the following requirements: Blinded comparison with a valid reference test ("gold standard"). Adequate spectrum of patients.
Level 2 Studies	They have only one of these biases: Unrepresentative population (the sample does not reflect the population to which the test applies). Comparison with the inadequate reference standard ("gold standard") (the test being evaluated as part of the gold standard or the test result affects the implementation of the gold standard). Unblinded comparison. Case-control studies.
Level 3 Studies	They have two or more of the criteria described in level 2 studies.

Recommendation	Evidence
A	Ia o Ib
B	II
C	III
D	IV

Recommendations of the CPG

Diagnosis of IMD

Warning signs and symptoms or red flag

√	Healthcare professionals should be trained on how to recognise and manage IMD.
D	The presence of a generalized petechial or purpuric rash, with capillary refill>2 seconds in a paediatric patient with impairment of the general condition, should suggest IMD and the need for urgent treatment.
D	In the ill paediatric patient, the presence of any of the following signs and symptoms should alert the clinician about the possibility of IMD: – Petechial rash (non-blanching) – Capillary refill time>2 seconds – Abnormal skin colour – Decreased level of consciousness – Pain in extremities – Cold hands and feet – Fever – Headache – Neck Stiffness – Photophobia
D	One must remain alert to the possibility of IMD when evaluating patients with acute febrile disease because in the first 4-6 hours of onset of the clinical IMD nonspecific symptoms such as fever, lethargy, refusal of food, nausea, vomiting, irritability, signs and / or symptoms of upper respiratory tract infection (runny nose, sore throat, etc.), diarrhoea, or abdominal pain may appear.
D	In the initial clinical evaluation (primary care), it should be noted that the following symptoms are very rare in the paediatric patient with mild febrile disease: leg pain, confusion, stiff neck and photophobia.
√	The clinicians will take into account the fact that the signs and symptoms of the disease can vary and become more specific over time.
B	The set of clinical and laboratory findings which strongly suggest that the causal agent of bacterial meningitis is *N. meningitidis* includes the presence of haemorrhagic rash + absence of seizures + headache + negative gram stain of CSF.

Clinical reassessment as strategy to improve diagnosis

D	In the presence of clinical signs or other symptoms suggestive of IMD, treatment should not be delayed waiting for a second clinical evaluation.
√	Children with nonspecific symptoms at initial presentation, in whom IMD cannot be excluded at the discretion of the physician, should be reassessed in a short period of time (hours).
√	The healthcare professional will inform caregivers about the need to seek health care if the patient's condition deteriorates during childhood before the planned revaluation for example, if the characteristics of the rash change. The degree of concern of parents or caregivers as well as their ability to act if the patient worsens must be taken into account and information on the availability of health services in the area must be provided.

Nonspecific laboratory tests

√	The following determinations should be performed in children with petechial rash of unknown origin and fever, or history of fever: – Blood cell counts – C-reactive protein or procalcitonin – Coagulation tests – Blood culture – Blood glucose – Pulse oximetry
C	If a paediatric patient has a petechial rash of unknown origin and fever, or history of fever, but none of the high-risk clinical features, the following are recommended: – Start the specific treatment immediately if the C-reactive protein or the white-cell count (especially neutrophil count) is high, since this indicates an increased risk of IMD. – Clinicians should be aware that although IMD is less likely with both normal C-reactive protein and white cell count, it should not be ruled out. Both parameters can be normal in severe or very short evolution cases. – Evaluate clinical progressions by monitoring vital signs, capillary refill time and oxygen saturation. Perform checks at least every hour for the next 4-6 hours. – Treat with antibiotics and admit to hospital if doubt persists.

√	The serum concentration of procalcitonin can be used as an early marker of IMD. Changes in the serum concentration of procalcitonin take place earlier and faster than those of the C-reactive protein.
√	The final assessment is as being of low risk of IMD and the patient is discharged, it is recommended to warn caregivers to return if they feel that he/she worsens (for example, if new spots appear or if the patient seems excessively sleepy or irritable).

Diagnosis of increased intracranial pressure

D	Clinical assessment, and not cranial computed tomography (CT), is recommended to decide whether it is safe to perform a lumbar puncture. CT is unreliable for identifying increased intracranial pressure.
D	If a CT has been performed, it is not recommended to do a lumbar puncture if there are radiological signs of increased intracranial pressure.
D	It is recommended not to delay the treatment while waiting for a CT to be performed.

Microbiological confirmation tests

C	To confirm the diagnosis in patients with suspected IMD, blood should be drawn for bacterial culture.
D	To confirm the diagnosis in patients with suspected IMD, blood should be drawn for meningococcal PCR (whole blood, with EDTA) in laboratories with sufficient technical capacity.
C	A lumbar puncture should be performed in patients with clinical features of meningitis without sepsis (purple), if there are no contraindications.
D	The CSF should be referred to a microbiological laboratory. The following techniques should be performed: – Microscopy – Cultivation of bacteria – Meningococcal PCR in technically able laboratories
D	None of the following techniques is definitive when IMD is to be confirmed or ruled out: skin scraping, skin biopsy, petechial or purpuric lesion aspirates (obtained with a needle and syringe).
√	Samples should be collected as soon as possible after establishing the clinical suspicion and preferably before starting the antimicrobial treatment. The sample collection must not delay the onset of the antibiotic treatment.

Pre-hospital Management of IMD

Pre-hospital Administration of antibiotics

√	Patients with suspected IMD will be sent to hospital urgently.
D	When suspecting IMD, intravenous antibiotics (ceftriaxone 50 mg / kg IV or IM) should be administered as soon as possible, both in primary care and at a higher level, but the urgent transfer to hospital should not be delayed.

Pre-hospital Resuscitation

√	In patients with suspected or confirmed meningococcal sepsis, resuscitation should be started immediately, if possible, prior to initiating patient transport or during transport.

Development and implementation of protocols

D	It is recommended to develop tools locally (clinical pathways, process maps, interdisciplinary agreements) to facilitate access and care of patients with IMD, taking into account the geography and the services available.
D	A periodic revision of the medical records of patients with IMD is recommended to identify avoidable situations and achieve optimal healthcare.

Hospital management of IMD

Antibiotic Treatment

B	First-line antibiotics for the treatment of confirmed IMD are intravenous ceftriaxone every 12 hours for a total of 7 days, or cefotaxime, every 6 hours for a total of 7 days.

Sampling for microbiological diagnosis

D	In a hospital emergency unit, when suspecting a case of IMD, obtaining samples from the patient for further confirmation of the diagnosis should not delay the beginning of the empirical antibiotic treatment.
√	Blood cultures should be performed as soon as possible, but should not delay treatment.

Indications for lumbar puncture in IMD

√	The lumbar puncture is not recommended in the initial evaluation for suspected IMD with features of septicaemia. The late realization of the lumbar puncture may be considered if the diagnosis remains uncertain or there is inadequate clinical progression and no contraindications.
C	Lumbar puncture should be performed in patients with clinical meningitis without septicemic features (purpura) if there are no contraindications.
D	The LCR will be sent to the laboratory for microscopy, culture and PCR.
D	In paediatric patients who are clinically well and without evidence of bacterial disease, it is reasonable to observe the patient and defer the realization of the lumbar puncture.
√	It is advisable to repeat the lumbar puncture in paediatric patients aged between 1 and 3 months who have not been previously hospitalized in the following circumstances: – Presence of persistent or recurrent fever – Deterioration of the clinical condition – New clinical findings (especially neurologically) or persistently altered inflammatory reactants
√	It is advisable to perform lumbar puncture to assess the success of the treatment in paediatric patients aged between 1 and 3 months who have not been previously hospitalized, in the following circumstances: – In the case of patients receiving antibiotic therapy adequately against the causative agent, and whose clinical outcome is still good – Before stopping the antibiotic treatment if their clinical response is good

Corticosteroids

A	The adjuvant administration of a corticosteroid (dexamethasone intravenously at a dose of 0.15 mg/kg/dose up to 10 mg/dose, 4 times a day for 4 days) should be considered when there is a suspicion of bacterial meningitis or once it has been confirmed; it should be administered as soon as possible and it should not interfere with the administration of antibiotics and the transfer to a specialized centre.
B	Do not administer corticosteroids to paediatric patients with meningococcal septicaemia, except in cases of meningococcal septic shock resistant to catecholamine.

Intravenous liquids

D	In patients with suspected or confirmed bacterial meningitis, the appearance of signs of shock, increased intracranial pressure and dehydration will be assessed.
D	The administration of fluids should not be restricted unless there is increased intracranial pressure or an increased secretion of the antidiuretic hormone.
D	A volume of fluids should be administered and maintained to avoid hypoglycaemia and maintain the electrolyte balance.
D	Use enteral feeds as maintenance fluid if tolerated.
D	If it is necessary to maintain intravenous fluids, the use of isotonic fluids (0.9% sodium chloride with 5% glucose, or 0.9% sodium chloride with 5% dextrose) is recommended.
D	The administration of fluids and urine output should be monitored to ensure adequate hydration and prevent over-hydration.
D	Electrolytes and glucose should be monitored regularly (if intravenous fluids are administered at least once a day).
D	If there are signs of increased intracranial pressure or shock, it is recommended to start the emergency procedures relevant to these situations and discuss the management of fluids with a paediatric intensive care physician.
D	If there are signs of shock, give immediately 20 ml/kg of 0.9% sodium chloride in 5 to 10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the patient immediately (see Table 5).

Resuscitation techniques: respiratory and circulatory support

D	In self-ventilating children with suspected bacterial meningitis or confirmed meningococcal septicaemia, and signs of respiratory distress, the use of a facial mask is recommended to provide 15 litres of oxygen through a mask with reservoir (see Table 6). If there is a threat of loss of airway patency, airway opening manoeuvres should be applied; positive pressure ventilation through a mask ventilation bag and finally isolation of the airway.

Stabilization and transport to a paediatric intensive care unit

D	In patients with suspected or confirmed diagnosis of IMD who require resuscitation and transfer to an ICU, it is recommended to inform the hospital or destination unit.
D	It is recommended that specialized transport units perform the transfer of patients with suspected or confirmed diagnosis of IMD to a reference centre.

Management of IMD in the ICU

Considerations before admission to an ICU

D	Patients who arrive at the hospital emergency unit with suspected IMD should be examined and treated immediately by an experienced physician, preferably a paediatric specialist.
D	In patients with clinical progression of IMD, it is advisable to contact the ICU in the early stages.

Supportive therapy in the ICU

D	Catecholamines are recommended at an early stage to manage patients with fluid resistant meningococcal septic shock and the support with mechanical ventilation should be considered for these patients.
√	In patients with meningococcal septic shock resistant to catecholamine, intravenous terlipressin and titrated doses of corticosteroids are considered proper rescue measures.
D	Paediatric patients with meningococcal septic shock resistant to catecholamines could benefit from the use of terlipressin as a rescue therapy.
D	Non-invasive monitoring (ECG, blood pressure, temperature, oxygen saturation) of patients with fluid sensitive meningococcal septic shock is recommended. A central access (arterial or venous) will be channelled in cases of fluid resistant meningococcal septic.
√	Patients with acute respiratory distress syndrome secondary to IMD who do not respond to standard therapy may benefit from extracorporeal membrane oxygenation.

√	Patients with fluid resistant meningococcal septic shock, severe metabolic acidosis, acute or impending renal failure, and complex or problematic fluid balance, may benefit from continuous venovenous haemofiltration.

Adjuvant therapies

A	The administration of activated C protein or recombinant bactericidal permeability increasing protein is not recommended for paediatric patients with severe IMD.
A	In case of severe sepsis, the use of an intravenous immunoglobulin treatment is not taken into consideration.

Surgical management of IMD

D	Monitoring of compartmental pressure in patients with IMD and extensive vascular involvement of a limb should be considered.
√	It is necessary to resort to a specialist urgently to assess and interpret the monitoring of compartmental pressure.
D	Urgent debridement is recommended if secondary infections of the wound appear in the paediatric patient, if the situation allows.
√	From the early hours of admission, orthopaedic and plastic surgeons should be consulted to assess the patient's needs.
√	The need in some cases to amputate large body areas poses an ethical conflict that should be discussed jointly by surgeons and intensive care physicians, taking into account the views of parents or caregivers.
√	In patients with meningococcal purpura fulminans and ischemia, the possibility of performing the arthrolysis technique when the human and technical resources are available, should be considered.

Prognostic and severity factors of IMD

Clinical factors as severity indicators

C	It should be taken into account that the following factors are associated with high mortality in paediatric patients with IMD: – A product of the platelet and neutrophil count < 40 x 10^9/l – A procalcitonin level > 150 ng/l

C	It will be noted that the presence of leukopenia (< 4,500 cells/mm^3) is a factor associated with an unfavourable clinical course in paediatric patients with IMD.
C	It should be taken into account that the following factors are associated with extreme severity in paediatric patients with IMD: – Evolution of symptoms less than 24 hours – Presence of a number of petechiae over 50 – Decreased level of consciousness – Presence of shock
D	It will be noted that meningococcal meningitis carries less risk of unfavourable neurological progression than the meningitis caused by other bacteria.

Severity and mortality risk scoring systems

√	In patients with suspected or confirmed diagnosis of IMD, a rating scale will be used to identify changes in the patient's condition.
B	For patients with suspected or confirmed diagnosis of IMD, the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) scale can be a good tool for identifying changes in the patient's health condition.
√	If a patient with suspected or confirmed diagnosis of IMD shows a worsening of his/her health condition, the intensive care unit will be contacted immediately.

Prevention and control of IMD

Indications for antibiotic prophylaxis

D	Chemoprophylaxis is recommended as soon as possible, preferably in the first 24 hours, for all those who have had close contact (see glossary) and prolonged exposure to a case of IMD in the family (living or sleeping in the same house) or in a comparable context (shared kitchen within a student residence, shared apartment, etc.) during the 7 days before the onset of symptoms.
D	In preschoolers (up to 6 years), the administration of chemoprophylaxis is recommended to all the students who attend the same classroom as the sporadic case as well as the classroom staff. Chemoprophylaxis is not indicated for the students and staff of other classes from the same school other than the IMD case.

D	It is not recommended to administer chemoprophylaxis for students attending the same class or the same primary, secondary school and university as a sporadic case, unless the case is in close contact with the rest.
D	Chemoprophylaxis should be offered to all healthcare workers whose mouth or nose may have been exposed to respiratory secretions from a patient with IMD before the patient has completed the first 24 hours of antibiotic therapy.
√	The following situations are not, by themselves, indicative of chemoprophylaxis: – Sharing drinks, food, cigarettes or kissing on the cheek or other acts involving a similar contact with saliva. – Sharing occasionally the same transport vehicle, even if it is occupying the seat next to the case of IMD.

Antibiotics of choice for the prophylaxis of IMD

√	Post-exposure chemoprophylaxis with rifampicin is recommended as first choice. The administration of ceftriaxone is recommended as an alternative in the following circumstances: – When rifampicin is contraindicated (see info: http://www.aemps.gob.es/). – If there is alcohol consumption and malnutrition, when it is considered that the risk exceeds the potential benefit for the patient – In contacts <18 years, when a new intervention is required in the context of an outbreak and the previous prophylaxis had been performed with rifampicin – When suspecting a possible breach of the oral chemoprophylaxis. And the administration of ciprofloxacin as an alternative to rifampicin in the following circumstances: – In contacts > 18 years, when a new intervention is in required in the context of an outbreak and the previous prophylaxis had been performed with rifampicin.

Meningococcal vaccination of patients with IMD

D	It is recommended to provide MenC vaccine before hospital discharge after having suffered from IMD to the following groups: – Patients with confirmed IMD by serogroup C who have been previously immunized with MenC. – All patients not previously immunized with MenC, regardless of the serogroup causing the episode.

Other infection control measures

D	Paediatric patients with suspected IMD should be initially admitted to a single room.
D	When a suspected case of IMD is admitted to hospital, droplet transmission precautions should be taken, which can be interrupted after 24 hours of effective treatment of the patient.
D	Health care staff at high risk of exposure to respiratory secretions must use appropriate individual protective equipment.

Follow-up after IMD

Sequelae associated to IMD and support to patients, families and caregivers

√	The patient who has suffered IMD must leave the hospital with an individualized care plan.
√	The individualized care plan for patients who have suffered IMD shall describe the monitoring to be performed in order to identify immediate complications that may occur in the long term. Furthermore, the individualized care plan shall include an extensive list of professionals, schools, associations, foundations and institutions that can help the patient affected and his/her families to manage their new life, not forgetting to include those public or private institutions, which can provide financial assistance.
√	The patient who has suffered from IMD and their families should be informed of the following potential long-term consequences: – Hearing loss – Orthopaedic sequelae (damage to bones or joints) – Skin lesions (scarring from necrosis) – Psychosocial issues – Neurological and developmental disorders – Renal failure They should be informed of the characteristics of the disease, its prevalence, case fatality, morbidity, and the usual means of transmission, etc., to try to minimize the feeling of guilt that usually appears in all those closely involved with the patient. The individualized care plan shall include delivery to the family of a free printed copy of this Clinical Practice Guideline in its version for patients, families and caregivers.

√	Hearing and neurologic tests should be performed to any patient who has suffered IMD, in order to establish a treatment if required as soon as possible if necessary.
D	Before discharge, the family should be offered the possibility to acquire the appropriate skills to engage with the basic care of the paediatric patient.
D	When the patient is far from the hospital, the opportunity to acquire skills related to specialized care should be offered.
D	viding the family with psychological support will help them to decide and mitigate the intensity of post-traumatic stress if it appears.
√	Healthcare professionals should be offered the means to enable them to acquire effective communication skills.

Impact on families and caregivers

C	Healthcare professionals involved in the monitoring of paediatric patients with IMD should be aware of the possibility of posttraumatic stress disorder with anxiety or depression in patients, their families and caregivers.
B	It is recommended that a psychologist or psychotherapist monitors in the short-term (up to 2 years) patients with IMD and their parents in the weeks following the discharge from the paediatric ICU, or if the patient dies, in order to reduce the scope of the psychological sequelae of the disease.

Awareness and information campaigns on IMD

√	The general population and other groups (such as pharmaceuticals, day carers, etc.) should be informed about IMD in order to suspect the disease at an early stage.
√	The general population should know the implications of the appearance of petechiae for early detection of the IMD.

1. Introduction

The high morbidity and mortality of the Invasive Meningococcal Disease (IMD), which sometimes follows a fulminant and unexpected course, its marked predilection for child and adolescent age and the endemic epidemiological pattern with epidemic waves make it a major health problem. Few diseases generate social unrest similar to that recorded when the population is unaware of cases of meningococcal infection in their environment.

IMD is caused by the bacterium *Neisseria meningitidis*. Historically, serogroups B and C have been responsible for most clinical cases in Spain, but the introduction in the vaccination calendar of the conjugate vaccine against meningococcal serogroup C (MenC) in 2000 reduced the incidence of serogroup C cases by 88%[2]. Coinciding with the publication of this CPG, the European Commission granted a marketing authorization valid throughout the European Union for a vaccine against meningococcal B infections (serogroup MenB), following the favourable opinion of the European Medicines Agency.

Despite the success of the MenC vaccination program, in terms of incidence and mortality due to IMD, between 2009 and 2010 the lethality rate for the total number of confirmed cases was 10%[3]. A number of factors, including public health measures, early resuscitation, improved resuscitation techniques, advances in intensive care, surgery and rehabilitation investment may have contributed to improve the prediction of IMD. However, there is a high mortality, particularly in the early hours of fulminant sepsis, which highlights the need for increased information, disease recognition and diagnosis of patients, and the need for urgent intervention.

The IMD may appear with a clinical spectrum ranging from acute meningitis with neck stiffness, photophobia and bulging fontanels (not all the symptoms may show), a rapidly progressive meningococcal sepsis with petechiae or purpura, a decreased level of consciousness, shock and multiorgan failure. The challenge for a family physician or a primary care paediatrician is to be alert to identify those patients who will progress from a non-specific clinical picture to a serious condition, particularly since the initial signs and symptoms may not be distinguishable from any banal infection. Most deaths continue to occur in the first 24 hours, many times before proper treatment is established.

In the past 40 years, there has been a dramatic improvement of septic shock prognosis in childhood, with a mortality rate, which has gradually declined. There have also been significant changes in the organization and delivery of health services, particularly with regard to the use of resuscitation and intensive care, which have been associated with a reduction in mortality.

The rapid onset and progression of IMD in a given patient require a Clinical Practice Guideline (CPG) to ensure the implementation of the most effective treatment within the context of the National Health System, with the provision of health care services, as close as possible, provided in a safe way and at a sustainable cost but with quick access to hospital care if necessary.

The creation of this Clinical Practice Guideline for the Management of Invasive Meningococcal Disease is justified by the magnitude of the problem, both medical and social, and the demand generated from different areas of the health system involved in the management of this condition.

2 Scope and aims

This Clinical Practice Guideline (CPG) provides healthcare professionals who work in the field of primary and hospital care with a set of recommendations for the clinical management of the invasive meningococcal disease (IMD) based on the best scientific evidence available.

This guide is aimed at the population group aged between one month and 19 years suspected of having an IMD or with confirmed IMD and their contacts. Some questions addressed in this CPG have focused exclusively on paediatric population. It does not include infants because the aetiology and pathogenesis of meningitis and sepsis during this age period is different.

This CPG is intended for any health professional who operates in the field of primary and specialty care, primarily specialists in paediatrics, family and community medicine, intensive care medicine, microbiology, internal medicine, preventive medicine, surgery and nursing, that relates at some stage with a patient with suspected or confirmed IMD. This guide also contains specific material intended for patients, families and caregivers, in order to inform them and help them to recognize the disease.

The areas addressed by this CPG are the following: epidemiology, diagnosis, treatment, prevention (primary, secondary and tertiary) and prognosis. Meningitis and sepsis are outside the scope of this CPG due to other etiologic agents and IMD in immunocompromised patients.

The ultimate goal of this CPG is to optimize the clinical management of the IMD among the young population, with recommendations aimed at achieving early detection and rapid initiation of the treatment to reduce the high morbidity and mortality associated with the disease.

3. Methodology

The methodology used in the preparation of this clinical practice guideline (CPG) is set out in the *Methodology Manual for Preparation of CPG in the NHS*[1].

The development of this CPG began with the establishment of the guideline development group (GDG), composed of 12 clinicians from diverse health fields: primary and hospital care, and other specialties such as nursing, paediatrics, internal medicine, family and community medicine, paediatric intensive medicine, microbiology, orthopaedics and preventive medicine and public health. Moreover, from the early stages a group of citizens supported by the Irene Megías Foundation against meningitis took part. There were also four additional citizens to review the information for patients, families and caregivers. The review focused on the understandability of the content and identifying the information that they felt should be included in the document.

The creation and selection of the clinical questions was conducted based on questions that address controversial issues in other guides, that is, questions which require a thorough review by the GDG to identify the latest advances in materials as well as questions that have arisen within the GDG itself, until a total of thirty-eight questions related to epidemiology, diagnosis, treatment, prevention and monitoring of IMD among the population described. The development of the clinical questions was conducted considering the PICO (Patient/Intervention/Comparison/Outcome) format.

The next step was to conduct an initial literature search in databases and other specialized sources (Medline, Embase, Excelencia Clínica, Trip Database, GuíaSalud, National Guideline Clearinghouse, Guidelines International Network-GIN), in order to locate other CPGs, national or international, dealing with similar topics.

This search resulted in the location of five guides[4-8], two of which were discarded because the population, topics, interventions, completion date or methodology did not meet the aims and scope of this CPG. The three remaining guides[4-6] were evaluated, using the AGREE instrument (*Appraisal of Guidelines Research and Evaluation*). All of them met the minimum requirement previously established to be a source of evidence in this guide: achieving a score above 65% in terms of rigour of development.

Two guides[5,6] have become secondary sources of evidence to answer several clinical questions, and it is indicated so in the different sections of this document where the conclusions or studies extracted from them have been set out. To adapt and update the evidence from the above guidelines, the methodology proposed by Osteba in its "*Informe de Evaluación sobre Descripción de la Metodología empleada en la GPC sobre Asma*"[9] was used. The guide of the *European Centre for Disease Prevention and Control* (ECDC)[4] focuses exclusively on the chemoprophylaxis of the contacts of patients with IMD.

For the nineteen clinical questions addressed in this guide, which the CPG *Scottish Intercollegiate Guidelines Network* (SIGN) already included, searches from 2006 until 2011, during the months between April and August, were carried out to update and adapt those used by SIGN 63. Likewise, for the thirteen questions already collected by the CPG *National Institute for Health and Clinical Excellence* (NICE)[5], these were updated with the searches from 2009 until 2011, during the months between April and August, adapting them to those used by NICE. For the six remaining questions, new specific search strategies were developed to expand the search period without a limiting date. Additionally, automatic email alerts were defined for new articles added to Medline (Pubmed).

The search strategies were conducted combining terms in controlled language within each database (Mesh, Emtree, and Decs) and free language, in order to improve and balance their sensitivity and specificity. The sources were Medline (Pubmed), Embase (Elsevier.com), Centre for Reviews and Dissemination (CRD) Databases, Cochrane Library, Índice Bibliográfico Español en Ciencias de la Salud (IBECs) and Latin American and Caribbean Literature on Health Sciences (LILACs).

The searches were based on the most appropriate types of studies in relation to the characteristics of each question and the following languages: Spanish, French, English, Catalan, Italian and Portuguese.

A reverse search of the references of articles identified and included in this guide was carried out. Grey literature was also searched in a non-systematic way.

The search results were peer reviewed; the clinical guide coordinator resolved any discrepancy situations. Initially, screening was done by title and abstract. In a second screening, studies were discarded and the causes of exclusion identified. Finally, the selected studies were evaluated by means of the critical reading tool of the Agency for Health Technology Assessment of the Basque Country-OSTEBA. These studies were classified according to the evidence levels proposed by SIGN for intervention studies and according to the adjustment of the levels of evidence of the Centre for Evidence-Based Medicine in Oxford, proposed by NICE for Diagnostic test studies[1] (Table 1 and Table 2).

The critical reading tool from OSTEBA simplifies the synthesis work of the literature, which, following a review by the GDG, served as material for any development of the recommendations through formal assessment or reasoned judgment. In addition to the volume and quality of evidence, the GDG should consider the applicability of the findings, the correlation of the data and the relevance of its application in our National Health System or its clinical impact. For those clinical questions for which the volume of evidence turned out to be little or none, poor methodological quality (level of evidence 1- and 2-) or inconsistent, recommendations were made based on the consensus of the group that had into account, as well as those factors mentioned above, others such as routine clinical practice, the availability of intervention in our environment, the benefit-risk ratio or even the data sheet of the drug.

Following the completion of a first draft, the text was submitted to a peer review process in two parts: one focused solely on the recommendations, carried out by expert contributors, andanother part of comprehensive review conducted by external reviewers. The expert contributors and the external reviewers in most cases have been nominated by their respective scientific societies. The reviewers completed a standard form with two different sections. The first consisted of closed questions aimed at knowing the general opinion on the draft of the guide and evaluate its applicability. The second consisted of sections for each chapter of the guide in which free text was included. One participant made a partial revision (one chapter). The comments and suggestions of reviewers and contributors were referred to the GDG for evaluation after being subjected to an initial screening (in terms of form and style). The external review resulted in the development of two new recommendations and the introduction of minor changes in 8 recommendations aimed at changing their scope.

The scientific societies involved in the development of this guide, represented by members of the development group, expert contributors and peer reviewers are the Spanish Association of Paediatrics, the Spanish Association of Primary Care Paediatrics, the Spanish Society of Clinical Microbiology and Infectious Diseases, the Spanish Epidemiology Society, the Spanish Society of Community Pharmacy, the Spanish Society of Paediatric Infectious Diseases, the Spanish Society of Family and Community Medicine, the Spanish Society of Paediatric Neurology and the Spanish Society of Paediatric Emergencies.

Finally, the CPG underwent a Public Exposure process, in which the draft of the CPG was revised by other organizations in the field of health, previously registered and interested in contributing to it. In the case of this CPG four organizations were involved, whose contributions and comments are available for viewing on the website of GuíaSalud: http://portal.guiasalud.es/web/guest/exposicion-pública

It is planned to update the guide in an interval of three to five years maximum, or less time if new scientific evidence that can change some of the recommendations it contains is available. Updates will be performed on the electronic version of this guide, available at the following URL: <http://www.guiasalud.es>.

In the website <www.guiasalud.es>, there is material available, which provides the detailed information on the methodology applied to the CPG (search strategies for each clinical question and tables summarizing the evidence from selected studies).

4. Review of the problem

The IMD is an infection caused by the bacterium *Neisseria meningitidis* or meningococcus belonging to the Neisseriaceae[10] family. Humans are the only known reservoir of this species, which is isolated from the nasopharynx of healthy people in percentages ranging between 4% and 20%; this variation is associated with factors such as age, conditions of endemic or epidemic, etc. Meningococcal strains are surrounded on the outside by a polysaccharide capsule, which is an important bacteria virulence factor of the bacteria. In cases of invasive disease, it is rare to isolate non-capsulated strains of meningococcus, very common, however, in the nasopharynx of asymptomatic carriers. A total of 12 known serotypes A, B, C, H, I, K, L, X, Y, Z, 29E and W135 have been defined based on this polysaccharide[11]. Strains A, B and C are responsible for 80% to 90% of the cases of IMD in the world. The disease most often affects children under five, although the peak incidence occurs in children under 1. Another peak occurs in adolescents aged between 15 and 19 in Europe and other geographical areas[2, 12, 13].

4.1. Situation of IMD in the world

N. meningitidis is a major cause of invasive bacterial infection. The annual number of cases worldwide is estimated at 1.2 million, with 135,000 deaths[14], although the actual burden of the disease is unknown in many countries due to lack of adequate epidemiological surveillance.

A striking feature of the IMD is the considerable cyclical fluctuations in its incidence, and the occurrence of outbreaks and epidemics. Serogroup B strains are generally responsible for epidemic waves with inter-epidemic periods of variable duration; serogroup C is associated with the production of buds and short-term waves, and serogroup A is the cause of major cyclical epidemics in sub-Saharan countries. There is a marked regional distribution regarding incidence and predominant serogroup[2, 12].

The so-called "meningitis belt" in sub-Saharan Africa is by far the region with the highest incidence of IMD in the world; during epidemics there can be up to 1,000 cases per 100,000 inhabitants, or 1% of the population. The predominant serogroup is A. In America the incidence of the disease is in the range of 0.1 cases per 100,000 inhabitants (Paraguay, Costa Rica and Mexico) to 2 cases per 100,000 inhabitants (Brazil)[15]. Most of the cases on this continent are due to serogroups C and B, although the serogroup Y is responsible for a considerable proportion of cases in some countries and serogroup W135 is increasingly common. Most isolated meningococcal strains in Europe belong to serogroup B, especially in countries that have introduced conjugate vaccines against serogroup C in their programs. Data on Asia, although limited, suggest that the disease is caused mostly by strains A and C[12].

In 2009, the last year for which data is available at European level, 29 countries reported a total of 4,495 confirmed cases of IMD, with an overall incidence of 0.89 per 100,000 inhabitants. The highest rates of confirmed IMD were in Ireland ($3.01/10^5$h) and the UK ($2.1/10^5$h) and the lowest in Cyprus ($0.13/10^5$h) Bulgaria ($0.21/10^5$h) and Latvia ($0.22/10^5$h). The most notable event in the epidemiology of IMD in Europe in recent years has been the increase and subsequent decrease in the number of cases related to the spread of the hyper-virulent complex ST-11 strain/ET-37 complex serogroup C in Belgium, Spain, Ireland, Iceland, the Netherlands, Portugal and the UK. The decline of the IMD caused by serogroup C is attributable to the use of vaccines against this serogroup. Following the introduction of the conjugate vaccine against meningococcal serogroup C circa 1999, there was a steady decline in rates of confirmed cases across Europe. However, since 2006, the incidence of IMD has remained stable[12, 16].

4.2. Situation of IMD in Spain

In Spain, serogroup B was predominant in the 70s and 80s. In 1971 a wave of epidemic outbreaks associated with this serogroup began, which peaked in 1979 with an incidence of 17.9 cases per 100,000 inhabitants, which declined from that year gradually to around 2-3 cases per 100,000 inhabitants in the early nineties. It's during the late eighties when a gradual increase in the percentage of cases by serogroup C is observed, more pronounced after 1994, thus, during 1996 and 1997, serogroup C became the dominant group (73% of cases confirmed). This increase was associated with an increase in the overall incidence rate of IMD, which was uneven in different regions (higher in the Northwest). At the beginning of 1997, there were 1,334 cases, 824 (62%) confirmed. C strains were characterized predominantly as C:2b:P1.2, 5, of the ST8/A4 clonal line, and showed a mortality rate greater than the strains belonging to serogroup B[17].

Being the situation such, a vaccination campaign started from December 1996 until the end of 1997 with the then available purified A + C polysaccharide vaccine which reduced by 45% the overall rate of IMD and a 76% the rate of disease in the population group targeted by the intervention (from 18 months to 19 years old). In subsequent years, an increase in the values of the attack rates of the disease due to the loss of protective antibodies was detected. This situation led to the inclusion in the immunization schedule of the new conjugate vaccine against meningococcal serogroup C in autumn 2000[2].

Between 2000 and 2011, the incidence of IMD in Spain has followed a downward trend: 1.78 cases per 100,000 inhabitants (716 of cases confirmed) between 2000 and 2001; 1.61 per 100,000 inhabitants (697 of cases confirmed) between 2004 and 2005; 0.96 per 100,000 inhabitants (438 of cases confirmed) between 2009 and 2010 until 0.92 per 100,000 inhabitants (424 of cases confirmed) obtained from data regarding the years 2010 and 2011. The decline was mainly due to the decrease of cases due to serogroup C. The figure between the years 2010 and 2011 (67 cases of serogroup C, rate of 0.15 per 100,000 inhabitants) was 84% lower than for the period prior to the introduction of the conjugate vaccine. The serogroup B became predominant again throughout the country. The 81.9% (n = 304) of the cases confirmed between 2010 and 2011 were due to serogroup B (0.66 cases per 100,000 inhabitants)[3, 18, 19].

4.3. Pathogenesis of IMD

The human nasopharynx is the only reservoir of *N. meningitidis*. Transmission occurs by the inhalation of droplets of respiratory secretions. The meningococcus is adhered to the microvilli of the non-ciliated columnar epithelium of the nasopharynx, where it multiplies[20]. Most people colonized by *N. meningitidis* remain asymptomatic, but at a lower rate, the meningococcus penetrates the mucosa and reaches the bloodstream, causing systemic disease. It is still unknown exactly how and why some strains of *N. meningitidis* overcome host defences and spread from their natural habitat to the intravascular compartment[10].

The cellular and molecular mechanisms leading to the development of IMD are extremely complex and not precisely known. A virulence factor essential for the survival of the bacteria in the blood is the polysaccharide capsule that allows it to evade the host immune response, particularly the activation mechanisms of complement-mediated lysis, and phagocytosis. The release of large amounts of lipooligosaccharide, an endotoxin, triggers the host inflammatory response, inducing a massive release of pro-inflammatory and anti-inflammatory cytokines, and the activation of complement cascades and coagulation, triggering a sepsis followed by septic shock, which can lead to organ failure and death[21]. Inflammatory and immune responses are essential for the host to halt the progression of the infection, but can also cause cardiovascular collapse and death. The final result depends on a delicate balance between the pathogen and the response of the host.

4.4. Clinical manifestations of IMD

IMD produces mainly a picture of meningitis, sepsis, or both. Although it is usually a mixed picture of sepsis and meningitis, it is traditionally known as meningococcal meningitis in cases of patients in whom meningitis is the only clinical manifestation, or the most prominent, and meningococcal sepsis when the systemic involvement is the most striking and meningitis is not present, or is not the most prominent component of the clinical picture.

Initial signs and symptoms may be nonspecific and common to other less serious infections. The characteristic petechial rash is present in 28 to 78% of patients with IMD at the time of admission[10]. Meningitis occurs in approximately 50% of cases and their signs and symptoms are indistinguishable from the signs and symptoms of acute meningitis caused by other pathogens[20]. From 5% to 20% of patients have a clinical picture of sepsis meningitis or meningococcemia, characterized by having a rapid development. In fulminant cases, purpura, disseminated intravascular coagulation, shock, coma, and death of the patient within a few hours[10.20] may occur.

Less common manifestations include transient bacteraemia and chronic meningococcemia. Invasive meningococcal infections may be complicated by arthritis, panophthalmitis, and pneumonia[10].

5. Diagnosis of IMD

5.1. Warning signs and symptoms or red flag

Question to answer:

- In paediatric patients who come to primary health care (or emergency), what set of signs and symptoms should arouse suspicion of IMD?
  - Fever
  - Neck Stiffness
  - Headache
  - Photophobia
  - Vomiting
  - Dizziness
  - Fast breathing
  - Drowsiness
  - Less than 50% of usual fluid intake in 24 hours (<1 year)
  - Strange pitched cry (<1 year)
  - Abnormal skin colour (pale, earthy, mottled, bluish)
  - Vascular collapse, hypotension, shock
  - Leg pain or refusal to walk
  - Rash
  - Changes in heart rate
  - Cold hands and feet

The clinical diagnosis of the IMD depends on the recognition of signs and symptoms characteristic of the disease, such as the presence of fever accompanied by rash, meningeal signs or decreased level of consciousness[10]. However, the IMD may occur at the beginning with nonspecific clinical features that are difficult to distinguish from other less severe infections. For this reason, the identification of a paediatric patient with possible IMD among those who appear with mild and self-limited infections is challenging for primary care and emergency professionals. An important fact to highlight is that only half of the cases are identified in the first primary care consultation[22]. It is therefore vital that clinicians have scientific evidence on which signs or symptoms are useful for discriminating IMD from other less serious infections and therefore avoid a potentially fatal diagnostic and therapeutic delay.

The clinical practice guideline (CPG) from NICE based its recommendations for this question in nine observational studies and a systematic review. According to a series of 448 paediatric patients with IMD, aged between 0-16 years old, the disease occurs in the first 4 to 6 hours with nonspecific signs and symptoms such as fever, lethargy, refusal of food, nausea, vomiting and irritability. Three clinical features of sepsis appeared at an early stage: leg pain (average 7 hours) in 36.7% of cases, cold hands and feet (12 hours) in 43.2% and abnormal skin coloration (described as pale or spotted) (10 hours) in 18.6%. 72% of patients in the study experienced some of these signs and symptoms. The common signs and symptoms of IMD, haemorrhagic rash, symptoms and signs of meningitis and commitment of the level of consciousness, appeared later (average between 13 to 22 hours)[5].

CPG
Case series 3

A prospective study carried out in 190 patients ranging from 3 months to 15 years of age who went to the emergency department with fever (> 38 °C) and petechial rash, observed an IMD prevalence of 7% (13/190). Patients with IMD were more likely to feel worse, showing signs of meningeal irritation and have petechiae below the nipple line than patients with petechial rash and fever caused by a nonbacterial disease[5].

CPG
Cohort study
2+

Very few studies have investigated the diagnostic validity of clinical findings in the IMD. The NICE CPG includes two studies of this nature. One was conducted in patients aged between 1 month and 16 years old with fever and bleeding skin on admission, 15% (39/264) of whom had IMD. According to the authors of the study, the following characteristics are independent predictors of IMD: characteristic skin haemorrhages, widespread distribution of haemorrhages, haemorrhage diameter > 2 mm, malaise and neck stiffness. Sensitivity and the rate of false positives were 97% and 49%, respectively, for a paediatric patient with one or more of these signs and symptoms; 97% and 12% for a patient with two or more, and 82% and 5% for a patient with three or more of these signs and symptoms[5].

CPG
Study of diagnostic tests II

The other diagnostic validity study included in the NICE CPG was performed with patients less than 16 years admitted to the emergency department with non-blanching rash. The presence of purpura presents the highest values of sensitivity (83%), specificity (88%), positive predictive value (PPV) (47%) and negative predictive value (NPV) (98%), followed by capillary refill > 2 seconds, malaise and temperature > 38.5 °C[5].

CPG
Study of diagnostic tests II

From a retrospective sample of 1,331 patients aged between 1 month and 14 years of age with confirmed bacterial meningitis, a study that investigates the likelihood of predetermining the aetiology by analysing a selection of clinical symptoms and laboratory findings. The grouping of diagnostic criteria most strongly associated with the diagnosis of meningococcal meningitis include haemorrhagic rash, absence of seizures, headache, and negative Gram of cerebrospinal fluid (CSF) stain, with a PPV of 96.4% (95% CI 87.7 to 99.6) and an NPV of 38.5% (95% CI 35.8 to 41.3)[23].

Study of diagnostic tests II

One of the gaps in research that the NICE CPG identifies is the absence of studies to determine the diagnostic accuracy of signs and symptoms of IMD in primary care before admission to hospital. To answer this question, a study carried out after the research period of the NICE´s CPG, investigated the frequency of both classic symptoms and the warning features or red flags of the disease (leg pain, cold hands and feet, and abnormal skin colour) in a prospective cohort of 407 patients aged under 16 with mild and self-limited infection with fever who go to a primary care consultation. The data are compared with those of a previous study carried out on 448 cases of IMD aged less than 16. Rash, drowsiness, irritability, nausea and vomiting were moderately sensitive (between 72.6% and 85.5%) for the diagnosis of IMD. Confusion, photophobia, leg pain and neck stiffness or pain showed high specificity (between 94.3% and 98.1%). According to the authors, the following clinical characteristics showed clinically useful positive likelihood ratio (LR+) values for the diagnosis of suspected IMD: confusion, 24.2 (95% CI 11.5 to 51.3), leg pain, 7.6 (95% CI 4.9 to 11.9), photophobia, 6.5 (95% CI 3.8 to 11.0), rash, 5.5 (95% 4.3 to 7.1), neck pain or stiffness, 5.3 (95% CI 3.5 to 8.3). Only two had clinical features had clinically useful negative likelihood ratios (LR-): drowsiness, 0.2 (95% CI 0.2 to 0.3) and rash, 0.3 (95% CI 0.2 to 0.3). In the analysis by age group, higher LR+ values were observed for photophobia and neck stiffness in patients younger than 1 year and aged between 1 and 4 years, compared with patients aged between 5 and 14 years. The presence of rash had a higher LR+ in older paediatric patients (5-14 years). Unlike to what is observed in other studies, headache and pallor does not discriminate between the two groups (IMD and mild infections), and the discrimination capacity of cold hands and feet is limited[22]. The authors hypothesize that the subjective interpretation of the parents may be the reason why paediatric patients with self-limited febrile infections had more often pallor and cold hands and feet, than these patients who do not show commitment to the peripheral circulation.

Study of diagnostic tests III

The rest of the evidence included in the NICE CPG comes from retrospective case series describing the frequency of different clinical findings present at the time of hospital admission of paediatric patients with IMD. The studies differ in the age range considered, the clinical spectrum (sepsis and / or meningitis), the selection criteria (confirmed and / or probable IMD) and data collection methods (telephone questionnaire, medical history). In summary, the results show that it is likely that at the time of admission, paediatric patients with IMD have nonspecific symptoms such as fever (71% to 100%), vomiting (34% to 82%), refusal of food (42 %) and irritability (45%). Often, but not in all cases, characteristics such as neck stiffness (11% to 87%), headache (27% to 86%) and drowsiness or sleepiness (28% to 89%) are present. A minority had seizures (4% to 21%). It is more likely that younger patients (under 2 years) present irritability, refusal of food, lethargy and decreased level of consciousness, while the characteristic symptoms of meningeal irritation (headache, neck stiffness, photophobia), confusion, haemorrhagic rash and pain in extremities are more likely in older paediatric patients 5. In a series of 103 cases, 31% of patients ranging between 0-4 years of age and 35% of patients between 5 and 14 years of age[24] underwent a shock.

CPG
Case series
3
Caseseries 3

In some series, the characteristic haemorrhagic rash is only present in about half of patients with IMD before hospital admission (48% to 80%). In a sample of 107 hospital patients with IMD under 16 years, 49% had a petechial rash, compared with 39% with no petechial rash[3].

The most common signs and symptoms of IMD are listed in Table 3.

Table 3. Signs and symptoms of IMD

NON-SPECIFIC signs and symptoms	MORE SPECIFIC signs and symptoms
Common	– Non-blanching rash
– Fever	– Capillary refill time> 2 seconds
– Nausea	– Leg Pain
– Vomiting	– Cold hands/feet
– Lethargy	– Altered mental state
– Irritability	– Unusual skin colour
– Ill appearance	– Hypotension
– Refusal of food	– Shock
– Headache	– Neck Stiffness
– Muscle ache or joint pain	– Bulging fontanelle
– Signs and/or respiratory symptoms	– Photophobia
Less common	– Kernig's sign
– Diarrhoea/abdominal pain	– Brudzinski's sign
– Sore throat	– Focal neurological deficits
– Coryza	– Seizures

WARNING signs and / or symptoms or RED FLAG:
– Leg Pain – Cold hands and feet – Unusual skin colour
Signs of SHOCK
– Capillary refill time> 2 seconds – Unusual skin colour – Tachycardia and / or hypotension – Respiratory symptoms or breathing difficulty – Leg Pain – Cold hands and feet – Mental confusion/decreased level of consciousness

Adapted from the NICE CPG (2010)[5].

When comparing the results of the initial clinical presentation of IMD, different studies agree that the pathognomonic haemorrhagic rash is absent in a significant proportion of patients before going to hospital, that most cases have nonspecific clinical symptoms and that the classic symptoms of meningitis may not be present in the early stages of the IMD. In this sense, and according to the experience of one of the experts who contributed to the revision of this guide, it is relatively common for teens and adults with IMD to have sore throat at the start of the disease, accompanied in some cases of purulent tonsillitis.

When making recommendations to this question, the relevance and clinical impact of the early diagnosis on prognosis of IMD has been taken into account. The guideline development group (GDG) considers health education of professionals at primary and hospital care essential to learn to recognize the early signs of IMD and distinguish it from probably benign febrile processes.

Summary of evidence

3	In the first 4-6 hours, IMD appears with nonspecific symptoms such as fever, lethargy, refusal of food, nausea, vomiting, or irritability. The following signs and symptoms characteristic of sepsis appear several hours preceding the classic signs and symptoms: leg pain (average 7 hours), cold hands and feet (average 12 hours) and unusual skin colour (average 10 hours). The classic signs and symptoms such as haemorrhagic rash, meningism and commitment level of consciousness appear later[5].
2+	Paediatric aged patients with IMD are more likely to have worse general condition, signs of meningeal irritation and petechiae below the nipple line than paediatric patients with fever (> 38 ° C) and petechial rash by non-bacterial disease[5].

II	The following features are independent predictors of IMD in paediatric patients with fever and bleeding skin: skin bleeding characteristics (OR 11.2, 95% CI 2.5 to 50.7); widespread distribution of skin haemorrhages, (OR 5.1, 95% CI 1.1 to 23.7); diameter of skin haemorrhages > 2 mm (OR 7, 95% 1.5 to 32); malaise (OR 14, 95% 3.1 to 62.6); neck stiffness (OR 6.9, 95% CI 1.1 to 44.0). Sensitivity and the false positive rate were 97% and 49%, respectively, for a patient with one or more of the above features, from 97% to 12% for a patient with two or more, and from 82% to 5 % for a patient with three or more[5].
II	The presence of purpura indicates the highest IMD diagnostic rates, with an 83% of sensitivity, 88% of specificity, 47% of PPV and 98% of NPV, followed by capillary refill > 2 seconds, malaise and body temperature > 38.5 ° C[5].
III	In primary care, the following symptoms have clinical utility of LR + when diagnosing IMD: confusion (LR+ 24.2, 95% CI 11.5 to 51.3), leg pain (LR+ 7.6, 95% 4, 9 to 11.9), photophobia (LR+ 6.5, 95% CI 3.8 to 11.0), rash (LR+ 5.5, 95% 4.3 to 7.1) and neck stiffness (LR+ 5, 3, 95% CI 3.5 to 8.3)[22].
II	The set of clinical and laboratory findings which strongly suggest that the causal agent of bacterial meningitis is *N. meningitidis* includes the presence of haemorrhagic rash + absence of seizures + headache + negative Gram stain of CSF, with a PPV of 96.4% (95% CI 87.7 to 99.6) and an NPV of 38.5% (95 35.8 to 41.3%)[23].
3	Frequency of clinical findings present in a paediatric patient with IMD[5.24]: – Fever (71% to 100%) – Headache (27% to 86%) – Vomiting (34% to 82%) – Haemorrhagic rash (48% to 80%) – Drowsiness / lethargy (28% to 89%) – Dielectric collar (11% to 87%) – Rejection of food (42%) – Irritability (45%) – Seizures (4% to 21%)
3	It is more likely that patients younger than 2 years present irritability, refusal of food, lethargy and decreased level of consciousness. Meningism, confusion, haemorrhagic rash and pain in extremities are more likely in older paediatric patients[5.24].
3	At the time of admission, approximately 49% of paediatric patients with IMD have a petechial rash, while 39% do present a non-petechial rash[5].

Recommendations

√	Healthcare professionals should be trained on how to recognise and manage IMD.
D	The presence of a generalized petechial or purpuric rash, with capillary refill > 2 seconds in a paediatric patient with impairment of the general condition, should suggest IMD and the need for urgent treatment.
D	In the ill paediatric patient, the presence of any of the following signs and symptoms should alert the clinician about the possibility of IMD: – Petechial rash (non-blanching) – Capillary refill time > 2 seconds – Abnormal skin colour – Decreased level of consciousness – Pain in extremities – Cold hands and feet – Fever – Headache – Neck Stiffness – Photophobia
D	One must remain alert to the possibility of IMD when evaluating patients with acute febrile disease because in the first 4-6 hours of onset of the clinical IMD nonspecific symptoms such as fever, lethargy, refusal of food, nausea, vomiting, irritability, signs and/or symptoms of upper respiratory tract infection (runny nose, sore throat, etc.), diarrhoea, or abdominal pain may appear.
D	In the initial clinical evaluation (primary care), it should be noted that the following symptoms are very rare in the paediatric patient with mild febrile disease: leg pain, confusion, neck stiffness, and photophobia.
√	The clinician will take into account the fact that the signs and symptoms of the disease can vary and become more specific over time.
B	The set of clinical and laboratory findings which strongly suggest that the causal agent of bacterial meningitis is *N. meningitidis* includes the presence of haemorrhagic rash + absence of seizures + headache + negative gram stain of CSF.

5.2. Clinical reassessment as strategy to improve diagnosis

Questions to answer:

- For a paediatric patient who goes to primary health care with symptoms suggestive of IMD, does a second specific clinical evaluation (after 4-6 hours) for disease progression improve the diagnosis?
- For a paediatric patient who goes to primary health care with symptoms suggestive of IMD, does a telephone evaluation for disease progression improve the diagnosis?

It is sometimes difficult to distinguish the IMD of self-limited febrile infections because in the first 4 to 6 hours after the onset of the clinical disease it may be nonspecific, especially in younger paediatric patients, with symptoms such as fever, vomiting, refusal of food and irritability[5]. Adopting a "wait and see" attitude could improve the diagnosis of these patients, since the classical clinical features of meningitis and sepsis appear later in the natural course of the disease. On the other hand, the IMD progresses rapidly. Most of the cases are admitted to hospital in an interval of 24 hours from the onset of the disease, which leaves very little room to see if the clinical picture evolves unfavourably or not.

No scientific evidence was identified to answer the question. Nor does the SIGN CPG find studies about this and thus its recommendation is based on that made by other CPG[25].

Paediatric patients in whom the diagnosis of IMD is likely to require urgent treatment should not be delayed waiting for a second clinical evaluation[6].

CPG
Expert opinion
4

The GDG believes that the health professional must consider the degree of anxiety of parents or caregivers to the paediatric patient's illness and their ability to understand the information they are transmitted over action patterns to be followed, and their ability to act during an unfavourable clinical evolution. The GDG believes that it is necessary to reassess the paediatric patient when the diagnosis of IMD cannot be ruled out, but decided not to establish a specific time interval (4 to 6 hours) because from an operational point of view, it may not be feasible in our environment.

Summary of evidence

4	Urgent treatment should not be delayed in cases with a probable IMD while waiting for a second clinical evaluation to improve the diagnosis[6].

Recommendations

D	In the presence of clinical signs or other symptoms suggestive of IMD, treatment should not be delayed waiting for a second clinical evaluation.
√	Children with nonspecific symptoms at initial presentation, in whom IMD cannot be excluded at the discretion of the physician, should be reassessed in a short period of time (hours).
√	The healthcare professional will inform caregivers about the need to seek health care if the patient's condition deteriorates during childhood before the planned revaluation for example, if the characteristics of the rash change. The degree of concern of parents or caregivers as well as their ability to act if the patient worsens must be taken into account and information on the availability of health services in the area must be provided.

5.3 Non-specific laboratory tests

Question to answer:

- Among paediatric population with petechial rash, can non-specific laboratory tests (C-reactive protein, white cell count, blood gases), help to confirm or refute the diagnosis of IMD?

The classic clinical presentation of IMD is the presence of a non-blanching rash in a paediatric patient with fever. As well as meningococcemia, there are many other causes of infectious aetiology of petechial rashes and fever in paediatric patients. Healthcare professionals should decide which patients with rash and fever have IMD and therefore require urgent antibiotic treatment and support, and which do not. The non-specific laboratory tests are part of the routine diagnostic study of these patients[5].

No diagnostic accuracy studies on nonspecific laboratory tests in the diagnosis of post-IMD subsequent to the literature search period carried out by the NICE CPG were found. The guide uses two prospective observational studies to answer this clinical question. These were performed in patients younger than 15 years who went to a hospital emergency unit with petechial rash and non-blanching rash, respectively. Both studies analysed the diagnostic validity of the white cell count in peripheral blood. Compared with patients without meningococcemia, patients with IMD are most likely to have higher white cell counts in peripheral blood, "band form" and elevated neutrophil counts. None of the above determinations had sufficient sensitivity and specificity to predict the diagnosis of IMD[5].

CPG
Cohort studies
2+

One of the studies cited above provides evidence on the diagnostic accuracy of the C-reactive protein. In hospital care, an initial determination of CRP <6 mg/L in a paediatric patient with petechiae and fever, practically excludes the diagnosis of IMD[5].

CPG
Cohort studies
2+

NICE identified no studies on the performance of arterial blood gases in the diagnosis of IMD in paediatric patients with petechial rash.

Summary of evidence

2+	The mean score of white cells and the absolute number of band forms in peripheral blood is significantly higher in paediatric patients with IMD, petechial rash and fever compared with paediatric patients with petechial rash and fever without bacterial disease[5].
2+	The probability of having a high neutrophil count is higher in patients with IMD and non-blanching rash (OR 2.7, 95% 1.1 to 6.5) than in patients with rash without IMD[5].
2+	Diagnostic accuracy in paediatric patients with petechial rash and fever[5]: White blood cell count in peripheral blood > 15,000 cells/ml: sensitivity 67%, specificity 85%, positive likelihood ratio (LR+) 4.5, negative likelihood ratio (LR-) 0.39. Absolute number of band forms in peripheral blood > 500 cells/μl: sensitivity 80%, specificity 74%, LR+ 3.0; LR- 0.27.
2+	Levels of C-reactive protein > 6 mg/L are very sensitive (100%, 95% CI 96-100), but not very specific (54%, 95% CI 47-62) for the diagnosis of IMD in paediatric patients with non-blanching rash[5].
2+	When, in a paediatric patient with petechial rash and fever, the count in peripheral blood of white cells and band forms (absolute) and the white cell count in cerebrospinal fluid (CSF) are all normal, the probability of IMD is low[5].

During the formulation of recommendations and in relation to their applicability and generalization, the GDG has taken into account that in primary care there is no possibility of carrying out non-specific laboratory tests.

Studies evaluating the diagnostic performance of serum procalcitonin levels, following the NICE guideline, were excluded from the body of evidence because they are not directly applicable to the target population of the guide. However, the GDG considered worth mentioning that recent studies have evaluated the clinical usefulness of serum procalcitonin in the diagnosis of invasive bacterial infection in childhood. According to a recent systematic review[26] on the diagnostic performance of inflammatory markers in paediatric patients with febrile syndrome without focus, the C-reactive protein and procalcitonin show similar diagnostic features. Their role in clinical practice is yet to be determined.

Recommendations

√	The following determinations should be performed in children with petechial rash of unknown origin and fever, or history of fever: – Blood cell counts – C-reactive protein or procalcitonin – Coagulation tests – Blood culture – Blood Glucose – Pulse oximetry
C	If a paediatric patient has a petechial rash of unknown origin and fever, or history of fever, but none of the high-risk clinical features, the following recommendations should be considered: – Start the specific treatment immediately if the C-reactive protein or the white cell count (especially neutrophil count) is high, since this indicates increased risk of IMD. – Clinicians should be aware that although IMD is less likely with both normal C-reactive protein and white cell count, it should not be ruled out. Both parameters can be normal in severe or very short evolution cases. – Evaluate clinical progression by monitoring vital signs, capillary refill time and oxygen saturation. Perform checks at least every hour for the next 4-6 hours. – Treat with antibiotics and admit to hospital if doubt persists.
√	The serum procalcitonin concentration can be used as an early marker of IMD. Changes in the serum concentration of procalcitonin take place earlier and faster than those of the C-reactive protein.
√	If the final assessment is as being of low risk of IMD and the patient is discharged, it is recommended to warn caregivers to return if they feel that he/she worsens (for example, if new spots appear or if the patient seems excessively sleepy or irritable).

5.4. Diagnosis of increased intracranial pressure

Question to answer:

- Among paediatric population with suspected or confirmed bacterial meningitis, can a cranial computed tomography reliably demonstrate an increase of intracranial pressure?

The assessment of CSF obtained by lumbar puncture is essential to identify the causative agent and ensure the optimal management of patients with suspected bacterial meningitis. The lumbar puncture (LP) is contraindicated when there is an increase in intracranial pressure (ICP) for the risk of brain herniation. The cranial computed tomography (CT) has been postulated as a test that can be useful in identifying increases in ICP in paediatric cases suspicious of bacterial meningitis.

No studies have been identified following the research carried out by the NICE CPG. The NICE recommendation is based on three low methodological quality studies, with a very small sample of paediatric patients with bacterial meningitis and increased intracranial pressure (10, 14 and 15 cases, respectively), which possibly used a now obsolete technology (year of publication 1992, 1993 and 2001). The evidence available, 50% (5/10), 36% (5/14) and 40% (6/15) of normal CT in the presence of ICP led the development group to make an unfavourable recommendation[5].

CPG Case Series 3

Summary of evidence

3	The CT showed signs of cerebral oedema only in 5/10 paediatric patients (aged between 2 to 16 years old) with bacterial and clinical signs of increased ICP, confirmed by invasive monitoring (> 20 mmHg)[5].
3	The CT was normal in 5/14 (36%) paediatric patients diagnosed with brain herniation[5].
3	Six out of 15 (40%) paediatric patients with bacterial meningitis and clinical signs of increased ICP had a normal CT result[5].

Recommendations

D	Clinical assessment, and not cranial computed tomography (CT), is recommended to decide whether it is safe to perform a lumbar puncture. CT is unreliable for identifying increased intracranial pressure.
D	If a CT has been performed, it is not recommended to do a lumbar puncture if there are radiological signs of increased intracranial pressure.
D	It is recommended not to delay the treatment while waiting for a CT to be performed.

5.5. Microbiological confirmation tests

Question to answer:

- In the case of patients with suspected IMD, what diagnostic tests done at an early stage are useful to confirm the diagnosis of IMD?
  - – Blood culture
  - – Skin scrapings
  - – Blood Polymerase Chain Reaction (PCR)
  - – Throat swab
  - – Urine rapid antigen testing
  - – Blood rapid antigen testing

Microbiological confirmatory diagnosis of IMD requires culture isolation or detection of the bacterial DNA of *N. meningitidis* in sterile fluids, such as blood or CSF. In the case of the IMD, the development of molecular diagnostic methods has been especially beneficial. These methods are more sensitive than culture, and its detection capacity is not affected by the administration of antimicrobials prior to sampling[27]. The latest report from the *European Invasive Bacterial Diseases Surveillance Network* (EU-IBD)[16] revealed that although culture is still the most used method to confirm the diagnosis of IMD, (47.9% in 2008 and 44.7% in 2009), molecular methods are used with increasing frequency. Thus in 2009, 25% of the cases were confirmed by polymerase chain reaction (PCR) and in some countries, such as Ireland (58.3%), the UK (51.6%) and Greece (42.7%), the number of cases confirmed only by PCR surpassed those confirmed by culture. The diagnostic yield of the different techniques and currently available diagnostic targets is the aim set in this review.

Blood culture is the reference diagnostic test in the diagnosis of IMD[6].	CPG Expert Opinion 4
The two CPGs[5,6] specifically addressing the issue and the three identified studies[28-30] agree that the genome *N. meningitidis* detection techniques, in either whole blood, serum or CSF, increase diagnostic certainty regarding the cultivation of IMD. According to the CPG by SIGN, the increase in the proportion of cases of IMD with aetiological diagnosis when performing real-time PCR is between 30% and 40%. The PCR remains positive up to 9 days in patients receiving antibiotic treatment[6].	CPG Observational study 2++ CPG Case series 3

The NICE CPG used four studies as evidence on the diagnostic accuracy of the Taqman™ PCR in real-time. Two prospective studies conducted the test in whole blood. They obtained a sensitivity of 88% (95% CI 68-97) and 88% (95% CI 81-95), respectively, and a specificity of 100% (95% CI 96-100). The sensitivity of the blood culture was 58% (95% CI, 37-78) and 33% (95% CI, 24-42), respectively. In addition, the PCR was positive and the blood culture negative in 29% (7/24) and 55% (52/95) of cases of IMD. In the first study, the PCR remained positive 72 hours after initiation of the treatment, whereas in the second, the pre-hospital administration of antibiotics did not change its sensitivity. The reference standard was constituted by microbiological findings and, in their absence, by agreed clinical criteria. A third prospective study comparing the whole blood Taqman PCR against Taqman PCR in serum showed an increase in the proportion of cases confirmed regarding the cultivation, 47% in serum in comparison to 88% in blood, $p < 0.0012$. Finally, a prospective study that evaluated the performance in LCR of a duplex real-time PCR for meningococcus and pneumococcus showed, for meningococcal disease, a sensitivity of 87% (20/23), higher than that of Gram (27%) and the culture (17%) of CSF[5].

CPG
Studies of diagnostic tests
1b II

Most techniques for real-time PCR described in the literature amplify fragments from the ctrA gene (capsular operon), exclusive of *N. meningitidis*. A retrospective study investigated the diagnostic accuracy of an alternative molecular target, 16S ribosomal DNA (rDNA), applied to the diagnosis of patients with clinical suspicion of acute bacterial meningitis. The authors pose a sequential diagnostic strategy. First, perform a real-time multiplex PCR that detects the 16S rDNA of *N. meningitidis, Streptococcus pneumoniae,* and *Listeria monocytogenes* in a single reaction. The samples with a 16S rDNA positive universal probe but with 16S rDNA negative specific meningitis probe were analysed by low-density microarray and 16S rDNA sequencing. For N. meningitidis, the sensitivity of the molecular strategy was 92% (95% CI 72.5 to 98.6), higher than the CSF culture, 64% (95% CI 42.6 to 81.3). The negative predictive value (NPV) was 97.7% (95% CI 90.7 to 99.6), while the NPV of the culture was 90.2% (95% CI 81.8 to 95.2)[28].

Studies of diagnostic tests
III

Another retrospective study developed and validated a technique for rapid detection of *N. meningitidis* (ctrA gene) using a new method of DNA amplification called LAMP (*loop-mediated isothermal amplification*)[31,32], which reduces the turnaround time and does not require a high degree of technological infrastructure as with the real-time PCR. The presence of a fluorescent detection reagent allows identifying positive samples by simple visual inspection (turning from pale yellow to green). 378 samples (whole blood, CSF, serum, throat swab, etc.) were analysed, 96% of which came from patients under 23 years who arrived to the emergency unit with signs or symptoms suggestive of meningitis or septicaemia. The test sensitivity and the NPV in blood and CSF relative to the reference standard, real-time PCR, was 100%. The blood specificity was 98.5% and the positive predictive value (PPV) of 80%. CSF obtained a specificity of 94.7% and a PPV of 75%. The authors estimated that the test is capable of detecting six *ctrA* gene copies per reaction (6.6 × 106 to 1.2 × 103 copies *ctrA*/mL) in a maximum time of 48 minutes (range 22-48 min). The reference standard did not include clinical diagnostic criteria in the presence of a negative real-time PCR. The number of samples analysed with real clinical interest (blood, CSF) was small[29].

Studies of diagnostic tests III

A study conducted in Spain that evaluated the usefulness of the amplification of a fragment of the insertion sequence IS*1106* by simple PCR and subsequent hybridization colorimetric detection was identified. Samples from 43 patients (aged between 3 months to 17 years old) with a diagnosis of IMD at discharge and samples of 67 patients without clinical criteria of IMD were analysed. The PCR increased the diagnostic certainty with regard to the culture by 37%[30].

Studies of diagnostic tests III

No studies on the diagnostic performance of the analysis of skin lesions common in IMD were identified. Both guides[5,6] collect evidence in this respect. The Gram stain petechiae scraping detected *N. Meningitidis* in 80% (n = 24) of the 30 cases in which Gram scraping was performed against 37% (11/30) of blood cultures in which meningococcus was isolated. When considering all cases of IMD confirmed (n = 52), the Gram petechiae scraping is not significantly more effective than other methods[5].

CPG
Studies of diagnostic tests III

The proportion of confirmed cases of IMD by Gram stain of skin biopsy (56%), blood (56%) and culture and/or Gram CSF (64%) is similar[5].

In patients with purpura fulminans, the real-time PCR skin biopsy was significantly more sensitive than the skin biopsy culture (p <0.0001)[5].

Studies show that the real time PCR is more sensitive than culture for confirming the diagnosis of IMD, and is also highly specific. The clinical impact of the molecular diagnosis of IMD is evident. In a high quality study included in the NICE CPG, the real-time PCR increased up to 55% the blood culture sensitivity. Another great advantage is the speed in obtaining results. When developing the recommendations, as well as the advantages, the GDG has also taken into account the main drawbacks of the real-time PCR, common to all molecular diagnostic techniques. Its high cost and the need for specially trained staff limit its availability in our reference laboratories (National Centre of Microbiology, Instituto de Salud Carlos III, tertiary hospitals). The blood culture, the Gram stain and the CSF culture are performed routinely in the NHS microbiology laboratories.

McKenna *et al*.[29] have optimized a rapid technique for molecular diagnosis that could be used in an environment, which is closer to the patients, but more studies are needed to assess its performance quality in clinical practice. In this sense, the GDG has considered necessary to establish a recommendation for future research.

In making the recommendation regarding the study of skin lesions for the diagnosis of IMD, the GDG has taken into account that the real-time PCR is not routinely performed in our environment, therefore the possibility of confirming the diagnosis is markedly reduced, and a positive microbiological study of the skin lesions can be very suggestive of IMD. Considering these factors, unlike the NICE CPG, no recommendation has been stated against the use of skin lesions for the diagnosis of IMD.

Finally, based on the fact that the meningococcus colonizes the nasopharynx in an asymptomatic way in over 10% of the population, and in the absence of scientific evidence in this respect, the GDG has decided not to make a recommendation in relation to the microbiological examination of throat swabs. Isolating the meningococcus in the throat swab may not be indicative of invasive disease. The confirmatory diagnosis must be carried out by the identification of the organism from normally sterile sites such as blood or CSF.

Summary of evidence

4	Blood culture is the standard reference of the confirmatory diagnosis of IMD[6].
3	The CSF examination by microscopy, culture and PCR is important in providing information about the aetiology of meningitis, especially in patients without the classic features of IMD[6].
Ib/II	The sensitivity of the real-time PCR (whole blood or serum) is higher than the blood culture. The real time PCR is more sensitive when using whole blood than when using serum. The PCR remains positive 72 hours after starting the antibiotic treatment[5].
2++/ 3	The increase in the proportion of cases of IMD with etiologic diagnosis by performing real-time PCR is between 30% and 40%. The PCR remains positive up to 9 days after starting the treatment[5].
III	A sequential strategy for molecular diagnosis (real-time PCR, microarray and sequencing) centred on an alternative molecular target, 16S ribosomal DNA, showed a higher sensitivity (92%, 95% from 72.5 to 98.6) than the CSF culture (64%, 95% CI 42.6 to 81.3)[28].
III	It is estimated that the LAMP (*loop-mediated isothermal amplification*) technique is capable of detecting 6 copies of ctrA 6 gene per reaction (6.6 × 106 to 1.2 × 103 ctrA copies/mL) in a maximum time of 48 minutes (range from 22 to 48 min). The sensitivity and NPV in blood and CSF were 100%. The blood specificity was 98.5% and the PPV 80%. In LCR, specificity was 94.7% and the PPV 75%[29].
III	The amplification of the fragment insertion sequence IS*1106* by simple PCR and subsequent hybridization colorimetric detection increased the confirmatory diagnosis of IMD by 37% with respect to the culture[30].

3[6]/ III[5]	The CSF of the PCR is more sensitive than culture in samples taken before and after the start of the antibiotic therapy. A duplex real-time PCR against meningococcus and pneumococcus shows a sensitivity of 87%, higher than that of Gram (27%) and culture (17%)[5,6] for meningococcal disease.
III	Gram-negative diplococci were observed in skin scraping in 80% of cases of confirmed IMD with petechiae; only 37% of them had a positive blood culture. When considering all cases of IMD, the Gram stain of petechiae scraping was not more effective than the blood culture and the CSF[5].
III	The proportion of IMD cases confirmed by examination (Gram stain) of skin biopsy (56%), blood culture (56%) and culture and / or CSF Gram stain (64%) is similar[5].
III	The real time PCR cutaneous biopsy line is significantly more sensitive than the skin biopsy cultivation (p <0.0001)[5].

Recommendations

C	To confirm the diagnosis in patients with suspected IMD, blood should be drawn for bacterial culture.
D	To confirm the diagnosis in patients with suspected IMD, blood should be drawn to perform a meningococcal PCR (whole blood, EDTA) in laboratories with sufficient technical capacity.
C	A lumbar puncture should be performed in patients with clinical features of meningitis without sepsis (purpura), if there are no contraindications.
D	The CSF should be referred to a microbiological laboratory. The following techniques should be performed: – Microscopy – Cultivation of bacteria – Meningococcal PCR in laboratories with sufficient technical capacity
D	None of the following techniques is definitive when IMD is to be confirmed or ruled out: skin scraping, skin biopsy, petechial or purpuric lesion aspirates (obtained with a needle and syringe).
√	Samples should be collected as soon as possible after establishing the clinical suspicion and preferably before starting the antimicrobial treatment. The sample collection must not delay the onset of the antibiotic treatment.

6. Pre-hospital Management of IMD

6.1. Pre-hospital administration of antibiotics

Question to answer:

- In patients with suspected IMD, does the pre-hospital administration of antibiotics reduce mortality?
- In patients with suspected IMD, does the pre-hospital administration of antibiotics affect morbidity and influence the admission to the ICU, the duration of hospital stay, admission costs, the duration of school absence, etc.?
- In patients with suspected IMD who come to primary health care, does the parenteral administration of antibiotics reduce mortality and morbidity more than the oral administration of antibiotics?
- In patients with suspected IMD who come to primary health care, does the intramuscular administration of ceftriaxone, have a similar efficacy and safety to its intravenous administration?

Pre-hospital administration of antibiotics in patients with suspected IMD could delay transport to the hospital and even be the cause of a definitive diagnosis masking. It is a fact that IMD, usually progresses rapidly and there is the belief that early administration of an active antibiotic against *N. meningitidis* would affect the reduction of morbidity and mortality. By contrast, it has been suggested that early administration of antibiotics in an environment outside the hospital would cause initial worsening of the IMD due to the bacterial lysis they induce and it would be safer to administer it in hospital.

A systematic review of 12 observational studies included in the NICE CPG asks whether pre-hospital administration of antibiotics to paediatric patients with IMD improves results. IMD mortality after receiving intravenous antibiotics before hospitalization varies in people of any age, including the following: RR 0.16 (95% CI 0.01 to 2.63) and RR 2.36 (95 0.25 to 22.54%). The results are contradictory: 8 studies showed a beneficial effect whereas in 4 studies, patients who received parenteral antibiotics before hospital admission had higher mortality. Only one study showed a statistically significant estimator: RR 0.35 (95% 0.16 to 0.80). The proportion of people with IMD who received pre-hospital treatment ranged between 15% and 59%, with an estimate of heterogeneity between studies. The authors of the review could not determine whether the administering or not of antibiotics before hospital admission had any effect on mortality rates[5].

CPG SR of observational studies
2+

One study included in the NICE CPG investigated the use of parenteral penicillin in primary care in 158 paediatric patients diagnosed with IMD. Pre-hospital treatment with penicillin was associated with an increased risk of death (OR 7.4, 95% CI 1.5 to 37.7) and for complications (OR 5.0, 95% CI 1.7 to 15.0), including renal, cardiovascular and respiratory failure, neurological complications and tissue necrosis with excisions and amputations. This might be because it was the sickest patients who received intravenous penicillin before being admitted to hospital ($p = 0.002$)[5].	CPG Case-control study 2+
A retrospective study in Spain and included in the NICE CPG evaluated the effectiveness of pre-hospital oral antibiotics in reducing the risk of death by IMD in 848 paediatric patients (mean age 10.4 years). In the group that received oral antibiotics prior to hospital admission (226 cases) 2.7% of patients died, while in the group who did not receive antibiotics mortality was 6.9% (OR 0.37, 95% 0.15 to 0.88). By excluding from the study those patients whose diagnosis was based solely on clinical suspicion (cases without microbiological confirmation), the estimator of mortality became OR 0.4 (95% CI 0.11 to 1.4)[5].	CPG Cohort study 2+
The analysis of the risk factors associated with mortality in 293 patients with IMD admitted to a Norwegian hospital found no significant difference between patients who received prior antibiotic therapy and those who did not ($p = 0.34$)[5].	CPG Case Series 3

In formulating recommendations, the GDG has been aware that the findings are contradictory. In some studies, patients who received parenteral antibiotics before hospital admission had higher mortality. One possible explanation is based on methodological aspects such as being poorly designed (cohorts) to answer the type of question asked (treatment).

The intervention shows an unclear balance between benefits and risks. While the benefits of the pre-hospital antibiotic treatment are potentially important because they have been shown to improve the prognosis of patients with sepsis[33], the GDG has taken into account the possibility that a firm recommendation can result in a delay in the transfer to hospital and at the start of other therapeutic measures.

As for the applicability and possible generalization of the pre-hospital treatment, the GDG has been aware that in Spain, since 1985, there have been increasingly isolated meningococcal strains with reduced susceptibility to penicillin, with minimum inhibitory concentrations (MIC) between 0,1 and 1 μg/mL, caused mainly by the decrease in affinity of the two PBP 2(*penicillin binding protein*) by penicillin[34]. Although rare, strains with high resistance to penicillin by beta-lactamase production[35] have also been identified. The standard treatment with benzylpenicillin reached in the CSF peak concentrations of 0.8 μg/mL, close to the MIC of some strains with reduced susceptibility isolated in our country[35], therefore, the use of benzylpenicillin to treat IMD within our context would require a culture and antibiogram. Instead, both CPGs (NICE and SIGN) agree on the recommendation, when there is a case of suspected IMD, to administer intravenous benzylpenicillin as soon as possible. The NICE CPG argues that penicillin is the antibiotic most used in primary care and found no evidence to recommend an alternative.

An update of the systematic review by Sudarsanam *et al*.[36], which was identified, included in the NICE CPG, adds nothing new. The report provides an update until 2011; however, in the

databases (MEDLINE, Cochrane), the quotation dates back to 2008 and is listed in the bibliography of this guide. Neither study refers to Gunnell *et al*.[37] in the volume of evidence due to its poor methodological quality and because that study is included in the systematic review by Hahne *et al*.[38]. No studies were found comparing the efficacy and safety of the intramuscular administration of ceftriaxone with its intravenous administration.

Summary of evidence

2+	The administration of pre-hospital intravenous antibiotics in patients of any age with IMD, against hospital administration, provides a range of values of relative risk for mortality between 0.16 and 2.36 with 95% CI between 0.01 and 22.54[5].
2++	The administration of pre-hospital intravenous penicillin for paediatric patients with IMD is associated with an increased risk of death (OR 7.4, 95% CI 1.5 to 37.7) and complications (OR 5.0, 95 % 1.7 to 15.0), bearing in mind that the clinical status of those patients receiving penicillin was significantly worse ($p = 0.002$)[5].
2+	Pre-hospital oral antibiotics are associated with a decreased risk of death by IMD (OR 0.37, 95% IC 0.15 to 0.88). Statistical significance is lost by excluding from the sample patients whose diagnosis was based solely on clinical suspicion of IMD (OR 0.4, 95% CI 0.11 to 1.4)[5].
3	A retrospective case series observed no significant differences in mortality by IMD (in all ages) among patients who received pre-hospital antibiotic treatment and patients who did not receive it[5].

Recommendations

√	Patients with suspected IMD will be sent to hospital urgently.
D	When suspecting IMD, intravenous antibiotics (ceftriaxone 50 mg/kg IV or IM) should be administered as soon as possible, both in primary care and at a higher level, but the urgent transfer to hospital should not be delayed.

6.2. Pre-hospital Resuscitation

Question to answer:

- In patients with suspected IMD, does resuscitation before reaching the hospital (in the ambulance) improve survival?, Can they reduce the severity of the disease and influence on the admission to the ICU, the duration of hospital stay, admission costs or the duration of school absence?

In the Spanish NHS, there have been major changes in the organizational models of health services that have positively influenced access to resuscitative measures associated with a reduction in mortality. The purpose of the question is to find out whether carrying out initial resuscitation before reaching the hospital improve the outcomes of patients with severe sepsis.

Initial resuscitation with fluids, airway care and early treatment with corticosteroids can be found in Chapter "Early support treatment".

No studies were identified comparing the start of resuscitation of patients with IMD before and after their admission to hospital.

Recommendations

√	In patients with suspected or confirmed meningococcal sepsis, resuscitation should be started immediately, if possible, prior to initiating patient transport or during transport.

6.3. Development and implementation of protocols

Question to answer:

- Do care processes ("process mapping programs") for those patients with progressive symptoms improve survival or reduce the severity of the disease?; do these have any effect on the admission to the ICU or the duration of hospital stay, admission costs, the duration of school absence, etc.?

One of the objectives of the Quality Plan for the National Health System is to ensure that health care is of the highest quality[39]. The current management models (EFQM, ISO 9000) include as a requirement: process management. Process management is a tool that analyses the various components that intervene in the delivery of healthcare, to sort the different workflows and integrate the same knowledge, taking into account the expectations of citizens and professionals, and trying to reduce the variability of the proceedings[40]. Process mapping is its graphical representation.

The Fundación Hospital Son Llàtzer designed in 2005 a computer protocol on integrated management of sepsis (PIMIS) in adults. Its implementation has resulted in a decrease in both hospital mortality in severe sepsis (11.4%) and septic shock (5.4%), and in a clear decrease in the length of hospital stays and economic cost associated[41].

Likewise, Menendez *et al*. have demonstrated the association between adequate compliance with the guidelines for the management of community-acquired pneumonia and improved

patient prognosis, reducing treatment failures and mortality[42]. Since the IMD is a situation that may initially appear before a number of different areas of health care, it seems necessary to try to identify whether adherence to relevant protocols can reduce the possible variability in medical practice and positively influence the outcomes for these patients.

The SIGN CPG proposes that protocols developed locally should ensure that the patient with IMD has timely access, adequate care and supervision, and take into account local services and location[6].	CPG Expert opinion 4
A study carried out in Australia reviewed the medical records of 24 patients with the aim of identifying improvement areas in the management of IMD, regarding the collection of information and the procedures performed on patients, such as sampling. The data collected in the anamnesis and the examination were recorded in 83% of medical records. 22.7% did not collect information on the physical examination of specific signs of IMD. Finally, sampling was inappropriate in one of the two cases with IMD, which required no admission to hospital[43].	Case series 3
A study in Spain reviewed 99 medical records to assess the appropriateness of care for patients (> 14 years) diagnosed with meningitis (bacterial and viral). Process indicators, treatment, and results selected from the CPG were used. In this study, prior antibiotic treatment was administered to 94% of cases, and cell count and Gram stain was performed in 99% and 95% of patients, respectively. The following process and outcome indicators showed a compliance of < 75%: description of the duration of symptoms, performance of blood culture (73.7%), simultaneous determination of glucose in serum and CSF, fundus examination, outlet pressure of CSF, appropriate use of CT and appropriate treatment[44].	Case series 3

The evidence identified for this question, scarce and of poor methodological quality, refers to the need to have the resources to conduct periodic reviews of medical records to identify areas for healthcare improvement.

The study by Callegaro *et al*.[45] investigating the implementation of a CPG for febrile seizures in the emergency units of two hospitals, an Italian and French one, has been excluded because no cases of IMD were diagnosed during the period analysed. The authors concluded that the implementation of guidance on febrile seizures in two emergency units in two different European countries changed the clinical management of patients, providing more comfort and improving the quality of healthcare.

Summary of evidence

4	Protocols that take into account local and geographic services should guarantee urgent access to adequate care and supervision of patients with IMD[6].
3	83% (20/24) of the medical records of patients with IMD contain data of the anamnesis and physical examination. 22.7% (5/22) contain no information about the presence or absence of specific signs of IMD[43].
3	Process and treatment indicators of meningitis in patients over 14 years old show an adequate microbiology and biochemical LCR study. Blood cultures and fundus were underutilized, whereas the CT was overused. The treatment adapts to the protocols in just over half of the bacterial meningitis[44].

Recommendations

D	It is recommended to develop tools locally (clinical pathways, process maps, interdisciplinary agreements) to facilitate access and care of patients with IMD, taking into account the geography and the services available.
D	A periodic revision of the medical records of patients with IMD is recommended to identify avoidable situations and achieve optimal healthcare.

7. Hospital management of IMD

7.1. Antibiotic Treatment

Question to answer:

- What antibiotic regimen should be used to treat bacterial meningitis or confirmed meningococcal septicaemia?
- In patients with IMD, is a short treatment (≤ 7 days) as effective or more and as safe as or more to than a prolonged treatment (> 7 days) to maintain or increase the cure rate of the disease and maintain or reduce the number of sequelae?

In patients with suspected IMD, it is primary to start empirical antibiotic treatment. The diagnosis is confirmed by isolation of the meningococcus or detection of its DNA in their CSF, blood or other normally sterile places. Antibiotic sensitivity testing may, if necessary, change the type of antibiotic to a more effectively one and adapt the dosage and duration of the treatment. Given the drawbacks that can arise due to the administration of a treatment lasting more than seven days, the noncompliance of the guidelines by the patient, resistance, or super-infection by other microorganisms, it is necessary to try to identify the effectiveness of short treatment guidelines (≤ 7 days).

The antibiotics proposed by the NICE CPG for the treatment of confirmed IMD are: ceftriaxone, cefotaxime and benzylpenicillin[5]. The guide includes a clinical trial conducted in Turkey, which compares hospital administration of intravenous ceftriaxone for 4 days (single daily dose) versus penicillin G for 5 days (6 times a day) in a sample of 42 patients with IMD from 1 month to 12 years of age. No significant differences were found between the groups in terms of mortality rates. Necrotic lesions appear on the skin of patients treated with intravenous penicillin G (p <0.05)[5].	CPG RCT 1-
The SIGN CPG recommends that the duration of antibiotic treatment for IMD last for 7 days[6].	CPG Expert opinion 4

The NICE CPG identifies no clinical trials to investigate the optimal time for administration of the antibiotics used in the treatment of IMD. Therefore, it includes bacterial meningitis studies of other etiologies, as an un-blinded clinical trial conducted in India, that compared the administration of ceftriaxone for 7 days (2 times a day) versus 10 days in 73 patients aged between 3 months and 12 years old of which 38% had confirmed meningitis caused by *Haemophilus influenzae, S. pneumoniae* or *N. meningitidis*. There were no statistically significant differences in the clinical response and in the proportion of neurological sequelae during the month following the start of the treatment. The duration of hospital stay was significantly shorter in the group receiving ceftriaxone for 7 days ($p < 0.05$)[5].

CPG RCT
1+

The NICE CPG includes a quasi-randomized clinical trial comparing a regimen of ceftriaxone for 4 days against an administration for 7 days on a sample of 102 paediatric patients older than 3 months with bacterial meningitis (13 cases with confirmed meningococcal meningitis). No differences were found between the groups regarding the proportion of patients with fever 5 to 7 days after starting the treatment ($p > 0.005$), the rate of neurologic sequelae ($p = 0.39$) or hearing loss after one month and 3 months ($p = 0.49$)[5].

CPG RCT
1-

A multicentre study carried out in 5 countries (Bangladesh, Egypt, Malawi, Pakistan and Vietnam) compared the parenteral administration of 80-100 mg/kg of a single daily dose of ceftriaxone for 5 days (496 patients) to a 10-day regimen duration (508 patients) in the paediatric population (aged between 2 months to 12 years) with purulent meningitis *H influenzae*, pneumococcus or meningococcus. The RCT found no significant differences between both groups regarding the following variables: mortality, hearing loss, visual and neurological deficit[46].

RCT
1+

A study, conducted in Angola, investigates the effect of initial slow infusion of beta-lactams and paracetamol on the prognosis of bacterial meningitis in childhood. During the first 24 hours of treatment, the administration of cefotaxime continuous infusion (two infusions of 125 mg/kg) did not show any statistically significant differences compared to the bolus administration of cefotaxime (250 mg/kg every 6 hours) in relation to the following variables[47]:

RCT
1+

Mortality or severe neurologic sequelae: cefotaxime infusion plus oral paracetamol (OR 0.97, 95% IC 0.64 to 1.47); cefotaxime infusion plus oral placebo (OR 1.09, 95% CI 0.72 to 1.66), cefotaxime oral bolus plus placebo (OR 1.20, 95% CI 0.79 to 1.81).

Deafness: cefotaxime infusion plus oral paracetamol (OR 1.05, 95% CI 0.45 to 2.48); cefotaxime infusion plus oral placebo (OR 0.95, 95% CI 0.39 to 2.32); cefotaxime oral bolus plus placebo (OR 0.92, 95% CI 0.37 to 2.29).

Mortality or any sequel: cefotaxime infusion plus oral paracetamol (OR 1.06, 95% CI 0.62 to 1.83); cefotaxime infusion plus oral placebo (OR 0.81, 95% CI 0.48 to 1.37), cefotaxime oral bolus plus placebo (OR 0.98, 95% CI 0.57 to 1.69).

Table 4. Dose and dose regimen of cefotaxime and ceftriaxone in patients with IMD

Antibiotic	Dose	Fractions/day
Cefotaxime IV	100 mg/kg/day (200-300 if there is meningitis)	4 doses
Ceftriaxone IV or IM	50 mg/kg/day (100 if there is meningitis and IV, not to exceed 4 g / day)	2 doses

Adapted from "*Sepsis grave. Proceso asistencial integrado*" by de la Torre MV *et al.*[40]

In formulating recommendations, the GDG has taken into account the consistency between the different studies, their applicability and the possibility of generalising the findings and their clinical relevance. The availability of effective antibiotics against *N. meningitidis* (penicillin, cefotaxime and ceftriaxone) is universal in our NHS, but it must be noted that, as discussed in section 6.1, the use of penicillin to treat a confirmed IMD within our environment would require a prior antibiogram

None of the identified studies observed differences in terms of the outcome with diverse duration of the antibiotic treatment (<7 days or ≥ 7 days). However, since there were no high-quality studies on the optimal duration of the antibiotic treatment for IMD and the external validity of the evidence found may be compromised because these are trials performed on patients with bacterial meningitis[5,46], the GDG saw no reason to change the current regime of 7 days of antibiotic treatment.

The developers of the NICE CPG performed a study on cost-effectiveness (for suspected bacterial meningitis or IMD) by comparing penicillin, cefotaxime and ceftriaxone, and concluded that for patients weighing 37 kg or less, ceftriaxone was the cheapest option; for patients between 37 kg and 51 kg, penicillin and ceftriaxone had similar costs and, for patients weighing more than 51 kg, the administration of penicillin was the cheapest option. They found that, for patients weighing 30 kg or less, penicillin was the most expensive option. Cefotaxime is the antibiotic most used in our environment; according to the NICE CPG an option with an average cost when compared to penicillin and ceftriaxone[5].

The systematic review conducted by Gaudio *et al.*[48], has been excluded from the body of evidence as it has significant limitations regarding literature search and it does not evaluate the quality of the identified guidelines.

Summary of evidence

1-	No significant differences were observed regarding mortality when administering intravenous ceftriaxone for 4 days (single daily dose) or intravenous penicillin G for 5 days (6 times a day) to patients with MDI aged between 1 month and 12 years old. More necrotic lesions were observed in the treated skin with intravenous penicillin G ($p < 0.05$)[5].

4	Experts suggest 7[6] days as the optimal duration for the treatment of confirmed IMD.
1+	When comparing the administration of ceftriaxone for 7 days (twice daily) with ceftriaxone for 10 days, in patients with bacterial meningitis, no statistically significant differences were observed either in the clinical response or in the proportion of neurological sequelae one month after the beginning of the treatment. The duration of hospital stay is shorter in the group receiving ceftriaxone for 7 days ($p<0.05$)[5].
1-	Patients older than 3 months of age with bacterial meningitis treated with ceftriaxone for 4 days did not show marked differences from those treated with ceftriaxone for 7 days, regarding the presence of fever 5 to 7 days after starting the antibiotic treatment, the rate of neurological sequelae or hearing loss after one and three months[5].
1+	In paediatric patients (aged between 2 months and 12 years old) with purulent meningitis *H. influenzae*, pneumococcus or meningococcus, the administration for 5 or 10 days of parenteral ceftriaxone (80-100 mg/kg in a single daily dose) showed no statistically significant differences on the following variables: mortality, hearing loss, visual and neurological deficit[46].
1+	In paediatric patients (aged between 2 months and 12 years old) with purulent meningitis H. influenzae, pneumococcus or meningococcus, the administration for 5 or 10 days of parenteral ceftriaxone (80-100 mg / kg in a single daily dose) showed no statistically significant differences on the following variables: mortality, hearing loss, visual and neurological deficit[46].

Recommendations

B	First-line antibiotics for the treatment of confirmed IMD are intravenous ceftriaxone every 12 hours for a total of 7 days, or cefotaxime, every 6 hours for a total of 7 days.

7.2. Sampling for microbiological diagnosis

Question to answer:

- In patients with suspected IMD treated at a hospital emergency unit, should the antibiotic treatment start immediately or should it start after the realization of the lumbar puncture and blood culture?

The clinical suspicion of IMD requires urgent decisions, sometimes with the uncertainty that some of them may negatively alter the course of the disease. On the one hand, empirical antibiotic treatment should be initiated as quickly as possible, and secondly, giving antibiotics before taking a sample of blood or CSF reduces the possibility of isolating *N. meningitidis* and therefore confirm the diagnosis of IMD. Determining what the best tool of intervention is for the patient with suspected IMD is the main aim of this question.

The development group of the SIGN CPG recommended the administration of parenteral antibiotics as soon as there is any suspicion on the diagnosis of IMD and that the administration is not delayed by the investigations that are under way[6].	Expert opinion CPG 4
A study published in 1972 investigated whether antibiotic treatment before taking samples may affect the results of microbiological diagnosis and modify the patient's prognosis, in a sample of 135 paediatric patients (between 1 month and 15 years old) diagnosed with bacterial meningitis. The bacteria *N. meningitidis* was isolated in 3% of the 60 patients who received prior antibiotic and 7% of the 75 patients who did not. The proportion of smear and/or positive CSF culture was higher in the group that received no antibiotic treatment (84% and 95%, compared to 68.4% and 67.8%, respectively). Blood cultures were positive in 50% of cases in both groups. The 4 deaths occurred in the group that received no prior antibiotic treatment[49].	Cohort study 2+

The possibility of generalisation of the study results just mentioned[49] may be compromised as it was carried out 40 years ago, which explains that the intervention (antibiotic treatment) does not correspond to what is currently indicated. In addition, the sample differs from the target population of the guide, as it is exclusively paediatric patients with acute bacterial meningitis; meningococcal sepsis is excluded.

Summary of evidence

2+	The probability of performing the etiologic diagnosis of acute bacterial meningitis by means of a smear and/or culture of CSF is greater if the patient has not received antibiotics before the lumbar puncture[49].
4	Samples should be collected as soon as possible after establishing the clinical suspicion and preferably prior to the start of the antimicrobial treatment. The sample collection must not delay the beginning of the antibiotic treatment[6].

Recommendations

D	In a hospital emergency unit, when suspecting a case of IMD, obtaining samples from the patient for further confirmation of the diagnosis should not delay the beginning of the empirical antibiotic treatment.
√	Blood cultures should be performed as soon as possible but should not delay treatment.

7.3. Indications for lumbar puncture in IMD

Questions to answer:

- In patients with suspected IMD, does the lumbar puncture (early/late), affect the early/late onset of the specific treatment, the final diagnose, as well as morbidity and mortality rates?
- Among paediatric population less than three months of age with bacterial meningitis, should a control lumbar puncture be done before stopping the antibiotic treatment?

The appropriateness of performing a lumbar puncture (LP) to all paediatric patients who come to an emergency unit for febrile seizure has been addressed in numerous studies[50-53] that either reiterate an unnecessary routine use[50-52] or advocate its realization based on the age group the patient belongs to[53].

When suspecting an infectious meningeal picture, a lumbar puncture must be performed to confirm the diagnosis. However, discussions arise regarding the need for puncture in suspected meningococcal sepsis without clinical signs of meningitis because it can imply a significant delay in the start of the treatment, it contributes little to the diagnosis in very obvious cases with fever and generalized purpura, and may cause a significant deterioration in severely ill patients[6].

This section presents the usefulness of the lumbar puncture to ensure the effectiveness of the treatment of bacterial meningitis in patients less than 3 months. Overall, there has been a recurrence of meningitis ranging from 1% to 3% of infants after having followed an adequate treatment[54]. Document the sterilization of CSF can increase the chances of success of the treatment in these patients. Some paediatricians have adopted the practice of performing a lumbar puncture during the treatment or when finishing it[5]. When addressing this issue it is important to note that the bacteria that most often cause meningitis in neonates (≤ 28 days) are as follows: *Streptococcus agalactiae* (or ß-haemolytic streptococcus group B), *L. monocytogenes*, and *Escherichia coli*. These bacteria are also responsible for sepsis or meningitis in patients ≥ 28 days hospitalized for being underweight or preterm. Infection by *N. meningitidis* is a rare cause of meningitis or sepsis during the neonatal period[55].

According to the SIGN CPG, the lumbar puncture in patients with clinical meningitis without purpura can help to make the diagnosis and to ensure that the correct antibiotic treatment and for the appropriate time is being administered. The CSF examination by microscopy, culture and PCR is important when providing etiologic information, especially in the absence of the typical characteristics of the IMD. The guide used six case series and a systematic review of observational studies[6] as a source of evidence.	SR of observational studies 2+ CPG Case series 3
The retrospective study of a series of cases with fever (rectal temperature ≥ 38 ° C) and bulging fontanelle, aged between 3 and 11 months who underwent lumbar puncture obtained as a result 27.7% (42/153) of patients with CSF pleocytosis, of which only one had bacterial meningitis (due to *S. pneumoniae*)[56].	Case series 3
The only scientific evidence found about the need for a lumbar puncture to verify CSF sterilization comes from the NICE CPG. A review of medical records of 27 patients (<2 years, 9 of them infants) with recurrence or relapse of bacterial meningitis concludes that neither the initial CSF findings nor subsequent follow-up can predict a recurrence or relapse of bacterial meningitis[5].	CPG Case series 3
A review of 21 medical records of infants with meningitis due to *S. agalactiae* observed that 72 hours after starting the antibiotic treatment, all samples tested (n = 6) were negative; between 24 and 72 hours, 3 of the 4 samples tested were negative; and of 5 samples tested within 24 hours, none was negative[5].	CPG Case series 3

The GDG decided not consider studies focusing on paediatric population who go to the emergency unit due to febrile seizures and who undergo a lumbar puncture because it believes that the results are not generalizable to the paediatric population with suspected IMD.

On the other hand, the NICE addresses the repeated performance of the lumbar puncture to ensure treatment effectiveness exclusively with studies conducted in neonates (≤ 28 days) born after the 37th week of gestation (term). In principle, neonatal meningitis is not among the targets of the guide because the aetiology and pathogenesis are different. However, due to the lack of studies in paediatric patients not previously hospitalized aged between one and three months, the GDG has seen appropriate to extrapolate the results of the NICE CPG as indirect scientific evidence.

Summary of evidence

2+/ 3	The analysis of CSF can provide essential information about the etiology of the disease, especially in patients without characteristic signs of IMD and to corroborate the choice and duration of the antibiotic treatment[6].
3	It is not possible to predict the recurrence or relapse of bacterial meningitis in patients < 2 years from the initial evaluation or the re-evaluation of CSF[5].

Recommendations

√	The lumbar puncture is not recommended in the initial evaluation for suspected IMD with features of septicaemia. The late realization of the lumbar puncture may be considered if the diagnosis remains uncertain or there is inadequate clinical progression and no contraindications.
C	Lumbar puncture should be performed in patients with clinical meningitis without septicemic features (purpura) if there are no contraindications.
D	The LCR will be sent to the laboratory for microscopy, culture and PCR.
D	In paediatric patients who are clinically well and without evidence of bacterial disease, it is reasonable to observe the patient and defer the realization of the lumbar puncture.
√	It is advisable to repeat the lumbar puncture in paediatric patients aged between 1 and 3 months who have not been previously hospitalized in the following circumstances: – Presence of persistent or recurrent fever – Deterioration of the clinical condition – New clinical findings (especially neurological) or persistently altered inflammatory reactants
√	It is not advisable to perform lumbar puncture to assess the success of treatment in paediatric patients aged between 1 and 3 months not previously hospitalized in the following circumstances: – In the case of patients, still receiving adequate antibiotic treatment against the causative agent, and whose clinical outcome is still good. – Before stopping antibiotic treatment if clinical response is good.

7.4. Early supportive therapy

Question to answer:

- In patients with suspected IMD, do the following treatments reduce mortality and morbidity?
  - Corticosteroid Therapy
  - Intravenous fluids to debate: colloid / crystalloid (Hartmann normal saline, Ringer's lactate), fresh frozen plasma (FFP), artificial colloids.
  - Resuscitation (oxygen, airway care and circulatory system).

Treatment of IMD should be performed in the hospital with intravenous antibiotics and the supportive care required according to the degree of clinical compromise. Sepsis is a time-dependent disease, defined as one in which the diagnostic or therapeutic delay negatively affects the evolution of the process. Classically, resuscitative measures in the first six hours are included in the concept of early treatment, after recognition or suspicion of the status of sepsis or septic shock, designed to restore cardiovascular stability (normalise the mental status, capillary refill < 2 seconds, palpable pulses with normal blood pressure and heart rate for the patient's age), normalise oxygenation and ventilation and correct critical metabolic alterations[57].

In case of cardiocirculatory failure, the intravascular volume resuscitation is crucial to prevent tissue and organ damage. It is often necessary to associate catecholamines to maintain cardiac output. The questions deals with the effectiveness of initial support measures, particularly if the aggressive treatment with fluids and catecholamines and respiratory support with opening of the airway, ventilation or intubation, directly affect the probability of survival of paediatric patients with IMD and signs of severe sepsis or septic shock.

The question is also investigating the benefit of the hormone replacement therapy in patients with IMD and severe sepsis. The physiological rise of corticosteroids (after a hypothalamic-pituitary activation by lymphokines) plays an important role in the ability the body has to deal with stressful situations, such as severe sepsis or septic shock. Besides maintaining the vascular tone and increasing cardiac output and blood pressure, they modulate the systemic inflammatory response. These effects justify their therapeutic use in patients with severe sepsis, however, the evidence for their effectiveness in the literature are scarce and contradictory, and even lead to discourage its use. Moreover, in septic shock associated with IMD, primary adrenal insufficiency may occur due to acute haemorrhage of the adrenal glands by coagulopathy or, less frequently, by ischemia or other mechanisms[58]. Reduced levels of cortisol associated with elevated ACTH levels have been associated with increased mortality in paediatric patients with IMD[5].

The NICE CPG addresses the question in a disaggregated way, highlighting the role of corticosteroids, intravenous fluid resuscitation and catecholamine and maintaining airway patency. The development group for the NICE CPG identified high quality studies for some of the interventions examined; low quality studies for most interventions, and in some cases found no studies. Following the NICE CPG, two studies on the use of corticosteroids were identified: one is a high quality systematic review[59] and the other is a clinical trial[60], which due to its low methodological quality and to its analysis on surrogate variables, has not been taken into account when answering this question.

Studies described in the NICE CPG with samples of paediatric patients, who as well as undergoing the required baseline in question, had other comorbidities, such as malaria or dengue were not taken into account either. However, they did consider studies with adult patients used as a source of indirect evidence.

7.4.1 Corticosteroids

The main variables on which information was collected were as follows: mortality, hearing loss, neurological damage and adverse effects of interventions. The first two reviews and a randomized clinical trial on the effects of corticosteroids in patients with bacterial meningitis[6,59] and then a review on the same subject, but in adult patients with severe sepsis or septic shock were presented. No evidence was found on the use of corticosteroids among paediatric and young patients with meningococcal septicaemia, and the studies identified for cases of sepsis or septic shock are of low quality.

A systematic review included in the NICE CPG identified 20 randomized clinical trials (RCTs) involving 2,750 patients of all ages with acute bacterial meningitis (2,074 patients < 16 years). It shows the results of the child population in developed countries (1,037 cases). Of these, approximately 61% had meningitis *H. influenzae* type B, 16.5% had pneumococcal meningitis, and 14%, meningococcal meningitis. These compared the intravenous administration of dexamethasone (0.4 mg/kg/day to 1.5 mg/kg/day for 2 to 4 days) or intravenous methylprednisolone for 3 days, versus placebo or no intervention. The results of the meta-analysis are as follows:

CPG SR of RCT
1 ++

- Mortality (11 RCTs, 1,037 cases): there is no appreciable beneficial effect in patients who were administered corticosteroids and antibiotics (RR 1.4, 95% CI 0.59 to 3.33, $p = 0.45$).

- Severe hearing loss (10 RCTs, 910 cases): there is a significantly reduced risk for severe hearing loss (bilateral hearing loss > 60 dB or requiring bilateral hearing aid) in patients who were administered corticosteroids and antibiotics (RR 0.32, 95% CI 0.18-0.57, $p < 0.0001$).

CPG SR of RCT
1++

- Neurologic sequelae (focal neurologic deficit, epilepsy with no previous symptoms, severe ataxia and severe alterations of memory or concentration): in the short-term (5 RCTs, 354 cases), no statistically significant differences were observed. In the long term (8 RCTs, 707 patients), there were statistically significant differences, with a major reduction of risk in patients treated with corticosteroids and antibiotics (RR 0.62, 95% IC 0.39 to 0.98 $p = 0.04$).
- Adverse effects (gastrointestinal bleeding, herpes zoster, herpes simplex, fungal infections or high fever): no significant increase was observed in any of the adverse effects already mentioned ($p = 0.98$).

This same review investigated the outcome depending on the time in which the corticosteroid is administered. When the corticosteroid is administered before the antibiotic or with the first dose of antibiotics, the risk of late neurological sequelae is reduced compared with controls (RR 0.48, 95% CI 0.25-0.92, $p = 0.03$). This beneficial effect does not occur if the corticosteroid is administered after the first dose of antibiotic. Regardless of the time of administration, the corticosteroid is associated with a reduced risk of severe hearing loss: early administration of corticosteroid (4 RCTs, 325 cases), RR 0.36 (95% IC 0.15 to 0.87), late administration of corticosteroid (5 RCTs, 501 cases), RR 0.29 (95% CI 0.14 to 0.63)[5].

An RCT conducted in six centres in Latin America and which has been included in the NICE CPG compared the treatment with intravenous dexamethasone (0.15 mg/kg/6h for 48 hours) versus placebo in 654 patients (aged between 2 months to 16 years) with bacterial meningitis. No significant differences were observed in terms of mortality (OR 0.82, 95% CI 0.45 to 1.49, $p = 0.509$), severe hearing loss (OR 0.79, 95% CI 0.33 to 1.91, $p = 0.604$) or risk of neurological sequelae (OR 0.48, 95% 0.21 1.07, $p = 0.072$)[5].

CPG RCT
1+

A systematic review[59] (24 studies) compared the adjuvant treatment with oral or intravenous corticosteroids (group of 2,024 patients) versus placebo (group of 2017 patients) in patients with bacterial meningitis of all ages. The results show that the use of corticosteroids reduced significantly the risk of severe hearing loss (RR 0.67, 95% CI 0.51 to 0.88), and the overall risk of hearing loss (RR 0.76, 95 % CI 0.64 to 0.89), but not the risk of neurological sequelae in the short (RR 0.83, 95% CI 0.69 to 1.00) or long term (RR 0.90, 95% CI 0.74 to 1.10). Corticosteroids do not significantly influence the risk of death (RR 0.92, 95% CI 0.82 to 1.04). Subgroups of patients with meningococcal meningitis (RR 0.71, 95% CI 0.35 to 1.46) and < 16 years (RR 0.95, 95% CI 0.78 to 1.14) also showed no significant differences in terms of mortality.

The moment when the corticosteroid is administered does not significantly influence the risk of death, severe hearing loss or short-term neurological sequelae. On the contrary, it seems that giving corticosteroid either at an early stage (before the antibiotic or with the first dose) or later (after the first dose of antibiotic), significantly reduces the overall hearing loss (RR 0.82, 95% CI 0.71 to 0.94 and RR 0.62, 95% CI 0.43 to 0.89, respectively)[59].

SR of RCT
1+

A systematic review included in the NICE CPG comprises 16 trials involving 2,063 patients with severe sepsis and septic shock, of which 207 (10%) were paediatric patients. The authors proposed a subgroup analysis evaluating different doses of corticosteroids due to the heterogeneity of the studies. The meta-analysis of 5 RCTs (involving 465 patients) showed that the use of corticosteroids for long periods of time at low doses (≤ 300 mg / day of hydrocortisone or equivalent for ≥ 5 days) in adults with catecholamine-dependent septic shock, significantly reduces mortality after 28 days (RR 0.80, 95% CI 0.67 to 0.95, $p = 0,01$). The review found no significant differences regarding mortality in patients receiving a high dose of corticosteroids[5] during a short period of time.

CPG SR of RCT
1++

A subsequent multicentre study, involving 499 adult patients with catecholamine-dependent septic shock, found no significant differences regarding mortality after 28 days between patients receiving low doses of hydrocortisone for a long period of time and patients who received placebo (RR 1.09, 95% CI 0.84 to 1.41, $p = 0.51$). The administration of hydrocortisone was associated with an increased risk of new episodes of sepsis or septic shock (OR 1.37, 95% CI 1.05 to 1.79)[5].

CPG RCT
1++

According to the GDG of the NICE CPG, the subgroup of paediatric patients with IMD and catecholamine-resistant septic shock may benefit from the use of low-dose corticosteroids[5].	CPG Expert opinion 4

7.4.2. Intravenous fluids

In paediatric patients with bacterial meningitis, no evidence has been identified to suggest the optimal volume of fluid for initial treatment of paediatric patients with IMD.

No evidence was found to determine the optimal volume of fluid for initial treatment of paediatric patients with bacterial meningitis. According to a systematic review included in the NICE CPG, in environments with high mortality and delayed access to health care (developing countries), fluid restriction (60-65% of the maintenance volume) appears to increase the risk of neurological sequelae. In paediatric patients with adequate nutritional status, there are no statistically significant differences in mortality or neurologic complications[5].	CPG SR of RCT 1+
The fluid-induced hyponatremia in patients under 18 years of age with bacterial meningitis was not statistically significantly associated with side effects[5].	CPG Case series 3

7.4.3. Resuscitation techniques: respiratory and circulatory support

No studies have been identified which establish the indications for resuscitation fluids or initiation of treatment with catecholamines. Likewise, no high quality studies have been found that determine what the fluids of choice for resuscitation in paediatric patients with IMD are.

An observational study included in the NICE CPG stated that insufficient administration of intravenous fluids and catecholamines during the first 24 hours is associated with an increased risk of death in paediatric patients with IMD and associated circulatory failure[5].	CPG Case-control studies 2++
In a retrospective study, also included in the NICE CPG, a rapid reversal of the shock by intravenous fluids and catecholamines is associated with lower mortality in paediatric patients with sepsis[5].	CPG Cohort study 2-
An RCT conducted in India, which compares the effectiveness of crystalloid (0.9% saline) versus colloids (Haemaccel™) showed no statistically significant differences regarding the ability to restore the circulating volume of paediatric patients with septic shock[5].	CPG RCT 1+

According to a multicentre RCT conducted in adult patients with severe sepsis, the administration of crystalloid (0.9% saline) or colloid (4% human albumin) showed no statistically significant differences in mortality after 28 days[5].

CPG RCT 1++

As no evidence was found, stating that one type of fluid was more effective and safer than another, the development group of the NICE CPG decided to carry out a cost-effectiveness study. The colloid solution was considerably more expensive (£ 34) than the crystalloid solution (£ 0.51). The crystalloid solution is considered more cost-effective than the colloid solution[5].

CPG Economic evaluation study

The NICE CPG has not identified studies evaluating the indications for endotracheal intubation in paediatric patients with bacterial meningitis or meningococcal septicaemia. Nor has it identified studies that provided results extrapolated to our population of interest to expand the search criteria to all age groups, patients with sepsis, septic shock or other type of bacterial meningitis[5].

When developing the recommendations on the use of corticosteroids, the GDG has taken into account, among other factors, the concordance of the results. The evidence suggests that the adjuvant corticosteroid treatment reduces the risk of severe hearing loss and long-term neurological sequelae in paediatric patients with bacterial meningitis. The RCT conducted in Latin America was the only one, which did not show statistically significant differences for the two variables mentioned. None of the studies found a statistically significant effect on mortality. The lack of conclusive evidence has also been taken into account to support a recommendation on what is the best time to start its administration. Finally, it is noteworthy that there were no studies evaluating the efficacy and safety of the use of corticosteroids in paediatric patients with sepsis or septic shock. Studies focusing on adult population show that the use of high doses of corticosteroids do not improve survival and may be detrimental.

Another factor that has been considered by the GDG is that in our setting, the interventions described are generally applicable to the corresponding units or services, being the identification of the patient with IMD the most important.

An update of a Cochrane systematic review included in the NICE CPG[61] has been identified, which introduces no new studies, and therefore, new evidence has not been taken into account.

Summary of evidence

1++/ 1+[5] 1+[59]	The adjuvant treatment with corticosteroids for bacterial meningitis in paediatric patients is not associated with a decreased risk of death or neurological sequelae in the short[5,59] or long-term[59].

1++[5]/ 1+[59]	The adjuvant treatment with corticosteroids for bacterial meningitis in paediatric patients (and adults) shows a significant beneficial effect on severe hearing loss (RR 0.32, 95% CI 0.18 to 0.57)[5] and (RR 0.67 CI 95% 0.51 to 0.88)[59] and overall risk of hearing loss (RR 0.76, 95% 0.64 to 0.89)[59].
1++	The use of corticosteroids in paediatric patients with bacterial meningitis shows a significant reduction in the risk of long-term neurological sequelae (RR 0.62, 95% 0.39 to 0.98)[5].
1++[5]/ 1+[59]	In paediatric patients (and adults) with bacterial meningitis, the administration of corticosteroids before the antibiotic, or with the first dose, reduces significantly the risk of late neurological sequelae (RR 0.48, 95% CI 0.25, 0.92)[5]. The observed beneficial effect on severe hearing loss 5 and overall hearing loss[59] is independent of the time of administration of corticosteroids.
1++	Studies on the use of long patterns of low-dose corticosteroids in adults with catecholamine-dependent septic shock show contradictory results regarding mortality after 28 days. The administration of hydrocortisone was associated with an increased risk of new episodes of sepsis or septic shock[5].
4	Paediatric patients with IMD and catecholamine-resistant septic shock may benefit from the use of low-dose corticosteroids[5].
1+	The optimal volume of fluid to be administered as initial therapy in paediatric patients with bacterial meningitis is unknown. In environments with high mortality and delayed access to health care, fluid restriction appears to increase the risk of neurological sequelae. In paediatric patients with adequate nutritional status, no statistically significant differences have been found between fluid restriction and maintenance volume in terms of mortality, complications or neurological sequelae[5].
3	The fluid-induced hyponatremia in patients under 18 years of age with bacterial meningitis has not been associated in a statistically significant way with the side effects[5].
2++	In paediatric patients with IMD and circulatory failure, the inadequate administration of intravenous fluids and catecholamines during the first 24 hours was associated with an increased risk of death[5].
2-	In paediatric patients with sepsis, the rapid reversal of shock with intravenous fluids and catecholamines was associated with lower mortality[5].
1+	The administration of crystalloids (0.9% saline) versus colloids (Haemaccel™) in paediatric patients with septic shock shows no statistically significant differences in terms of mortality[5].
1++	The administration of crystalloids (0.9% saline) or colloids (4% human albumin) in adult patients with severe sepsis shows no statistically significant difference in terms of mortality after 28 days[5].

	The colloid solution was more expensive (£ 34) than the crystalloid solution (£ 0.51); the crystalloid solution was considered more cost-effective than the colloid solution[5].

Recommendations

A	The adjuvant administration of a corticosteroid (dexamethasone intravenously at a dose of 0.15 mg/kg/dose up to 10 mg/dose, 4 times a day for 4 days) should be considered when there is a suspicion of bacterial meningitis or once it has been confirmed; it should be administered as soon as possible and it should not interfere with the administration of antibiotics and the transfer to a specialized centre.
B	Do not administer corticosteroids to paediatric patients with meningococcal septicaemia, except in cases of meningococcal septic shock resistant to catecholamine.
D	In patients with suspected or confirmed bacterial meningitis, the appearance of signs of shock, increased intracranial pressure and dehydration will be assessed.
D	The administration of fluids should not be restricted unless there is increased intracranial pressure or an increased secretion of antidiuretic hormone.
D	A volume of fluids should be administered and maintained to avoid hypoglycaemia and maintain the electrolyte balance.
D	Use enteral feeds as maintenance fluid if tolerated.
D	If it is necessary to maintain intravenous fluids, the use of isotonic fluids (0.9% sodium chloride with 5% glucose, or 0.9% sodium chloride with 5% dextrose) is recommended.
D	The administration of fluids and urine output should be monitored to ensure adequate hydration and prevent over-hydration.
D	Electrolytes and glucose should be monitored regularly (if intravenous liquids are administered at least once a day).
D	If there are signs of increased intracranial pressure or shock, it is recommended to start the emergency procedures relevant to these situations and discuss the management of fluids with a paediatric intensive care physician.
D	If there are signs of shock, give immediately 20 ml/kg of 0.9% sodium chloride in 5 to 10 minutes. Give the fluid intravenously or via an intraosseous route and reassess the patient immediately (see Table 5).
D	In self-ventilating children with suspected bacterial meningitis or confirmed meningococcal septicaemia, and signs of respiratory distress, the use of a facial mask is recommended to provide 15 litres of oxygen through a mask with reservoir (see Table 6). If there is a threat of loss of airway patency, airway opening manoeuvres should be applied; positive pressure ventilation through a mask ventilation bag and finally isolation of the airway.

Table 5 shows the suggested guidelines for the use of fluid therapy in paediatric patients with IMD.

Table 5. Management of paediatric patients with IMD: Intravenous fluids

If there are signs of shock, an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% in 5 to 10 minutes should be administered. Administer intravenously or via an intraosseous route and reassess the patient immediately afterwards.

If the signs of shock persist, immediately administer a second bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution in 5 to 10 minutes.

If the signs of shock still persist after the first 40 ml/kg:

- Immediately administer a third bolus of 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution in 5 to 10 minutes.
- Call for anaesthetic assistance for urgent tracheal intubation and mechanical ventilation.
- Start treatment with vasoactive drugs.
- It must be noted that some patients may require large volumes of fluid over a short period of time to restore their circulating volume.
- Giving further fluid boluses at 20 ml/kg of intravenous or intraosseous sodium chloride 0.9% or human albumin 4.5% solution in 5 to 10 minutes should be considered, based on clinical signs and appropriate laboratory investigations including urea and electrolytes.

Discuss further management with a paediatric intensive care physician.

If shock persists despite fluid resuscitation (more than 40 ml/kg) and the treatment with either intravenous adrenaline or intravenous noradrenaline or both, potential reasons (such as persistent acidosis, incorrect dilution, extravasation) should be considered and further management options should be discussed with a paediatric intensive care physician.

Use protocols for the administration of vasoactive agents in children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia.

Adapted from the NICE CPG (2010)[5]

Table 6 shows the suggested guidelines for the management of respiratory support in paediatric patients with IMD.

Table 6. Management of respiratory support in paediatric patients with IMD

A healthcare professional with expertise in paediatric airway management should undertake tracheal intubation.

It must be noted that children and young people with suspected or confirmed bacterial meningitis or meningococcal septicaemia are very ill and at grave risk of sudden deterioration during intubation. Anticipate aspiration, pulmonary oedema or worsening shock during intubation. Ensure that the patient is fasting from hospital admission and that the following elements are available before intubation:

- Facilities to administer fluid boluses
- Appropriate vasoactive drugs
- Access to a healthcare professional experienced in the management of critically ill paediatric patients

Tracheal intubation and mechanical ventilation should be undertaken for the following indications:

- Threatened (for example, loss of gag reflex), or actual loss of airway patency.
- The need for any form of assisted ventilation.
- Increased work of breathing.
- Hypoventilation or apnoea.
- Features of respiratory failure, including:
  - Irregular respiration (for example, Cheyne–Stokes breathing)
  - Hypoxia (PaO_2 less than 97.5 mmHg) or decreased oxygen saturations in air by pulsioximetry (Sat O2 < 92%)
  - Hypercapnia ($PaCO_2$ greater than 45 mmHg)
- Continuing shock following infusion of a total of 40 ml/kg of resuscitation fluid
- Signs of raised intracranial pressure
- Impaired mental status:
  - Reduced or fluctuating level of consciousness (Glasgow Coma Scale score less than 9 or a drop of 3 or more)
  - Moribund state
- Control of intractable seizures
- Need for stabilisation and management to allow brain imaging or transfer to the paediatric intensive care unit of another hospital

Use local or national protocols for intubation

Adapted from the NICE CPG (2010)[5].

7.5. Stabilization and transportation to a paediatric intensive care unit

Question to answer:

- Do specialized transport teams improve outcomes and reduce adverse incidents during the transport of patients with IMD at paediatric age?

Paediatric patients with IMD may evolve to a clinical instability, which requires an aggressive treatment approach and admission to a paediatric ICU. After resuscitation and before transferring the patient, the necessary steps (hemodynamic, respiratory, neurological manoeuvres) to stabilize the patient are to be taken. During transportation, the maintenance of the airway, mechanical ventilation, central lines and arterial venous, cardiac monitoring, etc. must be ensured. Transportation is a period of high risk and problems can occur, such as endotracheal tube obstruction, loss of venous line or secondary hemodynamic destabilization to movement. It is therefore essential that the transfer is performed by specific paediatric trained staff[62].

The NICE CPG collects evidence of two descriptive studies. The first was a prospective study, which concluded that a team specialized in the transport of paediatric patients, may stabilize the critically ill patient effectively and safely, with manoeuvres such as endotracheal intubation and re-intubation, central venous catheter insertion, arterial catheter, and administration of colloids and vasoactive drugs. It is argued that the *Paediatric Risk of Mortality Score* (PRISM) at admission of 51 critically ill paediatric patients (47% with IMD) was reduced in 28 patients and remained stable in 23 patients (average 1.0, range 0-24, p <0.001). During the stabilization and transfer, the PRISM was reduced in 34 patients, remained stable in 11 patients and increased in 6 patients (average 3.0, range -6 to 17, p <0.001)[5].

CPG Case series 3

The second was a retrospective study, which described an annual death probability decrease of 59% between 1992 and 1997, following the introduction of a transport team with paediatric specialists and an ICU specializing in the care of patients with IMD[5].

CPG Case series 3

A study on stress-induced shock, vibration and noise to which a critically ill neonate is exposed during emergency transport (ambulance and helicopter) was identified. The number of instantaneous accelerations and decelerations, vibration or shock was higher when transported in an ambulance. More noise, but more stability was observed when transported by helicopter, and a rate of twists and variations on the vertical angle without differences between both means of transport. The authors conclude that there is a significant exposure to physical stress by critical patients during transportation, although it was not possible to quantify changes in their physiological constants from data extracted from the study[63].

Case series 3

Summary of evidence

3	The medical transport by specialized paediatric teams is effective and safe[5].
3	The availability of a team specialized in the transport of paediatric patients and an ICU specialist in the care of paediatric patients with IMD is associated with a decline in mortality[5].
3	The critical patient is subjected to physical stress during transport, induced by instantaneous accelerations and decelerations, vibration or shock (ambulance), and noise (helicopter)[63].

Recommendations

D	In patients with suspected or confirmed diagnosis of IMD who require resuscitation and transfer to an ICU, it is recommended to inform the hospital or destination unit.
D	It is recommended that specialized transport units perform the transfer of patients with suspected or confirmed diagnosis of IMD to a reference centre.

8. Management of IMD in the ICU

8.1. Considerations before admission to an ICU

Question to answer:

- In patients with IMD requiring admission to the ICU, is there evidence that the time delays in consultation at a specialist centre or paediatric ICU affect the results (mortality and residual disability)?
- In patients with IMD requiring admission to the ICU, is there any evidence that the following factors affect the results?
  – Stabilisation and transport by a specialized paediatric team
  – Paediatric Intensive Care
  – Remote telephone support
  – Early referral and/or recovery (or quick resolution of the process)

The progressive clinical deterioration sometimes experienced by patients with IMD requires that they be treated in an ICU.

The evidence found in this regard is limited to three observational studies that rely on the recommendations of the SIGN CPG. Among the risk factors that might be associated with higher mortality in the management of paediatric patients with IMD, the following have been identified: the lack of a specialist in paediatric care in the emergency, anaesthesia and ICU units, and lack of specialist supervision for the first 24 hours[6].

CPG
Case series
3

In another study, patients with IMD increased their survival probability when being seen in a paediatric ICU (59% reduction in mortality per year, or annual trend OR 0.41, 95% IC, 0.27 to 0.62). In addition, early consultation with a paediatric ICU specialist helped to improve the prognosis in patients who required intensive care[6].

CPG
Case series
3

One study with a broader clinical spectrum, performed on critically ill paediatric patients, concluded that the cases admitted to a non-specialized centre had higher risk of death than those treated at a paediatric ICU (OR 2.09, 95% CI 1.37 to 3.19)[6].

CPG
Case-control study
2+

Summary of evidence

3	Risk factors potentially associated with increased mortality in the management of patients with IMD[6]: – Absence of a specialist in the paediatric emergency, anaesthesia and ICU units – Not seeing a specialist within 24 hours
3	Managing the patient in a paediatric ICU contributes to improving the prognosis and survival probability of patients requiring intensive care[6].
2+	Critically ill paediatric patients hospitalized in a non-specialised centre have a higher risk of death than those receiving care at a paediatric ICU[6].

Recommendations

D	Patients who arrive at the hospital emergency unit with suspected IMD should be examined and treated immediately by an experienced physician, preferably a paediatric specialist.
D	In patients with clinical progression of IMD, it is advisable to contact the ICU in the early stages.

8.2. Supportive therapy in the ICU

Question to answer:

- In patients requiring intensive care, is there evidence that the following interventions influence on mortality and morbidity?
  - Ventilation/airway management
  - Catecholamines
  - Invasive monitoring
  - Haemofiltration, continuous venovenous haemofiltration, plasmapheresis
  - ECMO (extracorporeal membrane oxygenation)
  - Mechanical Circulatory Support (hyperosmolar fluids)
  - Plasmafiltration
  - Corticosteroids, high-dose or physiological replacement
  - Invasive management of intracranial hypertension

Septic shock is a complex pathophysiological state characterized by circulatory failure. Its treatment focuses on aggressive volume resuscitation in the cardiocirculatory support by vasopressor and inotropic effects of catecholamines and the early mechanical ventilation, as well as aiming at the antibiotic treatment. Despite this approach, the monitoring and intensive care, mortality and

morbidity due to septic shock remain high among paediatric patients. A review conducted on 80 cases of IMD admitted to a paediatric ICU observed 35% of mortality due to septic shock[2-64].

The main aim of this question is to evaluate the effectiveness and safety of interventions mentioned in patients with IMD requiring admission to a paediatric ICU. Fluid resuscitation, management of the airway and ventilation, and the corticosteroid treatment in intensive care follow the principles in the initial support treatment and can be found in Chapter 7.4.

8.2.1. Catecholamines

When the following circumstances remain: hypotension, abnormal capillary refill, tachycardia or coldness of extremities despite aggressive volume contribution, there is a flid resistant shock (or refractory to fluid). In this phase, in addition to continuing with fluid intake, it is necessary to start the treatment with catecholamines (such as dopamine or dobutamine). If despite the treatment with dopamine or dobutamine no therapeutic goals are achieved, then this is a dopamine-dobutamine resistant shock that will require a treatment with epinephrine or norepinephrine to restore blood pressure. If there is no response, it is a case of a catecholamine resistant shock, and the administration of hydrocortisone will be assessed according to the risk of adrenal insufficiency[57].

Both of the CPGs assessed[5, 6] suggest that treatment with catecholamines should be started early in cases with IMD and fluid resistant shock. Not administering the necessary catecholamines required during the first 24 hours was independently associated with increased mortality rate (OR 23.7, 95% CI 2.6 to 213, $p = 0.005$) in patients with IMD and circulatory failure[5].	CPG Case-control study 2++
The SIGN CPG refers to the successful use of intravenous vasopressin (0.02 to 0.06 units/kg/h), or its analogues, in a small group of patients with catecholamine-resistant septic shock. The CPG warns that if these patients present hypoglycaemia and hyponatremia, absolute adrenal insufficiency and the administration of hydrocortisone administration[6] should be considered.	CPG Case series 3
A prospective study carried out in 9 Spanish paediatric ICUs evaluated the effect of terlipressin (0.02 μg/kg/4h up to 72 h) in the survival of 16 patients aged between 1 month and 13 years of age with catecholamine-resistant septic shock. 50% had meningococcal sepsis with purpura fulminans. Mean blood pressure within 30 minutes of the infusion of terlipressin increased from 50.5 (37 to 93) to 77 (42 to 100) mmHg (p <0.05). The infusion of noradrenaline after 24 hours of terlipressin decreased from 2 (1 to 4) to 1 (0.2 to 5) μg/kg/min (p <0.05). A total of 5/16 patients had ischemia possibly related to terlipressin. The study had significant limitations that affect its external validity. Terlipressin was administered according to the procedure of compassionate use of drugs to a very small number of extremely ill patients[65].	Case series 3

8.2.2. Invasive monitoring

Two retrospective observational studies that evaluated the clinical effectiveness, in terms of survival, invasive blood pressure monitoring (IBPM)[66] and intracranial pressure (ICP)[67], respectively were identified. The first included 46 paediatric patients with purpura fulminans and IBPM matched by age and PRISM (*Pediatric Risk of Mortality*) with 46 paediatric patients with purpura fulminans and blood pressure monitoring by the oscillometric method. The IBPM group came from the paediatric ICU of a French hospital; the control group from the paediatric ICU of a Belgian hospital. In 79% of cases, the meningococcus in blood was isolated. The mortality rate of the IBPM group was 19.5% (95% CI 8.1 to 30.9), similar to that observed in the control group (21.7%, 95% CI 9.8 to 33.6, $p = 0.8$). The rate of skin necrosis and members was identical in both groups (19.5%, 95% CI 8.1 to 30.9). The catheter complication rate was 17.5%, none of them serious[66]. The study has a moderate quality of evidence, the sample is small, which leads to inaccurate results on mortality, and there are confounding factors that were not controlled, such as the difference in the treatments carried out in each paediatric ICU.

Cohort study 2+

Odetola *et al*. analysed the data recorded in the *Kids' Inpatient Database* from the U.S.A. during the years 1997 and 2000. The authors found no statistically significant association between ICP monitoring and mortality in paediatric patients diagnosed with viral or fungal bacterial meningitis who required mechanical ventilation (OR 1.00, 95% CI 0.46 to 2.18, $p = 0, 99$)[67]. The risk of bias is moderate; the potential confounding factors were well controlled, but the interventions made to address the PIC, which vary from one hospital to another, were not taken into account. The external validity is seriously jeopardised, it is unknown if any case of meningococcal meningitis was included, and the technology used is obsolete.

Cohort study 2-

The SIGN CPG, based on expert opinion suggests the non-invasive monitoring of patients with shock responsive fluid and central venous access and invasive blood pressure monitoring in patients with fluid resistant shock[6].

The SIGN CPG found insufficient evidence, for or against, the following interventions in patients with septic shock: echocardiography, gastric tonometry, thermodilution catheter or intracranial pressure monitoring[6].

CPG Expert opinion 4

8.2.3 Haemofiltration

The continuous venovenous haemofiltration is a technique that allows cleaning circulating pro-inflammatory cytokines, enhancing hemodynamic stability and can avoid multiorgan failure. Best et al. achieved a 100% survival in relation to the early use of venovenous haemofiltration in 4 patients with purpura fulminans, which according to the *Glasgow Meningococcal Septicaemia Prognostic Score* (GMSPS), had a 75% risk of death[68]. The aim of the question asked is to know the role this vital support measure can play for patients with severe meningococcemia.

No studies were identified comparing the morbidity and mortality of paediatric patients with severe sepsis with or without renal replacement therapy. The SIGN CPG also found no controlled studies in paediatric patients with sepsis. According to a study in adults with septic shock, the high volume venovenous haemofiltration improves hemodynamic stability and reduces the need for catecholamines (statistically significant) and mortality (not statistically significant)[6].	CPG Case series 3

8.2.4. Extracorporeal membrane oxygenation (ECMO)

According to a study with a small number of patients included in the SIGN CPG, severe cases of IMD in which the main pathophysiologic alteration is acute lung injury or acute respiratory distress syndrome, these may benefit from extracorporeal membrane oxygenation (ECMO); however, the reduction in mortality does not extend to patients with refractory shock[6].	CPG Case series 3

No scientific evidence was found on the following interventions: plasmafiltration and invasive management of intracranial hypertension.

When developing the recommendations, the GDG has been aware that both CPGs[5,6] collect evidence from studies conducted in paediatric patients with sepsis or septic shock from other aetiologies, because of the scarcity of studies focusing on the IMD. For the same reason, the SIGN CPG[6] extrapolated the results of a study on the effectiveness of high volume venovenous haemofiltration performed in adults. The GDG also took into account that vasopressin is not marketed in Spain[57], and that the scientific evidence on terlipressin is limited to its compassionate use. The treatment of catecholamine-resistant septic shock is not among the approved indications in the data sheet of the drug.

Summary of evidence

1+/3/4	The catecholamines treatment should be started rapidly in patients with IMD and fluid resistant shock. The intervention may include supportive treatment with catecholamines, vasopressor or vasodilator according to the clinical disorder[6].

2++	In the case of patients with IMD and circulatory failure, the non-administration of catecholamines required during the first 24 hours is associated with an increased mortality[5].
3	Terlipressin is a potentially valid alternative rescue treatment for catecholamine-resistant septic shock in paediatric patients. It must be considered that, when associated with high doses of catecholamines, it entails the risk of excessive vasoconstriction and ischemia[65].
2+	Invasive blood pressure monitoring seems to have no effect on the mortality rate of paediatric patients with purpura fulminans. No differences were observed with the control group in the rates of skin and limb necrosis. The catheter complication rate is 17.5% (bleeding, hematoma, thrombosis, transient distal ischemia)[66].
2-	The mortality of patients with meningitis and mechanical ventilation was not statistically associated with the use of monitors to measure the ICP[67].
4	Experts suggest the use of non-invasive monitoring for patients with shock responsive to fluid and central venous access and invasive monitoring pressure for patients with fluid resistant shock[6].
3	The high-volume venovenoushaemofiltration in adults with septic shock improves hemodynamic stability, reduces the need of catecholamines (statistically significant) and reduces mortality (not statistically significant)[6].
3	The most severe cases in which acute lung injury or the acute respiratory distress syndrome prevail may benefit from extracorporeal membrane oxygenation, but the reduction in mortality does not extend to patients with refractory shock[6].

Recommendations

D	Catecholamines are recommended at an early stage to manage patients with fluid resistant meningococcal septic shock and the support with mechanical ventilation should be considered for these patients.
√	In patients with meningococcal septic shock resistant to catecholamine, intravenous terlipressin and titrated doses of corticosteroids are considered proper rescue measures.
D	Paediatric patients with meningococcal septic shock resistant to catecholamines could benefit from the use of terlipressin as a rescue therapy.
D	Non-invasive monitoring (ECG, blood pressure, temperature, oxygen saturation) of patients with fluid sensitive meningococcal septic shock is recommended. A central access (arterial or venous) will be channelled in cases of fluid resistant meningococcal septic.
√	Patients with acute respiratory distress syndrome secondary to IMD who do not respond to standard therapy may benefit from extracorporeal membrane oxygenation.
√	Patients with fluid resistant meningococcal septic shock, severe metabolic acidosis, acute or impending renal failure, and complex or problematic fluid balance, may benefit from continuous veno-venous haemofiltration.

8.3. Adjuvant therapies

Question to answer:

- In patients with IMD in the ICU, is there any evidence that the following hematologic and immunologic measures reduce mortality and morbidity?
  - Activated protein C and protein C
  - Immunoglobulins
  - Heparin
  - Fresh frozen plasma (FFP)
  - PG12
  - Tissue plasminogen activator (t-Pa) antagonists of the platelet activating factor (PAF), antithrombin III

Some patients with IMD develop septic shock with a major organ damage that can lead to death within hours. Advances in the understanding of the pathophysiology of sepsis have allowed the development of new therapies that claim to stop or limit the detrimental effect of physiological changes that accompany severe sepsis and septic shock. Host inflammatory response becomes excessive and uncontrolled, which triggers the mass production of inflammatory mediators in turn, induces the leukocyte-endothelial adhesion and the uncontrolled and excessive activation of coagulation, causing the clinical syndrome of disseminated intravascular coagulation (DIC). The purpose of this question is to know what is the clinical effectiveness and safety of anticoagulant therapy and the treatments aimed at modulating the inflammatory activity.

8.3.1. Coagulation

This section deals with whether the normalization of coagulation parameters improves the prognosis of severe meningococcal sepsis in patients with severe DIC. A disproportionate inflammatory reaction produces a marked decrease in the levels of protein C (PC), which, along with other mediators may lead to the formation of microthrombi, tissue perfusion and organ failure. Protein C has a potent antithrombotic, profibrinolytic and anti-inflammatory effect. A natural anticoagulant inactivates coagulation factors Va and VIIIa. Activated protein C is generated by the interaction of the thrombin and thrombomodulin protein C with the specific receptor on the surface of the endothelial cell.

Following the publication of the results of the PROWESS trial, the European Medicines Agency in 2002 approved the use of the recombinant human activated protein C, drotrecogin alpha activated (DrotAA) in adult patients with severe sepsis and high risk of death[69].

The use of other anticoagulant therapies in adults with severe sepsis (antithrombin-III, a tissue factor pathway inhibitor or TFPI) has shown no benefit, and has even been associated with an increased risk of bleeding[6].

The two CPGs[5,6] used discourage the use of activated protein C (APC) in patients with severe IMD. The SIGN CPG based its recommendation in an open clinical trial that compared the incidence of serious bleeding events in paediatric patients (30%) and adults (6.9%) with sepsis treated with APC[6].

The NICE CPG used as a source of evidence the RESOLVE study, a randomized clinical trial that evaluated the efficacy and safety of recombinant APC in 477 patients younger than 17 years with sepsis caused by *N. meningitidis* in 11% of cases. The authors found no significant differences in mortality after 28 days between recombinant APC and placebo (17.2% with recombinant APC versus 17.5% with placebo, RR 1.06, 95% CI 0.66 to 1.46, $p = 0.93$), although *post-hoc* analysis of subgroups showed a trend towards a reduction in mortality in patients with DIC (14% with recombinant APC versus 22% with placebo, $p = 0,05$). Patients receiving recombinant APC suffered more CNS haemorrhages than those who received placebo. The study was stopped early in an interim analysis[5].

CPG RCT 1+

Beyond the search period covered by the CPG, a retrospective and multicentric case series of 94 patients under 18 with purpura fulminans (in 80% of cases the meningococcus was isolated), who were treated with human not activated protein C concentrate (Ceprotin®, Baxter AG, Vienna, Austria) was identified. 77.7% of patients survived; 9.6% required grafting, and 5.3% suffered amputations. No serious adverse effects were observed. The authors reviewed the published data on the prognosis of purpura fulminans and concluded that activated protein C does not appear to improve survival and reduce amputations and dermoplastias in patients with purpura fulminans. The study has methodological limitations. The data come from the database of the company that markets the drug therefore there is the possibility of existing conflicts of interest[70].

Case series 3

8.3.2. Immunomodulators

Endotoxin is a central molecule in the pathophysiology of meningococcal sepsis. Its levels are directly related to the severity of the IMD and the release of inflammatory mediators. It can be captured by different serum proteins, such as bactericidal/permeability-increasing protein (BPI) which binds to the lipid A of endotoxin and neutralizes its biological effects. A recombinant form of the 21 amino acid BPI (rBPIP21) has been studied in paediatric patients with severe meningococcal septicaemia[5]. The anti-endotoxin antibodies (HA-1A) and anti-TNF monoclonal antibodies are other therapies designed to modulate the exaggerated inflammatory response.

The NICE CPG includes a phase III RCT from the year 2000 that evaluated the effects of rPBIP21 in paediatric patients with severe IMD. The study lacked sufficient statistical power to detect differences in mortality after 60 days (OR 1.31, 95% CI 0.62 to 2.74, $p = 0.48$)[5].	CPG RCT 1+
The SIGN CPG includes two systematic reviews in which the effect of intravenous immunoglobulin (IVIG) on mortality in sepsis and septic shock does not support its use in clinical practice. One is a Cochrane review that has been subsequently updated[71]. The review states as being an update from the year 2010, however, in the databases (MEDLINE, Cochrane) the quotation dates back to 2002 and is listed in the bibliography of this guide. The update is not included in the volume of evidence because, although it contains four studies conducted in the age group < 18 years, these do not change the meaning of the estimates obtained and the conclusions of the authors listed in the previous review.	CPG SR of RCT 1++

Concerning activated protein C, it must be noted that in November 2011 the European Medicines Agency withdrew the marketing authorization for DrotAA (Xigris®) or drotrecogin alpha (activated), motivated by the results of the clinical trial (PROWESS - shock) which the EMA required to the pharmaceutical company Eli Lilly to maintain such authorization. The trial found no significant clinical benefit in terms of survival of adult patients with septic shock and high risk of death[72].

There are no quality studies on paediatric use of antithrombin-III, tissue plasminogen activator (thrombolytic), fresh frozen plasma or PG12 (vasodilator and platelet aggregation inhibitor) in the treatment of coagulation disorders associated with IMD.

Due to manual research, a study from 1994[73] was identified on the effectiveness of heparin in preventing necrosis of fingers and limbs in patients with meningococcal purpura fulminans. The year of publication precedes the search period of the SIGN CPG, which found no evidence for the use of heparin in these patients. The study was excluded as evidence because its methodological quality is very low. No publications have been found after 1994 on the potential benefits of the use of heparin in patients with IMD. There are studies in previous years, especially in the seventies and eighties, including three RCTs 74-76 in which the authors found no difference in mortality between the group receiving heparin and the group that did not receive it. In some cases, the authors did observe a trend towards a favourable effect on the reduction of necrosis[76].

Summary of evidence

1+[5]	The incidence of serious bleeding events in paediatric patients with severe sepsis following a treatment with APC is higher than that observed in adults 6. Administering recombinant APC to paediatric patients with severe sepsis does not significantly reduce mortality[5].
3	No serious adverse effects associated to the administration of non-activated protein C in patients < 18 years with purpura fulminans have been observed. Apparently, the treatment with activated protein C did not reduce the number of deaths and the need of amputation and dermoplasty[70].
1+	No significant differences were observed in mortality in patients <17 years with severe IMD receiving rPBIP21and those receiving placebo[5].
1++	The analysis of the higher quality studies of two systematic reviews does not support the use of intravenous immunoglobulin in the treatment of severe sepsis[6].

Recommendations

A	The administration of activated C protein or recombinant bactericidal permeability increasing protein is not recommended for paediatric patients with severe IMD.
A	In case of severe sepsis, the use of an intravenous immunoglobulin treatment is not taken into consideration.

8.4. Surgical Management of IMD

Questions to answer:

- In patients with extensive skin affection, do compartment pressure control and fasciotomy reduce the number and extension of tissue necrosis, amputations and degree of residual disability?
- In patients with IMD and complications, what is more effective and safe to reduce tissue necrosis or prevent amputation or secondary infection: early surgical debridement or the conservative treatment?

Extremity amputations are a result of the serious sequelae of peripheral ischemia associated to IMD. Compartmental pressure monitoring in the acute phase of the disease and carrying out releasing incisions by fasciotomies before irreversible ischemic injuries occur, could improve the chances of preserving the limbs of these patients[77]. This approach is controversial: its usefulness is questioned in the presence of acute compartment syndrome and ischemia of the fingers or absence of peripheral pulses, since in these cases surgery shows that the deep tissues are not feasible. The occurrence of bleeding diathesis would contraindicate surgery because of the risk of bleeding, according to some authors[78].

It is difficult to establish the ideal time of surgical debridement of necrotic lesions. It is important to allow the necrosis plates to be completely delimited, which can take several weeks. Moreover, although conservative treatment can prevent excessive and inefficient amputation performed as an emergency measure, necrotic tissue promotes bacterial overgrowth, which increases the risk of infection and invasive sepsis[77,79].

The SIGN CPG found no studies that address this issue, and its recommendations are based on expert opinion. Compartment pressure monitoring during the first 24 hours can reduce muscle necrosis when extensive vascular compromise exists (peripheral oedema or confluent purpuric rash). When there is increased compartment pressure, fasciotomies can reduce the requirements of proximal amputation[6].	CPG Expert opinion 4
There is no consensus on the surgical management of necrotic lesions. Some authors recommend early debridement, while for others the best option is close monitoring of necrosis plates: see how they are defining and forming a scab and then performing debridement and escharotomy[6].	CPG Expert opinion 4
The SIGN CPG found no quality studies that support early approach against the conservative approach. Expert opinion considers that when a secondary infection appears, an urgent debridement should be performed[6].	CPG Expert opinion 4

A randomized clinical trial (RCT) evaluating the effectiveness of early microsurgical arthrolysis to reduce the number of amputations in paediatric patients with meningococcal sepsis was identified. The intervention includes fasciotomy along the main blood vessels to allow decompression, accompanied by the microsurgical release of the artery to restore circulation. The peripheral arteries of the limbs were explored every hour using a Doppler probe 8-MHz. In the absence of blood flow (ischemia) at some point, patients were randomly assigned to the experimental group (n = 7) or control group (n = 7), to which the intervention was not performed. In the experimental group, the amputation was avoided in 82% (37/45) of the fingers and 76% (38/50) of initially ischemic toes. In the control group, the percentages were 1.7% (1/60) and 1.8% (1/55), respectively. When comparing the level of ischemia with the level of amputation, all the patients who had undergone surgery experienced improvement in their upper and lower limbs, whereas no clinical improvement was observed in the upper limbs of any of the patients in the control group (p = 0.0006). Only one patient in the control group showed clinical improvement in the lower limbs (p = 0.005). The methodological quality of the study is low. The characteristics of the patients in both groups (intervention and control) in terms of the severity of ischemia secondary to meningococcal sepsis are unknown. The authors do not say whether the study has been approved by an ethics committee or has obtained the consent of parents[80].

RCT
1-

The GDG believes that better methodological quality studies are needed that do not only confirm the excellent results obtained in the RCT[80], but also precisely define the indications for early microsurgical arthrolysis.

Summary of evidence

4	Compartment pressure monitoring during the first 24 hours can reduce muscle necrosis in patients with vascular compromise in patients with extensive vascular compromise in a limb (peripheral oedema or confluent purpuric rash). With increased compartment pressure, the fasciotomy can reduce the need for more proximal amputations[6].
4	There is no consensus regarding the exact time to perform the surgical debridement of necrotic tissue. Some authors recommend early intervention, while for others the best option is to wait for the demarcation between viable and necrotic tissue. In case a secondary infection appears, an emergency surgical debridement should be performed[6].
1-	The early microsurgical arthrolysis reduces the requirements of proximal amputations in paediatric patients with IMD[80].

Recommendations

D	Monitoring of compartmental pressure in patients with IMD and extensive vascular involvement of a limb should be considered.
√	It is necessary to resort to a specialist urgently to assess and interpret the monitoring of compartmental pressure.
D	Urgent debridement is recommended if secondary infections of the wound appear in the paediatric patient, if the situation allows.
√	From the early hours of admission, orthopaedic and plastic surgeons should be consulted to assess the patient's needs.
√	The need in some cases to amputate large body areas poses an ethical conflict that should be discussed jointly by surgeons and intensive care physicians, taking into account the views of parents or caregivers.
√	In patients with meningococcal purpura fulminans and ischemia, the possibility of performing the arthrolysis technique when the human and technical resources are available, should be considered.

9. Prognostic and severity factors of IMD

9.1. Clinical factors as severity indicators

Question to answer:

- In patients with suspected invasive meningococcal disease, what clinical factors are useful to predict survival, mortality or sequelae?
  - Clinical signs: tachycardia, tachypnoea, hypotension, poor peripheral perfusion, central and peripheral temperature difference, severity or extent of the eruption, eruption progression, presence of fever, stiff neck, irritability or nervousness, lethargy, fatigue, drowsiness, level of consciousness.
  - Laboratory study: white blood cell count, coagulopathy, CRP, platelets, blood gases, kidney function, liver function, cortisol, glucose, other (CPK, rhabdomyolysis).

Prognostic factors can be defined as those data capable of providing information about the evolution that a particular patient may experience. This information may relate to the patient's overall survival or the possibility of the occurrence of a particular complication. The identification of prognostic factors in IMD may help to select patients who may benefit from the management provided in a paediatric ICU and to establish a monitoring plan to ensure long-term rehabilitation.

The SIGN CPG based its recommendations with regard to this question on scientific evidence from 17 observational studies. The following factors were associated with an unfavourable clinical outcome of IMD: duration of symptoms less than 24 hours, signs of sepsis in the absence of meningitis, acidosis, coma, poor perfusion, hypotension, admission between 07:00 am and 11:00 am and the presence of a number of petechiae above 50[6].

CPG
Cohort study
2+

In paediatric patients with bacterial meningitis, the following predictors of neurological sequelae were identified: presence of seizures during the acute phase, cranial nerve involvement, low CSF glucose levels and high protein levels in CSF. However, in a subgroup of 60 cases with meningococcal meningitis, none of these parameters was significantly associated with hearing loss, the most common complication of IMD[6].

CPG
Case series
3

The studies included in the SIGN CPG regarding the relationship between the results of the laboratory tests and the prognosis of patients with IMD show that a low platelet count, a low neutrophil count or a procalcitonin level greater than 150 ng / ml were associated with an increased risk of death. The Casado-Flores *et al*.[81] study showed that all patients with procalcitonin level < 10 ng/ml survived the IMD. The positive predictive value (PPV) of the product of the platelets and neutrophils initial count less than 40 x 10^9/l for fatal outcome is 66%. The presence of a high bacterial load estimated by PCR has also been associated with an unfavourable clinical course. In contrast, plasma lipids and vasopressin studies have failed to show association, and the presence of adrenal insufficiency does not predict mortality[6].

CPG
Cohort Studies
2+
CPG Case Series
3

Further evidence to the search period carried out by the SIGN CPG is of low methodological quality, with poorly designed studies for the analysis of prognostic factors. They are mainly retrospective case series of small sample size, which aim to identify predictors of mortality in patients with IMD, or predictors of sequelae and mortality in patients with bacterial meningitis.

One of the two studies focusing specifically on IMD, conducted in Brazil, sets the product threshold of platelets and neutrophils to identify IMD cases with increased risk of death in ≤ 113 (PPV 66.7%)[82].

Case Series
3

In a study with a sample of patients over 14 years (n = 167) with IMD, the following factors were associated with higher mortality (p <0.05): temperature above 40 °C, bradycardia, leukopenia <4,500 cells / mm 3, platelets <125,000 cells/mm^3, < 5 leukocytes/mm3 in CSF, CSF protein ≤ 50 mg/dL and no previous contact with the health system before diagnosis.

Case Series
3

The possibility of generalisation of the study results is limited to the group of patients aged between 14 and 19 years. There is also no multivariate analysis to rule out the interaction between the different variables[83].

A review of data from 15 studies collects the factors that were significantly associated with an unfavourable outcome of bacterial meningitis (0-18 years). The results are as follows[84]:

SR of observational studies
1-

– Predictors of hearing loss (4 studies): meningitis by *S. pneumoniae*, low level of CSF glucose.
– Predictors of mortality (10 studies): coma, convulsions, shock, peripheral circulatory failure, severe respiratory distress, low white blood cell count, high protein in CSF.
– Predictors of neurological sequelae (10 studies): coma, seizures, fever for 7 days or more, and low white blood cell count in blood.
– Predictors of unfavourable clinical outcome (mortality and neurological sequelae): coma, convulsions, shock, low white blood cell count in blood or low CSF glucose level and high protein in CSF, age less than 2 years and duration of seizures over 12 hours.

The authors only refer to the statistical significance of the variables, without providing absolute values. No pathogen analyses were performed, thus their external validity is limited.

A study carried out in 44 paediatric patients (aged between 2 months and 12 years) with bacterial meningitis analysed the influence of different factors on the occurrence of acute neurological complications (seizures, cranial nerve involvement, epilepsy status, coma, motor deficits, ataxia, alterations conduct) and neurological sequelae (behavioural disorders, developmental delay, mental retardation, epilepsy, cranial nerve involvement). The study found as independent factors associated with risk of acute neurological complications the following: neutrophils <60% (p <0.01), and *S. pneumoniae* as an etiologic agent (OR 6.4, 95% CI 1.7 to 24.7) and associated with neurological sequelae the following: CSF protein concentrations > 200 mg/dl (p <0.01) and convulsive episodes during hospitalization (OR 5.6, 95% CI 1.2 to 25.9). These did not differ by microorganism either[85].

Case series
3

The analysis of a series of 375 patients aged between 1 month and 14 years with acute bacterial meningitis showed that the presence of leukopenia (< 4,500 cells/mm^3) and counts < 10 cells/mm^3 in CSF were significantly associated with increased risk of complications (shock, brain oedema, refractory seizures and cranial nerve involvement), sequelae (cranial nerve disorders, motor disorders) and death. These did not differ by microorganism either[86].

Case series
3

Summary of evidence

2+[6]/ 3[6.83]	In paediatric population with IMD, the presence of signs of sepsis in the absence of meningitis, a number of petechiae over 50, acidosis, coma, poor perfusion, hypotension, bradycardia or symptoms lasting less than 24 hours are associated with unfavourable clinical evolution[6.83].
2+[6.81]/ 3[6.83]	In paediatric population with IMD the presence of neutropenia, thrombocytopenia, a product of platelet and neutrophil counts < 40 x 10^9/l (PPV of 66%), procalcitonin > 150 ng/ml, < 5 leukocytes/mm^3 in CSF or CSF protein ≤ 50 mg/dL are associated with unfavourable clinical evolution[6.83]. All patients with a level of procalcitonin < 10 ng/ml survived the IMD[81].
3	No association was found between the severity of the IMD and plasma lipids or vasopressin. The presence of adrenal insufficiency does not predict mortality[6].
1-[84]/ 3[6.85]	In paediatric population with bacterial meningitis, the following were predictive of neurological sequelae: presence of seizures during the acute phase, cranial nerve involvement, low CSF glucose and high protein levels[6,84,85]. None of these factors was significantly associated with hearing loss, the most common complication of IMD[6].
1-[84]/ 3[86]	In paediatric population with bacterial meningitis, the presence of leukopenia (< 4,500 cells/mm^3) and < 10 cells/mm^3 in CSF were associated with increased risk of complications, sequelae and death[84,86].

In developing the recommendations, the GDG has considered that further studies to the SIGN CPG have certain limitations as to the applicability of their results to the target population of this CPG, either because the study was conducted in a developing country[5.85], because the age range of the patients is different[83] or because they investigate prognostic factors of bacterial meningitis without distinguishing the causative agent[84-86]. The latter is important because the meningococcal meningitis carries less risk of neurological complications those other bacteria such as meningitis *S. pneumoniae*[6].

In relation to the consistency of the results, the study carried out by da Silva *et al*.[82] defined a threshold for the product of platelet and neutrophil count different from the SIGN CPG. The authors note that this product needs to be validated in the population in which it will be applied.

In addition to the studies described in this guide, two other studies[87,88], which were excluded from the volume of evidence due to their low methodological quality, were identified.

Recommendations

C	It should be taken into account that the following factors are associated with high mortality in paediatric patients with IMD: – A product of the platelet and neutrophil count < 40 x 10^9/l – A procalcitonin level > 150 ng/ml
C	It should be taken into account that the presence of leukopenia (< 4,500 cells/mm^3) is a factor associated with an unfavourable clinical evolution in paediatric patients with IMD.
C	It should be taken into account that the following factors are associated with extreme severity in paediatric patients with IMD: – Evolution of symptoms in less than 24 hours – Presence of a number of petechiae over 50 – Decreased level of consciousness – Presence of shock
D	It should be taken into account that meningococcal meningitis carries less risk of unfavourable neurological evolution than the meningitis caused by other bacteria.

9.2. Severity and mortality risk scoring systems

Question to answer:

- In patients with suspected IMD, is there any evidence that the use of any of the following prognostic scales can predict the severity of the disease or the risk of poor clinical results?
  - Leclerc
  - *Glasgow Meningococcal Septicaemia Prognostic Score* (GMSPS)
  - Gedde-Dahl's MOC score

There are many scales developed to measure the severity of paediatric patients with IMD. All of them use clinical features, and in some cases, laboratory data, to give a score, the higher the score, the greater risk of mortality or morbidity for the patient. The principle behind them is the early start of the appropriate treatment and the admission of the patient with increased risk of sudden deterioration in a paediatric ICU. The care of critically ill patients in an ICU is a factor that appears independently associated with a better prognosis (see section 8.1).

Both the SIGN CPG and the NICE CPG are referenced to a prospective study comparing the performance of the *Glasgow Meningococcal Septicaemia Prognostic Score* (GMSPS) with the performance of 9 other severity scales (Stokland, Stiehm and Damrosch, Ansari, Niklasson, Leclerc Kahn and Blum, Lewis, Istanbul, and Bjark) and laboratory markers of severity. The study involved 278 patients (< 16 years) from 6 hospitals in the UK, with suspected or confirmed (73%) IMD. The GMSPS was recorded on admission and repeated if there was any deterioration in the condition of the patient. A ≥ 8 GMSPS showed a sensitivity of 100%, specificity of 75%, a positive likelihood ratio (LR+) of 4.2 and a positive predictive value (PPV) for the exitus of 29%, with a statistically significant correlation of laboratory markers, including endotoxin and cytokine levels (p <0.0001). Other scales, such as Lewis (≥ 2) Istanbul (≥ 5), and Ansari (≥ 3) showed similar results. The authors note that GMSPS is the only scale that uses exclusively clinical criteria[5,6].	CPG Diagnostic trial Test II
The NICE CPG includes a study comparing the forecast accuracy of 8-specific IMD severity scales (GMSPS, Gedde Dahl MOC, Stiehm, Niklasson, Leclerc, Garlund, Treasury and Tüysüz). It analyses prospectively and retrospectively a cohort of 125 cases of IMD (< 17 years) confirmed by culture. The results of the study show that the discriminatory capacity of GMSPS is significantly better than that of other scoring systems, except when compared to the MOC scale, which showed no significant differences regarding the ability to distinguish between survival and death[5].	CPG Diagnostic trial Test III

The evidence found suggests that the GMSPS scale (Table 7) provides better performance in the early identification of patients with IMD in terms of risk of death or sequelae than that offered by other severity scales specific of the disease. The GDG also took into account in its recommendations that GMSPS primarily used clinical parameters. By eliminating the waiting times of the laboratory tests results, agility is achieved in a clinical setting, which may worsen suddenly.

No prospective studies have found the performance of the specific scale for IMD developed in Spain called MSSS[89] (meningococcal septic shock scale).

Studies[90] with other scales have been identified, such as the *Paediatric Logistic Organ Dysfunction Score*, developed for early detection of organ impairment, which is not taken into account for the heterogeneity of the samples with up to 55% of individuals with trauma or congenital diseases, and because it was not possible to disaggregate the information and analyse the data of the subgroup of patients with infectious pathology.

A communication made to a Congress[91], from which no further publication was found, or a study comparing severity scales with poor prognosis independent variables instead of comparing the accuracy among different scales have not been included[88].

Table 7. ***Glasgow Meningococcal Septicaemia Prognostic Score*** **(GMSPS)[92]**

INITIAL ASSESSMENT VARIABLES	YES	NO
Systolic hypotension (no distal pulse) (< 75 mmHg in children under 4 years or < 85 mmHg in children over 4 years)	3	0
Differential temperature (rectal/skin) > 3 °C	3	0
Coma score (Simpson & Reilly) < 8 at any time (Table 8) or decrease ≥ 3 points in 1 hour	3	0
Absence of meningismus	2	0
Paternal or maternal review of clinical deterioration in the last hour	2	0
Rapid spread of petechial purpura or presence of ecchymosis	1	0
Base deficit (< - 8 mmol/l) in capillary sample	1	0
In the hospital setting, if the blood gas analysis is not available to know the base deficit, the value of 1 will be considered for this item. GMSPS < 6: mild meningococcemia GMSPS 6-7 stable severe meningococcemia GMSPS 7-8: high-risk severe meningococcemia GMSPS > 8: severe meningococcal sepsis GMSPS > 10: fulminant meningococcemia		

Table 8. Paediatric coma scale (Simpson & Reilly)[93]

Score	Eye Opening	Best verbal response	Best motor response
5		Oriented	Obeys orders
4	Spontaneously	Words	Locates pain
3	To call	Vocal sounds	Flexion to pain
2	To pain	Shouting	Extension to pain
1	None	None	None
Maximum expected score for each age			
0 to 6 months: 9	6 to 12 months: 11	1 to 2 years: 12	2 to 5 years: 13	> 5 years: 14

Summary of evidence

II	A score ≥ 8 on a GMSPS scale has a PPV for predicting mortality due to IMD of 29% and a CPP of 4.2. It shows a diagnostic yield similar or superior to other IMD-specific scales[5,6].
III	The discriminatory power of gravity of GMSPS was statistically better than other scoring systems used[5].

Recommendations

√	In patients with suspected or confirmed diagnosis of IMD, a rating scale will be used to identify changes in the patient's condition.
B	For patients with suspected or confirmed diagnosis of IMD, the *Glasgow Meningococcal Septicaemia Prognostic Score* (GMSPS) scale can be a good tool for identifying changes in the patient's health condition.
√	If a patient with suspected or confirmed diagnosis of IMD shows a worsening of his/her health condition, the intensive care unit will be contacted immediately.

10. Prevention and control of IMD

10.1. Indications for antibiotic prophylaxis

Question to answer:

- What evidence is there that the following groups, after having had contact with a patient with IMD in the past seven days, should receive antibiotic prophylaxis?
  - People who have had contact within the household
  - Students from the same class or school
  - People who have had contact with body fluids (after resuscitation)
  - People who have exchanged kisses
  - People who have shared drinks
  - People who have shared any means of transportation

While most cases of IMD are sporadic (up to 97%, according to Hastings *et al*[94]), outbreaks can also occur. The main aim of chemoprophylaxis is to reduce the transmission of the meningococcus to non-susceptible individuals carriers of *N. meningitidis* in the nasopharynx and also eliminate the carrier status of the neo-colonised (recent acquisition of the carrier status during the first seven days after the onset of the index case) that could develop the disease. To achieve this, it is essential to define in what groups it is indicated to intervene with the appearance of a case of IMD, taking into account the benefit of preventing the risk of adverse reactions.

A systematic review of retrospective cohort studies included in the SIGN CPG estimated a relative risk of 0.11 (95% CI 0.02 to 0.58) between the cohabitants (1,249 cases and 4,271 contacts), from 1 to 30 days after the onset of the symptoms in the index case, demonstrating that chemoprophylaxis reduced by 89% the secondary cases of IMD. The absolute risk reduction was 46/10.000 (95% CI 9/10.000 to 83/10.000), and the number needed to treat to prevent one case was 218 (95% CI 121-1135)[6].	CPG SR of cohort studies 2++
A systematic review of observational studies estimated an attack rate of the disease during the first 14 days of 3.1/1000 to 28.5/1,000 household contacts without chemoprophylaxis (or with an incorrect pattern), a rate considerably higher than that observed in the group that received the correct chemoprophylaxis (0.0 / 1000 to 0.2 / 1,000)[95].	SR of observational studies 2-
According to the SIGN CPG in England and Wales, from 1995 to 2001 after a case of IMD in preschool, primary or secondary education, the absolute risk for a student from the same institution of disease within 4 weeks was 1/1.500, 1/18.000 and 1/33.000, respectively[6].	CPG Expert opinion 4

No studies were found comparing the incidence of secondary cases of IMD among contacts within educational centres who received chemoprophylaxis and the contacts who did not. A systematic review assessed the effectiveness of chemoprophylaxis of contacts within an academic environment calculating the risk of developing the disease compared to the inherent risk of being a sporadic case. The relative risk, from 1 to 30 days after having had contact with a case, was estimated at 22.3 (95% CI 12.1 to 40.9) in preschool contacts (3 studies), and 1.5 (95% CI 0.6 to 3.5) in university contacts (1 study). The school contacts relative risk was elevated in the 4 studies included in the review, however the risk difference in the preschool level was much higher than that the observed in schools: 58.2/10^5 (95% CI 27, 3/10^5 from to 89.0/10^5) vs. 4.9/10^5 (95% CI 2.9/10^5 to 6.9/10^5) in primary and 8.8/10^5 (95% CI 0,046/10^5 to 17.7/10^5) in high school. In summary, the contacts that share classrooms in schools are more likely to be a secondary case than a sporadic case of IMD, although the difference is statistically significant only in the preschool environment. In addition, from 3 studies on household contacts, a relative risk of 1110.2 (95% CI 760.1 to 1621.4) and a risk difference of 480.1/10^5 (95% CI 321.5 / 10 5 to 639.9/10^5) was calculated in this group[96]	SR of observational studies 1-
Possible risk of infection in health care workers exposed at least to 0.5 hours with an infected patient was estimated at 0.8/100,000[6]. No studies have been identified on the effectiveness of chemoprophylaxis in people who had shared the same drink or the same vehicle (car, bus, plane, etc.) with an infected patient.	CPG Case series 3
The "Monitoring Protocol and Meningococcal Disease Alert" of the National Epidemiological Surveillance Network recommended the administration of chemoprophylaxis as soon as possible after the diagnosis of the case, in the first 24 hours, with dubious usefulness after 10 days[97].	Expert opinion 4

The concordance of evidence is one of the factors that the GDG has considered when formulating the recommendations on this question. The CPGs that specifically address the issue[4,6] as well as the two identified systematic reviews[95, 96] agree in their results: the highest risk of disease is among close contacts of the case, especially among relatives, and in the first 7 days of the onset of symptoms in the index case. However, they differ on the recommended administration of chemoprophylaxis for pre-school (nursery schools and preschools).

Hellebrand *et al*. recommend to administer chemoprophylaxis for preschool contacts with a case of IMD as a preliminary evaluation of the duration and proximity of the contact; in secondary schools and universities, only those individuals who meet the criteria for close contact[96]. The SIGN CPG recommends not administering chemoprophylaxis in day-care, except in those cases that meet the criteria for close contact (see glossary) as outbreaks are rare (3 per year in England and Wales). The time between the case identification, notification and administration of antibiotics decreases its effectiveness due to adverse effects and resistances associated with intervention during childhood and, finally, because the antibiotic eradicates the comensal flora of the nasopharynx (*Neisseria lactamica*), which protects against colonization by *N. meningitidis*[6].

By contrast, in most European countries, attendance to the same preschool centre as a case with IMD is an indication for chemoprophylaxis[4]. In Spain, chemoprophylaxis is administered to all students and classroom staff when a case of IMD arises in kindergartens and preschools, an intervention that the GDG has not changed in its recommendation.

Regarding sporadic contact with a case of IMD, the GDG has considered that *N. meningitidis* is transmitted from droplets of respiratory secretions and that saliva inhibits the growth of bacteria. It is therefore necessary to distinguish the contact through saliva from the contact through droplets of respiratory secretions. There are sporadic contact situations (intimate kissing) involving both types of exchange. In principle, other contacts, such as sharing food, drink, cigarettes or kissing on the cheek, are not considered close contac[t4].

The systematic reviews on antibiotic chemoprophylaxis to prevent meningococcal infections by Fraser *et al*.[98] and Zalmanovici *et al*.[99], which updates the previous one, are excluded as a source of evidence because no secondary cases of IMD were identified during follow-up and base their conclusions on the eradication of healthy carriers of *N.meningitidis* in the nasopharynx.

Summary of evidence

2++	The administration of chemoprophylaxis to household contacts during the first 30 days after the onset of the symptoms in the index case reduces by 89% the secondary cases of IMD. The number needed to treat to prevent one case is 218 (95% CI 121-1135)[6].
2-	The attack rate of IMD, during the first 14 days is 3.1/1000 to 28.5/1,000 household contacts without chemoprophylaxis (or incorrect pattern) vs. 0.0/1000 against 0.2/1,000 household contacts with the correct chemoprophylaxis[95].
2-	The contacts that share classroom within schools (primary, secondary and university) are more likely to be a secondary case of IMD than a sporadic case, although the difference is statistically significant only at preschool level[96].
4	The absolute risk of illness for a student from the same institution within 4 weeks after the appearance of a IMD case is 1/1.500 in preschool, 1/33.000 in primary and 1/18.000 in high school[6].
3	Possible risk of infection in healthcare workers exposed to over 0.5 hours to a case is estimated at 0.8/100,000[6].
4	The National Epidemiological Surveillance Network recommended the administration of chemoprophylaxis in the first 24 hours after the diagnosis of the case[97].

Recommendations

D	Chemoprophylaxis is recommended as soon as possible, preferably in the first 24 hours, for all those who have had close contact (see glossary) and prolonged exposure to a case of IMD in the family (living or sleeping in the same house) or in a comparable context (shared kitchen within a student residence, shared apartment, etc.) during the 7 days before the onset of symptoms in the case.
D	In preschoolers (up to 6 years), the administration of chemoprophylaxis is recommended to all the students who attend the same classroom as the sporadic case as well as the classroom staff. Chemoprophylaxis is not indicated for the students and staff of other classes from the same school other than the IMD case.
D	It is not recommended to administer chemoprophylaxis for students attending the same class or the same primary, secondary school and university as a sporadic case, unless the case is in close contact with the rest.
D	Chemoprophylaxis should be offered to all healthcare workers whose mouth or nose may have been exposed to respiratory secretions from a patient with IMD before the patient has completed the first 24 hours of antibiotic therapy.
√	The following situations are not, by themselves, indicative of chemoprophylaxis: – Sharing drinks, food, cigarettes or kissing on the cheek, or other acts involving a similar contact with saliva. – Sharing occasionally the same transport vehicle, even if it is occupying the seat next to the case of IMD.

10.2. Antibiotics of choice for the prophylaxis of IMD

Questions to answer:

- What evidence is there that the following antibiotics are effective for the prevention of IMD in contact groups?
  - Rifampicin
  - Ciprofloxacin
  - Ceftriaxone
- In people who have maintained close contact with a case of IMD, what is more effective in preventing secondary cases: oral rifampicin or intramuscular ceftriaxone?
- In people who have maintained close contact with a case of IMD, what is more effective in preventing secondary cases: oral rifampicin or oral ciprofloxacin?

Rifampin, ceftriaxone and cipr3ofloxacin are universally accepted antibiotics to prevent secondary cases of IMD. Rifampin is the antibiotic of choice in Spain; it is administered orally (syrup or tablets) every 12 hours for 2 days. Its use is contraindicated in pregnant women, during lactation, for cases of alcoholism and liver disease. Rifampicin interacts with oral contraceptives, anticoagulants and some anticonvulsants, reducing its effectiveness. Other limitations are the fulfilment of the guideline: many parents do not repeat the dose if the child vomits; the emergence of resistance, associated with mass chemoprophylaxis and in cases of re-colonization; and that it is not easy to find in pharmacies.

The advantage of ceftriaxone compared to rifampicin is, besides the fact that it can be administered to pregnant women and children, that it is administered as a single intramuscular dose, which ensures compliance with chemoprophylaxis. Its use limitations derive from its route of administration: it is less accepted than oral ingestion. Ciprofloxacin has the advantages compared to rifampicin that it is administered orally in a single dose and that it is easier to find in pharmacies, but cannot be administered to pregnant or lactating women. The data sheet contraindicates its use in paediatric patients because it causes arthropathy in juvenile animals. Table 9 shows the guidelines of the IMD antibiotic prophylaxis.

The systematic review of Zalmanovici *et al*.[99] on antibiotic chemoprophylaxis to prevent meningococcal infection includes, among other studies, an RCT conducted in Saudi Arabia during a meningitis outbreak by serogroup A, which compares the prophylaxis with rifampicin with the prophylaxis with ceftriaxone in terms of effectiveness and safety. No secondary cases were observed in any of the two groups (168 contacts received rifampicin, and 179 received ceftriaxone), thus there was no difference between administering rifampicin or ceftriaxone to prevent the disease. However, the administration of ceftriaxone instead of rifampicin increased de novo nasopharyngeal colonization by approximately 4% 6 days after the start of the antibiotic prophylaxis, and 1.5% after 14 days, although these differences were not significant. Colonized de novo cases were those with negative nasopharyngeal culture before starting the chemoprophylaxis, which after 1 or 2 weeks, showed a positive culture for *N. meningitidis*. The GDG estimated the effectiveness of chemoprophylaxis in terms of de novo colonization from the survey data[100].

RCT 1-

2 RCTs included in the systematic review by Zalmanovici *et al*.[99] were recovered for individual analysis. Simmons *et al*.[101] assessed rifampicin against ceftriaxone, while Cuevas *et al*.[102] compared 3 antibiotics: rifampicin, ceftriaxone and ciprofloxacin. In both RCTs, the study population are household contacts with a case of IMD. The authors determine the effectiveness of the antibiotic based on its ability to eradicate *N. meningitidis* from the nasopharynx of contacts carrying the bacteria. There were no secondary cases of IMD among the contacts within 2 weeks of receiving prophylaxis with rifampicin, ceftriaxone or ciprofloxacin[101,102].

RCT 1-

Table 9. Guidelines chemoprophylaxis of IMD

Drug	Age Group	Dose	Duration
Rifampicin (oral)	Children ≥ 1 month	5 mg/kg every 12 hours	2 days
	Children ≥ 1 month	10 mg/kg every 12 hours	2 days
	Adults	600 mg every 12 hours	2 days
Ceftriaxone (intramuscular)	Children < 15 years	125 mg	Single dose
	Older children and adults	250 mg	Single dose
Ciprofloxacin (oral)	Adults	500 mg	Single dose

Adapted from Bilukha *et al.* (2005)[103].

In the process of developing the recommendations, the GDG has considered the applicability and generalizability of the evidence found, its consistency, relevance and impact.

Both the SIGN CPG[6] and the review of Zalmanovici *et al*.[99], which updates the review on the same topic of Fraser *et al*.[98], included in the CPG SIGN, are excluded from the volume of evidence because they use the eradication of the meningococcal carrier status in the nasopharynx as a source of indirect evidence. According to the authors, the absence in the various studies of secondary cases of IMD during follow-up implies that the effectiveness of antibiotics in preventing the disease cannot be investigated directly.

The aim of the chemoprophylaxis is to prevent individuals susceptible to developing the disease from being colonized de novo from the case or close contacts with the case, especially during the first 7 days after onset of the index case, as the recent acquisition carrier status carries a higher risk of developing systemic infection. The GDG considered that a consequence of the failure of eradication of the de novo nasopharyngeal colonization is a more appropriate approach to the eradication of the carrier status.

Moreover, the study conducted in Saudi Arabia has limitations regarding the generalization of its results to an environment like ours, where the predominant is serogroup B, which has a pattern of epidemic waves with interepidemic periods of varying duration, different from serogroup A, responsible for major cyclical epidemics. In this context, the availability of an antibiotic, which ensures the compliance of the chemoprophylaxis as ceftriaxone (intramuscular single dose), may have more value.

Additional considerations that the GDG has taken into account are related to patient preferences and contraindications of use specified at the start. It was decided to keep the contraindication for the use of ciprofloxacin in children just as it is stated in the data sheet of the drug. By contrast, the CPG of the Health Protection Agency 2011[104] recommends extending its use to all age groups and pregnant women, and the ECDC CPG 4 recommends the use of ciprofloxacin in children, but not in pregnant women. Both CPGs are based on the fact that no joint toxicity has been observed in studies in which ciprofloxacin has been widely used for patients under 18.

In Spain, rifampicin is the antibiotic of choice for the antibiotic chemoprophylaxis of close contacts to cases of IMD. The adherence these patients and their caregivers may have to the treatment with rifampicin is unknown, but given the threat of IMD present in the media, the GDG considered unlikely that such adherence is low, although there is no scientific studies thereon. Probably, patients and their families prefer oral to intramuscular treatment (ceftriaxone) if they are informed that it has the same effectiveness against *N. meningitidis* as a prophylactic. Moreover, the massive use of ceftriaxone or ciprofloxacin as the antibiotic of choice for preventing secondary cases of IMD could favour the emergence of resistance and limit its availability as treatment drugs.

Summary of evidence

1-	There is no difference between the effectiveness of ceftriaxone and rifampicin in preventing secondary cases of IMD in close contacts (see glossary) of cases with the disease[100].
1-	The administration of ceftriaxone as prophylaxis of IMD increases the risk of nasopharyngeal de novo colonization with respect to rifampicin by 4% after 6 days and 1.5% after 14 days. These differences are statistically insignificant[100].

Recommendations

√	Post-exposure chemoprophylaxis with rifampicin is recommended as first choice. The administration of ceftriaxone is recommended as an alternative in the following circumstances: – When rifampicin is contraindicated (see info: http://www.aemps.gob.es/). – If there is alcohol consumption and malnutrition, when it is considered that the risk exceeds the potential benefit for the patient. – In contacts < 18 years, when a new intervention is required in the context of an outbreak and the previous prophylaxis had been performed with rifampicin – When suspecting a possible breach of the oral chemoprophylaxis. And the administration of ciprofloxacin as an alternative to rifampicin in the following circumstances: – In contacts > 18 years, when a new intervention is in required in the context of an outbreak and the previous prophylaxis had been performed with rifampicin.

10.3. Meningococcal vaccination of patients with IMD

Questions to answer:

- Can the meningococcal vaccination of cases of IMD, reduce the risk of a second IMD when compared to patients who have been diagnosed and treated by IMD and have not been vaccinated?

The severity of the IMD in terms of morbidity and mortality requires health professionals to take extreme care on the precautionary measures. Currently it has a monovalent conjugate vaccine regarding safety and efficacy proven against *N. meningitidis* serogroup C (MenC); its inclusion in the routine vaccination schedule was approved by the Inter-territorial Council of Health in December 2000. It is important to know whether its administration is indicated for patients who have suffered from IMD, in order to prevent recurrences.

No studies have been found on the MenC vaccine effectiveness in preventing recurrences of IMD. The SIGN CPG based its recommendation on the opinion of experts of another CPG[25] who recommend offering the vaccine against meningococcal serogroup C before hospital discharge to all patients who have undergone IMD[6]. CPG Expert opinion 4

Despite the absence of studies demonstrating that vaccination with MenC protects against recurrence of the disease, the GDG has taken into account, in making the recommendation, the inherent gravity to the IMD, and the possibility that the intervention may be effective. Having had IMD by serogroup C is not a contraindication for immunization with MenC. The immune response to natural infection may be inferior to that induced by the conjugate vaccine, especially in young children.

Summary of evidence

4	Experts advise offering the MenC vaccine before hospital discharge[6]

Recommendations

D	It is recommended to provide MenC vaccine before hospital discharge after having suffered from IMD to the following groups: – Patients with confirmed IMD by serogroup C who have previously been immunized with MenC. – - All patients not previously immunized with MenC, regardless of the serogroup, causing the episode.

10.4. Other infection control measures

Questions to answer:

- In patients with suspected IMD, are measures such as the isolation in an individual room, the use of individual protection equipment (non-sterile clean gloves, non-sterile clean gown, waterproof mask, eye or facial protector) and chemoprophylaxis effective in hospital care to reduce the risk of secondary infection associated to health care by clinical staff (except laboratory staff), family or people living with the index case?

No studies were identified that compared the incidence of secondary cases of IMD among health care workers exposed and without effective protection (barrier or chemoprophylaxis) and among health care workers exposed but equipped with appropriate protective measures. The SIGN CPG based its recommendation on the opinion of experts collected in two CPGs, one on the prevention of infection transmission within the hospital setting and the other specific to IMD.

CPG
Expert opinion
4

N. meningitidis in nasopharynx is undetectable 24 hours after starting the treatment with intravenous ceftriaxone[6]. While the risk of transmission exists, patients should be installed in a room alone, implementing the measures of protection against microorganisms transmitted by large droplets (> 5 mm diameter). Among healthcare personnel, procedures such as manipulation of the endotracheal tube, intubation, mouth-to-mouth breathing or oropharynx examination pose a risk of contact with respiratory secretions. Those who make such manoeuvres should use appropriate protective equipment (mask, goggles, visor and gloves)[6].

Special precautions to prevent the transmission of infectious agents by drops (>5 mm diameter) are described in Table 10.

Table 10. Precautions to prevent droplet transmission of IMD[105]

- Patients should be installed in individual rooms.
- People having close contact with the patient (within one meter) must use disposable masks.
- The use of gloves and disposable gowns is not recommended.
- When the patient is transferred out of his /her room, he/she must wear a mask.

Summary of evidence

4	IMD patients become non-infectious within 24 hours following the beginning of the intravenous treatment with ceftriaxone. While there is a risk of transmission through respiratory droplets, the patient should be installed alone in a room and the appropriate protective measures should be taken. Likewise, health-care staff must use the appropriate protective equipment during the procedures that pose a risk of contact with respiratory secretions[6].

Recommendations

D	Paediatric patients with suspected IMD should be initially admitted to a single room.
D	When a suspected case of IMD is admitted to hospital, droplet transmission precautions should be taken, which can be interrupted after 24 hours of effective treatment of the patient.
D	Health care staff at high risk of exposure to respiratory secretions must use appropriate individual protective equipment.

11. Follow-up after IMD

11.1. Sequelae associated to IMD and support to patients, family and caregivers

Questions to answer:

- What are the sequelae associated to IMD and what aspects need greater support and information for patients and their families and caregivers?
- What proportion of the paediatric population with bacterial meningitis develops physical or psychological morbidity?
- What proportion of the paediatric population with meningococcal septicaemia develops physical or psychological morbidity?

The spectrum of complications in the short and long term after suffering IMD is very broad. Not all paediatric patients suffering from IMD develop sequelae, and it is difficult to predict which cases and in what proportion they are at greater risk[6].

11.1.1. Hearing loss

Hearing loss is the most frequent complication associated with IMD, with a range of incidence ranging between 1.6% and 25%[6,106]. The incidence in developing countries (9.4%-25%) is higher than that observed in developed countries (1.9%-4.2%)[6], and it is more common in meningitis than in the meningococcal sepsis. A Dutch study conducted on 120 patients over 18 years of age with a history of meningococcal septic shock (MSS) observed only two (1.6%) cases with hearing loss[106].

A study conducted in the UK investigated the effects of the disease in a series of 101 patients ranging between 15 and 19 years of age who suffered from IMD (39.6% meningitis and sepsis, 32.7% meningitis, and 26.7 % sepsis) and observed a 12% of cases of hearing loss[107].

A review that includes studies in both developed and developing countries estimated, from 17 observational studies, the risk of severe hearing loss by *N. meningitidis* was of 3.8% (95% CI, 1.2% to 7.3%) with an adjusted median of 2.1%[108]. Hearing loss was defined as severe bilateral sensorineural hearing loss with a threshold higher than 26 dB.

Finally, in reviewing the medical records of 541 patients with sequelae due to IMD, an Icelandic study showed hearing loss in 2.6% of cases[109].

11.1.2. Orthopaedic complications

According to the SIGN CPG, the most common sequel is the injury to the growth plates, which can manifest years after discharge by IMD[6].

A study in the Netherlands reported 10 (8%) patients with amputations in a cohort of 120 patients under 18 who survived a meningococcal septic shock. Four of them had complications from the stump or bone overgrowth. In addition, 7 (6%) patients had impaired growth, with 3 to 13 cm longitudinal discrepancies, *genu varus* of a lower limb, lameness and pain at the time of the follow-up visit, between 4 and 16 years after discharge of the ICU[110].

11.1.3. Cutaneous complications

According to the SIGN CPG, skin grafts or more complex reconstructive surgery may be required[6].

Study Borg *et al*. recorded cutaneous scars in 18% (18/101) of cases[107].

A total of 58/120 (48%) patients who survived a meningococcal septic shock presented from barely visible to very severe necrotic skin scars by purpura. Of these, 19/58 (33%) required skin grafts in the weeks after admission to the ICU and 5% reported discomfort at the time of the study (between 4 and 16 years after the IMD)[110].

11.1.4. Psychosocial and psychiatric complications

According to a study included in the SIGN CPG, IMD survivors of paediatric age and adults reported a decline in their quality of life (increased anxiety, decreased energy and reduced capacity for work and leisure activities). A 15% had confirmed physical sequelae and the 19% of those without physical consequences related an adverse impact on their quality of life[6].

A study conducted in the Netherlands in 120 survivors of meningococcal septic shock (< 18 years) did not identify any association between the physical (scars, amputations, neurological disorders) and psychological (behavioural disorders, IQ < 85) sequelae[111].

Borg *et al*. studied 101 pairs of cases of IMD and controls matched by age and sex, aged between 15 and 19 years. The monitoring was conducted between 18 and 36 months after the IMD. It was found that, when compared with controls, IMD survivors had poorer scores on questionnaires regarding quality of life and mental fatigue. Cases of IMD were more likely to have depressive symptoms. Unlike the previous study, the physical sequelae were associated with lower mental health performance[107].

According to a study included in the SIGN CPG, IMD survivors scored significantly worse than controls in the following areas: visual-motor integration, (important for proper development of writing), verbal and performance intelligence and higher cognitive problems (related to the mental processes of comprehension, judgment, memory and reasoning) and on measures of attention deficit disorder and hyperactivity[6].

A second study conducted in the Netherlands investigated the long-term cognitive capacity (4 to 16 years after the event) of 77 paediatric patients who survived meningococcal septic shock, and who received a set of standardized questionnaires. The results were compared with normative data from the general population. Altogether, the results obtained by the meningococcal septic shock survivors were similar to those of the reference population group. However, had poorer long-term outcome in terms of the verbal understanding capacity, visual-motor integration, executive function and attention (selective focus and concentration). The percentage of patients with mental retardation or *borderline* was comparable to that of the general population[112].

A third study conducted in the Netherlands compared the emotional and behavioural problems as well as long-term PTSD (from 4 to 16 years after discharge from the ICU) of 89 survivors of a meningococcal septic shock (ranging between 6 to 17 years old) with normative data of the general population. The evaluation was performed by standardized questionnaires completed by patients, mothers, fathers and teachers. Collectively, the results obtained by the meningococcal septic shock survivors were similar to those of the reference population group. The only significant difference observed was that the mothers of surviving patients reported more somatic complaints in their children than the reference group. The parents of cases that sickened at a younger age reported significantly more emotional and behavioural problems as well as long-term PTSD with regard to their children, than the parents of cases who sickened at an older age[113].

A retrospective study included in the SIGN CPG on the frequency of psychiatric disorders in patients from 4 to 17 years after IMD showed psychiatric disorders in 23/40 patients who were over six years. The most common were depressive, oppositional and anxiety disorders. Thirteen of 40 patients aged more than 6 years and 7 out of 16 patients younger than 6 years had psychiatric disorders during the follow-up year. The severity score of IMD, clinical shock at admission and the presence of emotional and behavioural problems before the IMD were independent predictors of psychiatric disorders during the follow-up year[6].

The branch of a prospective study conducted in Iceland that evaluated the frequency of depressive disorder and post-traumatic stress 16.6 years after the IMD, found no differences in the general population[109].

A prospective study carried out in the UK compared the psychological status of paediatric patients with IMD (ranging between 3 to 16 years) at the time of admission (premorbid status, according to the authors), 3 months and 12 months after discharge. Fifty-six out of the 118 eligible families completed the study, partial information was obtained from 22 families. The significant increase in symptoms of emotional and behavioural disorders observed after 3 months was reduced to 12 months. After 12 months, 5 (11%) of 43 patients were at risk for PTSD (12% after 3 months). The 4 patients with acute physical sequelae did not rate significantly higher on the questionnaire than the rest of the sample[114].

11.1.5. Neurological complications

A study by Buysse *et al*. made with 120 survivors of meningococcal septic shock observed in 33% of cases, at least one of the following neurological sequelae: chronic headache (n = 34), loss of sensation in the arm, paresis of one arm, paresthesia in the foot and/or hand, and tremor in both hands[106].

The systematic review identified for this question found a risk of seizures (5 studies) of 0.9% (95% CI, 0.1% to 2.0%) with a median adjusted to 0.5%[108].

11.1.6. Other complications

According to SIGN CPG, patients who required renal dialysis are more likely to develop permanent kidney damage[6]. In the series of patients who suffered a meningococcal septic shock, 1 case out of the 4 who required renal replacement therapy in the ICU presented chronic renal failure years after discharge[106]. According to the study by Gottfredson *et al*., acute renal failure is the second most common complication (2.8%, 15/541) after arthritis (5.7%, 31/541) and before hearing loss. Other long-term complications were: epilepsy (0.6%, 3 patients), migraine (3), pericarditis (3), adrenal insufficiency (1), psoriasis (1), strabismus (1), Henoch-Schönlein purpura (1), focal deficits (1), rheumatoid arthritis (1) and systemic lupus erythematosus (1 patient with complement deficiency)[109].

11.1.7. Information and Support Needs

No studies have been identified to assess the needs for information and support specifically required by those patients who survive to IMD but suffer some sequel.

A qualitative study investigated, through semi-structured and group interviews, the concerns of parents when their young children (<5 years) were acutely ill. Parents (n = 95) were concerned about symptoms such as fever, cough, the possibility of meningitis and the lack of recognition of a serious problem. The deepest fears that their children would die or suffer serious losses crystallized in the form of meningitis. According to the authors, these results should be interpreted in the light of recent awareness campaigns that could have increased the pressure experienced by parents with messages like "*knowing the symptoms of meningitis could mean the difference between life and death.*" Parents immediately assumed the need to remain vigilant to the appearance of any rash, although self-limited eruptions are frequent in childhood. The authors need to inform including photos that show how to distinguish the rash that appears on the IMD[115].

A qualitative study investigated the needs of parents during the hospitalization of the paediatric patient with acquired brain injury (28 patients, 7 with meningitis). The study was conducted about 2 years after hospital discharge, using semi-structured interviews to 27 mothers and 7 fathers who described their experiences during the hospitalization of their child and the needs that they stated. Three main issues were identified[116]:

– Services aimed at the recovery of the patient, including a rapid and accurate diagnosis to start the treatment as soon as possible, adequate physical space and the need for a multidisciplinary approach (Multidisciplinary Rehabilitation Unit).

– Support services for parents, to enable them to cope with a sick child. Encourage them to participate in their care while hospitalized. Teach them to perform specialized treatments that will be needed to reduce stress at the time of discharge. Provide counselling. In the acute phase of the disease, provide information on the diagnosis, the treatment plan, the prognosis, the reason and the results of diagnostic tests, and an explanation of the monitoring equipment used. During the sub-acute and rehabilitation phases, information about medication, treatment, testing, predictable behavioural changes, and indications of the likely course of recovery are required.

– Services aimed at maintaining the stability of the family unit.

The Irene Megías Foundation developed in 2007 the national sociological research *Awareness, knowledge and attitudes regarding meningitis in Spain*. 60% of respondents in the course of this research stated being very or in some way interested in receiving information. According to the study, when conducting an information campaign, the following objectives have to be taken into account:

– Strengthen public confidence in the quality and preparation of the Spanish health system, and its ability to prevent, control and treat cases of meningitis.

– Reassure the population that the meningitis is well controlled and its incidence has been reduced significantly, thanks to surveillance and vaccination campaigns.

– Make the existence of vaccines and preventive measures currently applied widely known.

– Report on what are the typical symptoms of meningitis and sepsis.

– Strengthen the awareness that when such symptoms appear it is necessary to go, as quickly as possible, to an emergency department.

The Irene Megías Foundation has a record of the most frequent requests for information and those areas in which more support is required. This information is available at the URL <http://www.contralameningitis.org/>

The most frequent inquiries are listed below[117]:

– Timing about prophylaxis.

– Common process of transmission of the disease.

– Reasons why the disease has not been detected in the first medical consultation:

– Reasons why the patient has contracted the disease while following his/her daily immunization schedule.

– General knowledge of the disease and its characteristic symptoms, in order to recognize them on time.

– Possibility that another family member can also have meningitis.

– Vaccination calendars in the regions, especially when a family moves to another area.

– Public financial assistance for survivors with sequelae.

The application areas with more support are:

- Second medical opinion on cases still hospitalized.
- Financial support to survivors with serious sequelae.
- Psychological support both coming from the Foundation and externally.

A study conducted in the UK by the University of Bristol and the *Meningitis Research Foundation* on 18 parents of children who had survived the IMD between January 2000 and May 2010 concluded that there are three important areas for parents: access to primary health care, communication, and the relevance and adequacy of aftercare[118].

When making recommendations, the GDG has taken into account that the identified studies to answer the type of questions asked in this section are invariably associated with low evidence level. No studies have been found on the proportion of the paediatric population that develops morbidities in dominant clinical function, sepsis or meningitis. The only information about it comes from the Dutch series of 120 patients surviving a meningococcal septic shock, the most severe subgroup within meningococcal sepsis. The study found that 61% of cases had at least one serious sequel[111].

The paediatric population that underwent IMD with shock is more likely to develop skin orthopaedic problems. In turn, those who had meningitis are at increased risk of suffering from hearing loss and other neurological problems, and to develop behavioural disorders[5]. This information should be provided to parents or caregivers at the time of discharge.

The GDG is of the opinion that a quality health system has to have the resources to identify possible sequelae and provide the treatment measures as well as the necessary needs to support the patient and his/her environment.

Recommendations

√	The patient who has suffered IMD must leave the hospital with an individualized care plan.
√	The individualized care plan for patients who have suffered IMD shall describe the monitoring to be performed in order to identify immediate complications that may occur in the long term. Furthermore, the individualized care plan shall include an extensive list of professionals, schools, associations, foundations and institutions that can help the patient affected and his / her families to manage their new life, not forgetting to include those public or private institutions, which can provide financial assistance.
√	The patient who has suffered from IMD and their families should be informed of the following potential long-term consequences: – Hearing loss – Orthopaedic sequelae (damage to bones or joints) – Skin lesions (scarring from necrosis) – Psychosocial issues – Neurological and developmental disorders – Renal failure They should be informed of the characteristics of the disease, its prevalence, case fatality, morbidity, and the usual means of transmission, etc., to try to minimize the guilt that usually appears in all those people closely involved with the patient. The individualized care plan shall include delivery to the family of a free printed copy of this Clinical Practice Guideline in its version for patients, families and caregivers.
√	Hearing and neurologic tests should be performed to any patient who has suffered IMD, in order to establish a treatment as soon as possible if necessary.
D	Before discharge, the family should be offered the possibility to acquire the appropriate skills to engage with the basic care of the paediatric patient.
D	When the patient is far from the hospital, the opportunity to acquire skills related to specialized care should be offered.
D	Providing the family with psychological support will help them to decide and mitigate the intensity of PTSD if it appears.
√	Healthcare professionals should be offered the means to enable them to acquire effective communication skills.

11.2. Impact on families and caregivers

Question to answer:

- Do families and caregivers of those who have suffered IMD suffer any psychosocial problems? And, if so, do the psychosocial interventions and supply of information improve their quality of life?

The clinical presentation of IMD is often dramatic and death can occur within hours. Family members or caregivers of patients living this experience are under tremendous stress, generated by the fear that the patient will die and the anxiety about his / her physical and mental state if he / she survives the disease. Invasive interventions to which the most severe cases are subjected can cause a deep shock to the parents, who also see how the look of their children is transformed dramatically. Therefore, the IMD is a huge psychological burden not only for patients but also for their families and caregivers.

Scientific evidence contained in the SIGN CPG, from five observational studies, shows that admission in an ICU by IMD can cause PTSD to patients and their caregivers. This is related to the duration of stay in the paediatric ICU. Mothers have higher risk of developing PTSD than fathers[6].

CPG
Observational studies 2+

A total of 3 observational studies conducted in the Netherlands investigated the psychosocial impact of the disease on the parents of a cohort of patients (< 18 years) who survived a meningococcal septic shock. The results are described as follows:

Cohort studies 2+

– Short term (up to 2 years, prospective study), 17% (8/47) of the mothers had anxiety or depression requiring professional help. This was related to the patient's age at the time of admission to the ICU. Mothers who needed professional help had children significantly younger than those who did not need help (p = 0.04). The severity of child's illness did not have a significant negative impact on the quality of life related to mother's health. Fathers make up only 4% of the sample[119].

– In the long-term (ranging from 4 to 16 years after, retrospective study), parents (n = 77) and mothers (n = 87) of patients who survived a meningococcal septic shock (n = 88) showed recovery. Similar levels of psychiatric symptoms (GHQ test) and similar coping (UCL test) were recorded, when compared with population normative data. Psychosocial disorders were still observed in a minority of parents because of the sequelae suffered by their children[120]. Cohort study 2+

  GHQ: *General Health Questionnaire*. It evaluates the psychological state. It contains 28 items in four domains (somatic symptoms, anxiety and insomnia, social dysfunction and severe depression). Mean scores ≥ 5 risk of psychiatric disorder.

  UCL: *Utrecht Coping List*. It assesses coping strategies. It contains 7 domains (active solution of problems, passive reaction patterns, seeking social support, etc.).

• In the long-term (ranging from 4 to 16 years after, retrospective study), the episode in the paediatric patient has no negative impact on the quality of life related to the health of parents (n = 134), who scored significantly better in 8 of the 10 domains of the SF-36 test. The comparison was performed with a random sample of the Dutch population[121].

  36-SF: *36-item Short-Form*. It evaluates the quality of life related to health in adults. Lower scores indicate poorer quality of life related to health[122].

A prospective study conducted in the UK compared the psychological status of parents of paediatric patients with IMD at the time of admission (premorbid status, according to the authors), 3 months and 12 months after discharge. The increase in psychological symptoms observed in parents 3 months after discharge of the child drops significantly after 12 months (GHQ tests and *Impact of Event Scale*). However, after 12 months, 23% (12/51) of mothers and 11% of parents (4/35) were at high risk of developing PTSD[114]. The study presents a high risk of bias because only the data from families who responded to the questionnaires is analysed: 47% of those eligible. Case series 3

No studies were found to investigate whether psychosocial interventions and providing information improved the quality of life of families and caregivers of those who have suffered IMD.

Summary of evidence

2+	Admission in the ICU due to IMD can provoke posttraumatic stress disorder on patients and their caregivers, which is related to the duration of stay in the paediatric ICU. The mothers of the patients have a higher risk of developing PTSD than fathers.
2+	In the short term, up to 2 years after, 17% of mothers of patients who survived a meningococcal septic shock had anxiety or depression requiring professional help. This relates to the patient's age at the time of admission to the ICU[119]. In the long term, from 4 to 16 years later, they have similar levels of psychiatric symptoms as the general population. Psychosocial disorders were still observed in a minority of parents because of the sequelae suffered by their children[120].
2+	The episode of meningococcal septic shock in the paediatric patient does not have any negative impact on the quality of life related to the health of parents in either the short[119] or long term[121].
3	The increase in other psychological symptoms in parents observed 3 months after the discharge of the child after an IMD drops significantly after 12 months. Despite this, 23% of mothers and 11% of fathers are at high risk for suffering from PTSD[114].

Recommendations

C	Healthcare professionals involved in the monitoring of paediatric patients with IMD should be aware of the possibility of posttraumatic stress disorder with anxiety or depression in patients, their families and caregivers.
B	It is recommended that a psychologist or psychotherapist monitors in the short-term (up to 2 years) patients with IMD and their parents in the weeks following the discharge from the paediatric ICU, or if the patient dies, in order to reduce the scope of the psychological sequelae of the disease.

12. Awareness and information campaigns on IMD

Question to answer:

- Do the educational programs aimed at health professionals and the population in general improve the speed of recognition, diagnosis, and treatment of IMD? Do they increase survival or decrease the severity of the disease and its complications? Do they have any effect on the admission to the ICU or the duration of hospital stay, admission costs, the duration of school absence, etc.?

Educational programs aimed at improving the knowledge about the warning signs and symptoms of IMD aim to reduce the time between the onset of the disease and the establishment of the appropriate treatment. The aim of this question is to know how they impact on the prognosis of the IMD.

The SIGN CPG found no scientific evidence for answering the question and proposes a recommendation for future research.

Case serie 3

A study carried out in Lille, France, investigates the ability of parents to recognize a haemorrhagic rash in a febrile paediatric patient and its relevance. 123 parents who came with their under 5 year old children to the emergency unit of a tertiary hospital for minor injuries were interviewed. None mentioned appearance of haemorrhagic rash when asked (open question) about the most worrying sign in the child with fever. When asked directly about the same issue, 22% considered it very alarming, 63% moderately alarming, and 15% little or not alarming. In terms of severity, it was ranked third, behind persistent fever after administration of antipyretics and neck pain. 96% of parents undress their children to help reduce the fever, but none does so specifically to identify a rash. By classifying photographs of rashes in decreasing order of severity, only 4% of parents chose the initial haemorrhagic eruption correctly in the second position, behind the extensive ecchymotic rash. Finally, only 7% (95% CI 3% to 12%) of parents were able to identify a petechial rash and knew about the glass test[123] (see glossary).

In October 2007, the Irene Megías Foundation against meningitis presented the results of sociological study *Awareness, knowledge and attitudes regarding meningitis in Spain*[117]. The methodology included focus groups, structured interviews and in-depth interviews. In the quantitative phase of the study a sample of 1,537 people representative of the Spanish population were interviewed by phone and online. Below are the results on the awareness the population has about meningitis as an infectious disease:

Qualitative study

- It is the most spontaneously remembered disease when the respondent recalls very serious diseases of childhood.
- It ranks fifth among all childhood diseases that are remembered spontaneously.
- It ranks sixth when respondents think spontaneously about contagious childhood diseases.

Regarding the knowledge that people have of meningitis, most do not know the following:

- What are the characteristic symptoms (only 8% know that patches may appear on the skin)?
- What age groups are at risk?
- What are the expected consequences?
- How to react to a possible case of meningitis?
- The high efficiency of our healthcare system.

No studies have been identified that assess the effectiveness of educational programs and information campaigns aimed at recognizing the IMD and by these means be able to implement a treatment at the earliest possible. The GDG has decided to take into consideration the evidence found regarding the profound ignorance among the general population of the characteristic symptoms of meningitis and, in particular, of the haemorrhagic rash as a warning sign of IMD. The GDG considered highly important to educate the NHS on the health interest the development of programs that periodically sensitize the population to the disease can have. Having an informed population and professionals who have in mind the possibility of encountering a case of IMD could result in a decrease in the number of cases with complicated or fatal evolution.

Summary of evidence

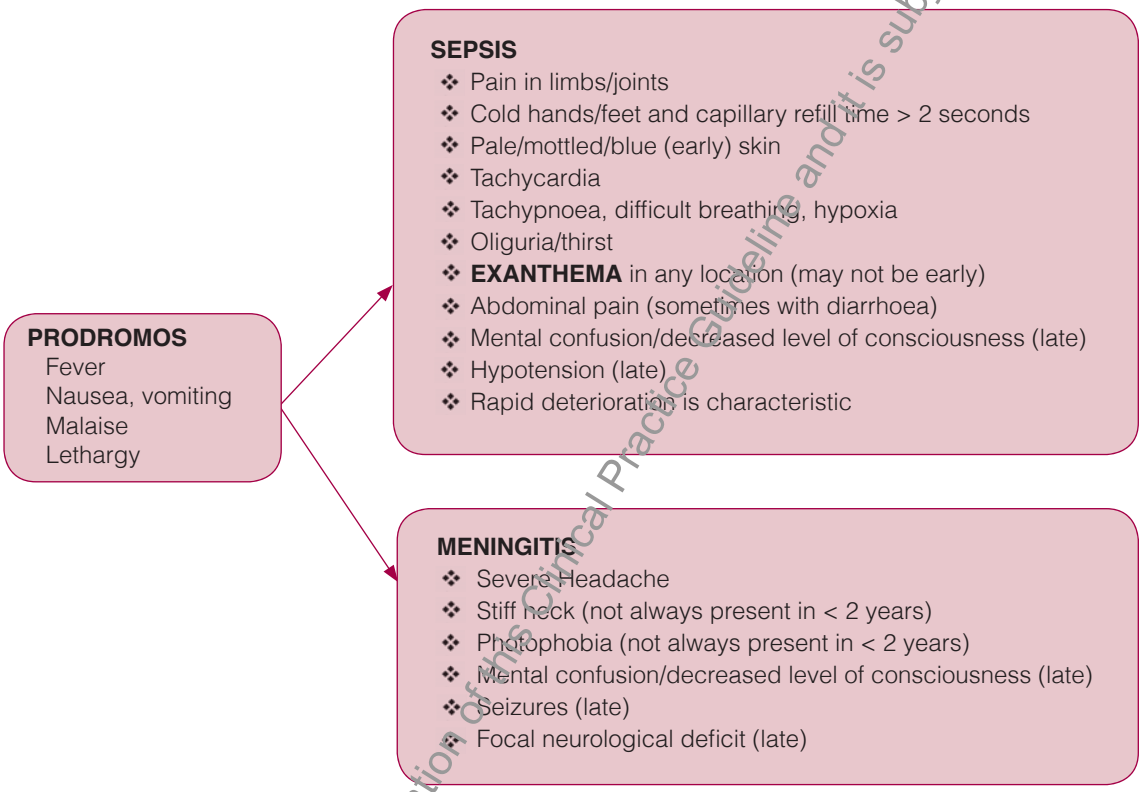
3	There is a widespread ignorance of parents about the haemorrhagic rash and its importance. Only 7% (95% CI 3% to 12%) is able to identify a petechial rash and knows about the glass test[123].
Q	Meningitis is a disease that a great number of the Spanish population knows about, but most do not know its characteristic symptoms, its possible side effects and how to deal with it[117].

Recommendations

√	The general population and other groups (such as pharmaceuticals, day carers, etc.) should be informed about IMD in order to suspect the disease at an early stage.
√	The general population should know the implications of the appearance of petechiae for early detection of the IMD.

13. Diagnostic and therapeutic strategies

Algorithm 1: Signs and symptoms of IMD



The order of appearance of symptoms can vary. Some symptoms may not be present.

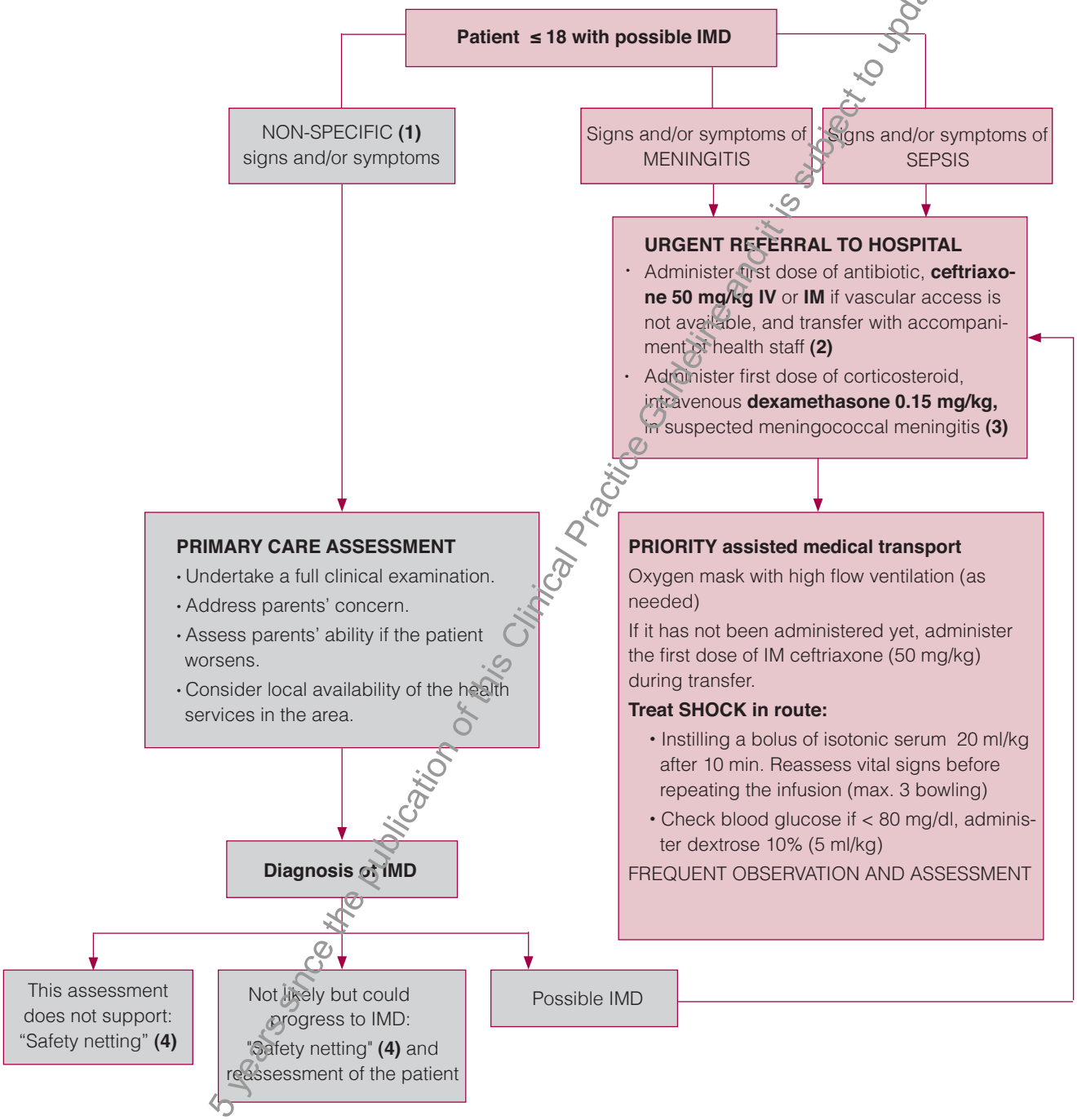
PAEDIATRIC PATIENTS < 2 YEARS CAN ALSO SHOW THE FOLLOWING SYMPTOMS: irritability with pitched cry or moan, refusal of food, unusual posture or tone, lethargy, bulging fontanelle, cyanosis.

EXANTHEMA characteristic of IMD: Non-blanching petechiae > 2 mm below the area of the superior vena cava.

The presence of a generalized petechial or purpuric rash, with capillary refill > 2 seconds in a paediatric patient with malaise, should suggest IMD and the need for urgent treatment.

In a previous initial phase the rash (maculopapular) may be atypical in some patients.

Algorithm 2: Pre-hospital management of IMD



Adapted from SIGN (2008)[6] and Meningococcal Disease. Meningitis Research Foundation (2009)[124].

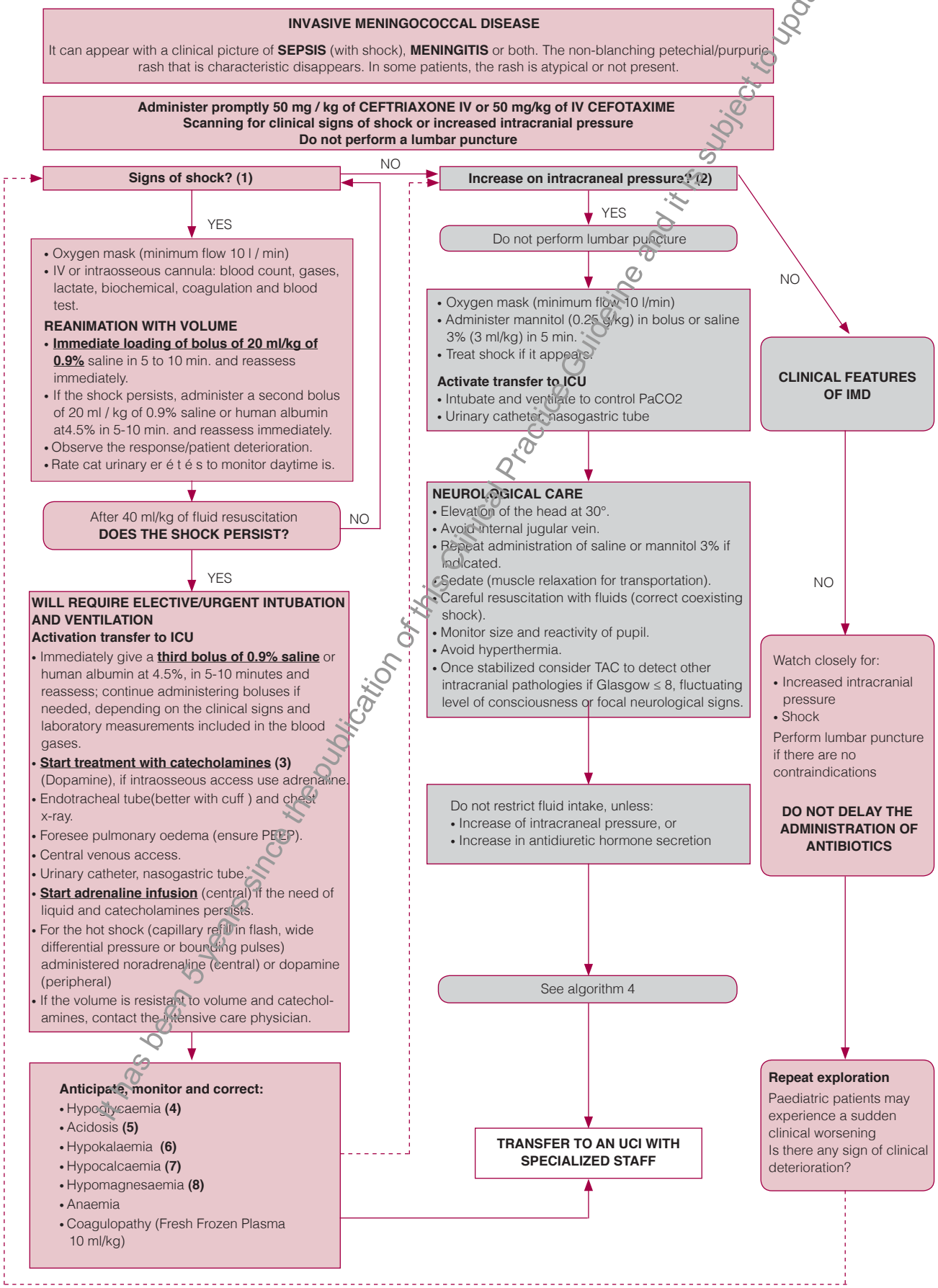
(1) In the first 4 to 6 hours of onset of IMD non-specific symptoms such as fever, lethargy, refusal of food, nausea, vomits, irritability, signs and / or symptoms of upper respiratory tract infection (runny nose, sore throat, etc.), diarrhoea, and abdominal pain may appear.

(2) On suspecting IMD, administer parenteral antibiotic at the earliest opportunity, both in primary and at a higher-level care, but do not delay urgent transfer to hospital.

(3) The adjuvant administration of a corticosteroid should be considered when suspecting meningococcal meningitis or after confirmation, as soon as possible and without interfering with the administration of the antibiotic or the transfer to a specialized centre.

(4) The healthcare professional will inform caregivers about the need to seek health care if the patient's clinical condition deteriorates, for example, if the characteristics of the rash change.

Algorithm 3: Hospital Management of IMD



Algorithm 3 adapted from: Management of meningococcal disease in children and young people. Meningitis Research Foundation (2009)[125]

(1) Signs of shock:

- Tachycardia and/or hypotension
- Capillary refill time > 2 seconds
- Unusual skin colour
- Shortness of breath
- Leg Pain
- Cold hands and/or feet
- Confusion
- Decreased level of consciousness

(2) Signs of increased intracranial pressure:

- Reduced (Glasgow ≤ 8) or fluctuating level of consciousness
- Relative hypertension and bradycardia
- Focal neurological signs
- Abnormal postures
- Seizures
- Unequal, dilated or poorly responsive pupils
- Papilloedema
- Abnormal "doll's eye" movements

(3) Dopamine at 10-20 mcg/kg/min. Make up 3 x weight (kg) mg in 50 ml 5% dextrose and run at 10 ml/hr = 10 mcg/kg/min. (These dilute solutions can be used via a peripheral vein).

Start Adrenaline via a central or IO line only at 0.1 mcg/kg/min. Add until the desired effect is achieved.

Start Noradrenaline via a central or IO line only at 0.1 mcg/kg/min. for 'warm shock'. Add until the desired effect is achieved.

Adrenaline & Noradrenaline: Make up 300 mcg/kg in 50 ml of normal saline at 1 ml/hour = 0.1 mcg/kg/min.

Increase until 0,3 mcg/kg/min.

(4) Hypoglycaemia (glucose < 3 mmol/l) 5ml/kg 10% Dextrose bolus i.v.

(5) Correction of metabolic acidosis pH < 7.2 Give half correction $NaHCO_3$ i.v.

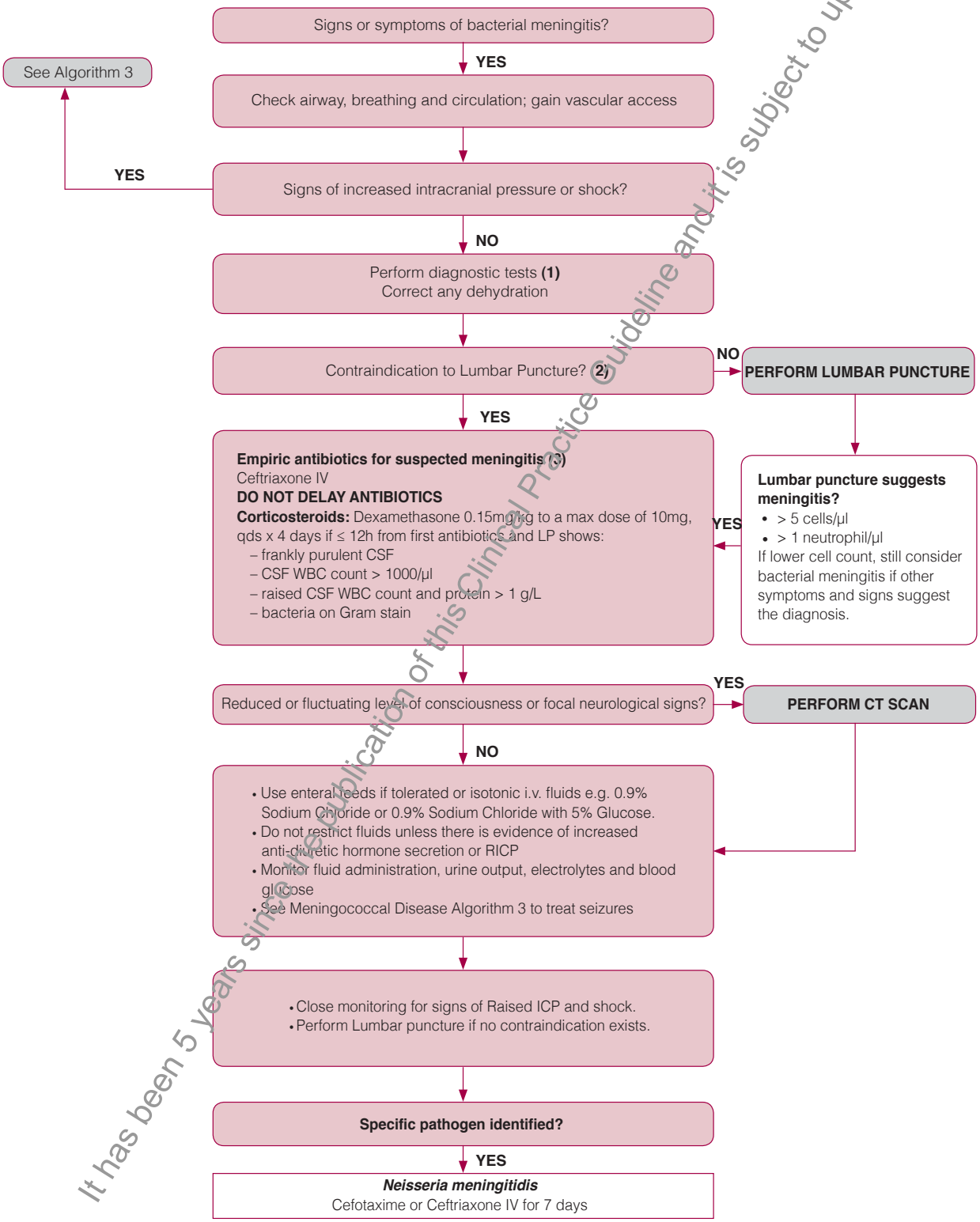
Volume (ml) to give = (0.3 x weight in kg x base deficit ÷2) of 8.4%NaHCO3 over 20 mins, or in neonates, volume (ml) to give = (0.3 x weight in kg x base deficit) of 4.2% NaHCO3.

(6) If K^+< 3.5 mmol/l give 0.25 mmol/kg over 30 mins i.v. with ECG monitoring. Central line preferable. Caution if anuric.

(7) If total Calcium < 2 mmol/l or ionized Ca^{++}< 1.0 give 0.1 ml/kg 10% $CaCl_2$ (0.7 mmol/ml) over 30 mins i.v. (max 10 ml) or 0.3 ml/kg 10% Ca gluconate (0.22 mmol/ml) over 30 mins (max 20 ml). Central line preferable.

(8) If Mg^{++}< 0.75 mmol/l Give 0.2 ml/kg of 50% $MgSO_4$ over 30 mins i.v. (max 10 ml)

Algorithm 4: Hospital management of meningococcal meningitis



Algorithm 4, adapted from Management of bacterial meningitis in children and young people. Meningitis Research Foundation (2009)[126]

(1) Diagnostic and other laboratory tests:

- blood cell count
- C Reactive Protein
- panel clotting
- blood culture
- blood glucose
- blood gas
- lumbar puncture unless contraindicated
- whole blood (EDTA) fot PCR, if testing is available

(2) Contraindications to lumbar puncture:

- clinical or radiological signs of increased intracranial pressure
- shock
- after convulsions, until stabilization of the patient
- coagulation abnormalities:
  - coagulation tests (if performed) outside the normal range
  - platelet count < 100 x 109/L
  - on anticoagulant treatment
- local infection at the lumbar puncture site
- acute respiratory failure

(3) See the NICE CPG regarding the empirical treatment of meningitis in neonates and other special situations that are beyond the scope and aims of this guide.

14. Dissemination and Implementation

This CPG is a helpful tool for professionals and users in making decisions on the most appropriate healthcare. It is therefore necessary to introduce and implement the recommendations of this guideline in those areas of the healthcare environment in which its application is relevant. The following strategies are recommended for these to be performed appropriately:

- Presentation of the CPG to the media by the health authorities.
- Presentation of the CPG to the various national associations and societies of paediatrics, family medicine, accident and emergency medicine, internal medicine, preventive medicine, microbiology and paediatric intensive care.
- Presentation of the CPG to the relevant regional associations.
- Distribution of the abridged version to various institutions and organizations in the healthcare environment.
- Collaboration with the scientific societies that have participated in the review of the CPG, to promote its dissemination.
- Sending and distribution of this CPG to different CPG collector databases, for their evaluation and inclusion in them.
- Free access to the different versions of the CPG in the web GuíaSalud, <http:// www. guiasalud.es >
- Dissemination and information on the CPG in scientific activities related to paediatrics, family medicine, accident and emergency medicine, internal medicine, preventive medicine, microbiology and paediatric intensive care.
- Translation of the full version into English.

15. Future lines of research

5.5. Microbiological confirmation tests

It is recommended to design and optimize cheaper and simpler techniques that would enable the widespread molecular diagnosis of IMD to most microbiology laboratories.

6.1. Pre-hospital administration of antibiotics

Studies should be carried out to determine the effectiveness and safety of the administration of intramuscular ceftriaxone in a poor tissue perfusion situation.

7.5. Stabilization and transport to a paediatric intensive care uni

Physical stress on people in critical condition during transport is a fact that opens doors to research on how to improve the transfer of critically ill patients with IMD.

Appendixes

Appendix 1. Information for patients. Invasive Meningococcal Disease

Information for patients, relatives, caregivers and other healthcare professionals

1. Definition of Invasive Meningococcal Disease

The invasive meningococcal disease (IMD) is a serious infection caused by the bacterium *Neisseria meningitidis* also known as meningococcus. The IMD may occur in the following ways:

1. *Meningococcal meningitis:* is an infection of the membranes that surround the brain and spinal cord. The person affected may show symptoms such as fever, headache, neck stiffness (unable to fully bend the neck forward), and sensitivity of the eyes to light (photophobia). Very small children can have a bulging fontanelle due to an increase of the pressure inside the skull.
2. *Meningococcal sepsis:* is a serious disease caused by the invasion and proliferation of meningococcus in the bloodstream and in various organs. It is a type of IMD, which evolves rapidly, by showing with red spots on the skin, known as petechiae that do not disappear when compressed with a crystal glass. The affected person may have chills, high fever, malaise, rapid breathing, rapid heart rate, excessive sleepiness, mental confusion, and can affect and alter several organs at once. Its prognosis is worse than the one for meningococcal meningitis.

3. Combination of both meningitis and sepsis.

Table 11 shows other signs and symptoms of the disease. Usually, it is difficult for a single person to have all the signs and symptoms described.

Meningococcal sepsis occurs in approximately 20% of cases.

2. Evolution of the IMD

When the meningococcus colonizes our body, it settles in the nose and pharynx. People who develop the disease are few, only those in which the meningococcus is able to surpass the immune system of the person previously colonized. The meningococcus access to the bloodstream and through the blood reaches the meninges. 50% of these patients will develop the disease with involvement of the circulatory system (sepsis) and meninges (meningitis), while in 20% of cases, the meningococcus develops high activity in the blood and produces a sepsis even before it reaches the meninges.

10% of people suffering from IMD die from the disease. This amount increases to 20% in cases of sepsis, and reaches 50% in those who come in shock before receiving medical treatment. Moreover, of those who survive the disease, between 11% and 19% suffer some sort of sequel, mainly neurological or due to complications caused by the sepsis[127].

3. Recognition of early signs and symptoms

The presentation of the IMD is varied. The disease can manifest in an easily recognizable way (i.e., severe headache with stiff neck and red spots or petechiae on the skin) or in situations that lead to a rapid association, such as after recent exposure to a patient with IMD. However, the manifestations of the disease can also be very non-specific, thus, making early diagnosis difficult. Non-specific symptoms (that is, symptoms that are very common and which appear before the symptoms characteristic of IMD) may appear in any order. The first signs are fever, vomiting, headache, and malaise, the same as those of many minor illnesses are therefore it is very difficult at first, to make a correct diagnosis. For this reason, parents and caregivers should be aware of situations that pose a high risk to the patient as these can be mistaken for benign conditions. Table 12 shows the chronology of symptoms, those characteristic of sepsis and meningitis and those, which are more serious[128]. Typically, the child also gives the impression of being really sick: does not play, does not smile, finds it difficult to talk, etc. In infants the disease manifestations are less obvious and should be suspected if there is refusal to food with a poor appearance, difficulty breathing and excessive irritability or decay.

Usually, the diagnosis of meningitis is made by lumbar puncture, which enables a sample of CSF to be analysed and cultured. If the meningococcal bacteria access the blood, this can be identified through a blood culture. Generally, the laboratory needs about 48 hours to obtain culture results and determine what type of organism is the cause of the disease[129].

4. Dimension of IMD

N. meningitidis only infects humans. The bacteria can be isolated from samples taken from the nose and throat of healthy people without symptoms of IMD (carriers). Carriers are so for a period of time, which varies very easily, though it is usually for several weeks. The percentage of meningococcal carriers in a given environment may vary between 5% and 25%. This variation depends on factors such as age (more common in children), crowded environment, smoking, or other situations such as an outbreak of IMD.

The bacteria are transmitted from person to person through droplets of large size from respiratory secretions or from the throat. The mechanisms by which *N. meningitidis*, only in some cases, exceeds the body's defences and causes the disease are complex and not precisely known. One important factor is the presence of the capsule that surrounds the bacteria and which is observed in the meningococcal isolates of patients with IMD. In people, who are healthy but meningococcal carriers, the bacterium appears without capsule.

The IMD is a compulsory notifiable disease, which means that doctors are required to report each case to the appropriate public health agency as it is a disease that poses a risk to the population. Public health professionals are responsible for identifying people who have been in close contact with the sick person to prevent the occurrence of more cases of IMD. In turn, health care professionals seek the best care for patients diagnosed with IMD and help them to recover as fast as possible.

Most cases of IMD occur during childhood. There are different bacteria that cause meningitis. The meningococcus is the most common cause of bacterial meningitis in this age group and the second most common in adults.

The infection takes place mainly in winter and spring and may cause local epidemics in boarding schools, hall of residences, military bases and, in general, more or less closed environments where people live.

Different meningococci have been identified according to the characteristics of the capsule surrounding the microorganism, and in Spain the most common are those known as B and C. At the moment, there is only one effective vaccine against meningococcal C bacteria. This has contributed to a decline in the number of cases of IMD due to meningococcal C bacteria and therefore, meningococcal B bacteria have become predominant in our country.

People most at risk of IMD are those:

- Who have had their spleen removed?
- Who have specific alterations of the immune system that favour the infection due to meningococcal bacteria?
- Who work in a microbiology laboratory?
- Who travel visiting areas where the disease is very common, such as the Middle East (Saudi Arabia) or countries of sub-Saharan Africa?[127].

5. Treatments for people affected and preventive measures for contacts

Antibiotic treatment should be started as soon as possible. Ceftriaxone is one of the antibiotics commonly used for IMD. Cefotaxime is the other antibiotic often used to treat IMD. Sometimes corticosteroids may be given, especially in children.

People who are in close contact or have been in very close contact with a person who suffers from meningococcal meningitis are those at greater risk of developing the disease. For this reason, they need to be treated with antibiotics to prevent any infection. Those most at risk include:

- √ Members of the same family
- √ Room mates
- √ People in close and prolonged contact (visit MedlinePlus®)[130]

6. Sequelae

Sepsis (growth of the microorganism within the blood) due to meningococcal bacteria results in the formation of thrombi or blood clots that can result in reduced blood flow on one or more organs or limbs (less frequently), leading to its gangrene. This increases the risk of infection and, therefore, endangers the life of the person affected even more. Paradoxically, sepsis and increased blood clotting can lead to difficult to control bleedings, which in turn worsen the blood flow in limbs and vital organs.

One in four patients who develops meningococcal sepsis will require amputation of a limb. In turn, the skin lesions can lead to scarring causing deformation and requiring surgical release and the application of skin grafts. These lesions have a very slow healing process and in order to accommodate the prosthesis to be used, the need to perform additional surgical interventions is very common. Thus, both the disease and subsequent treatment needs may have important consequences in the subsequent appearance of the person.

During the phases of puberty and adolescence, people develop and settle a stable image of themselves, increasing their autonomy and independence from the family. Changes occur where appearance and attractiveness play a role in the development of each person's personality. The IMD, which seriously jeopardizes the lives of these people, may be responsible for a series of non-recoverable or slowly recoverable changes in their appearance at a time when to the development of people the most important factor for an appropriate self-esteem is appearance. The family and social support at this stage of life is essential for the individual to successfully adapt to the new situation.

Although rapid healing of a wound can be considered a successful step within the treatment, from a medical perspective it is necessary to note that, for the person concerned, the same injury can have a negative symbolism that affects both his / her personal and social environment[131].

Hearing loss is the most common sequel of meningitis, so it is important to diagnose it as early as possible. Diagnosis can be made through various tests adapted to the age of the patient and the characteristics of the hearing loss. Once the hearing loss has been identified, and depending on the degree of involvement of the auditory system, various assistive devices shall be proposed[132].

7. Preventive habits and behaviours

The meningococcus colonizes the human nasopharynx and is transmitted by direct contact with large-sized droplets that are expelled in respiratory secretions. Meningococcal colonization in humans may be temporary, intermittent or long lasting. People with upper respiratory tract infections typically see increased chances of being colonized, like those living in overcrowded conditions or smokers, active and passive. Some authors claim that even contact with smokers may be a crucial risk factor due to the high number of carriers and the cough that characterizes smokers. It would be useful if the messages of the health authorities would not only address the need to limit smoking areas outside the home, but also insisted on the need to quit smoking[133].

Meningococcal colonization induces an immunological response in such a way that the majority of young adults have antibodies against meningococcus. Most often, the IMD occurs in people who have not been in contact before with the meningococcus and change their lifestyles (like starting to stay in halls of residences or military institutions)[127].

8. Overcoming grief

The death of someone close due to the IMD is traumatic, painful and generates anguish. The suddenness of death can lead to confusion, feelings of isolation and disbelief. There may be many questions about the death, the disease and what to expect in the coming weeks and months.

Grief means the range of emotions, changes, experiences and disorders that occur after a death.

Affliction is the sequence of reactions a person can have when dealing with bereavement.

There is no right or wrong way to feel after the death of someone close. It is an individual experience. One may experience grief through physical symptoms such as headache, feeling of emptiness in the stomach, shortness of breath, dry mouth and physical pain. It is also common to feel guilt, anger, confusion, resentment, despair, disbelief, shock, sadness, loneliness and isolation. It is important to recognize that these feelings are part of the grieving process.

Grief can also influence the behaviour in such a way that it can cause sleeping disorders, crying, changes in appetite and isolation from society. Crying is a natural and beneficial way to release emotions. Some people realize that they way to socialize and interact with others changes after bereavement.

It is very important to remember that, despite what others may say, there is no time limit for grief. One has to do the things when the person is ready to make them and feels well.

Grief also occurs at an early age after the loss of a loved one. All children need, like adults, honesty, information and involvement. The exclusion at the time of death can be interpreted as a form of protection, but it can also lead to confusion and anxiety that affect and alter children's affliction. Talk to them using words they can understand and invite them to share their thoughts and feelings is important. All children need to feel they can talk openly about the person who has died. Occasionally, they may need professional help.

It is important to recognize that grief is a natural response to the death of someone close. There is no need to hide or deny the feelings and emotions, and being aware of it and knowing how to respond, helps in the grieving process.

Having the support of friends and family, and talking about death can be beneficial. It can be difficult and sometimes painful, but it is important to talk about the person who died and share memories of him or her with the people who are close[134].

9. Helpful Resources. Organizations and entities to help those affected

- National Library of Medicine, USA. National Institutes of Health. MedlinePlus®, Health Information for you. X-Plain patient education. Interactive Tutorial from the Patient Education Institute. Available since September 2012 in the following link:

  <http://www.nlm.nih.gov/medlineplus/spanish/tutorials/meningitisspanish/htm/ 50 does not 0.htm>

- Irene Megías Fundation against Meningitis
- The Irene Megías Foundation against Meningitis was created in 2006 by Jorge Megías and his wife, Purification Roca, following the death of her daughter, Irene Megías Roca, in August 2005 at the age of 17 years by a meningococcal sepsis. Available since September 2012 in the following link: <http://www.contralameningitis.org/>
- Meningitis Research Foundation
- Foundation dedicated to research to prevent meningitis and septicaemia, and to improve survival rates and outcomes. It promotes education and awareness to reduce mortality, sequelae and offers support to those affected. It is available since September 2012 in the following link: <http://www. meningitis.org/>
- Centres for Disease Control and Prevention
- Their mission is to collaborate to create the expertise, information, and tools that people and communities need to protect their health – through health promotion, prevention of disease, injury and disability, and preparedness for new health threats. Available since September 2012 in the following link: <http://www.cdc.gov/>

Table 11. Manifestations of acute meningitis

Fever and chills
Changes in mental status (confusion)
Nausea and vomiting
Purpurish areas, bruise-like (purple)
Rash, red spots on the skin (petechiae)
Sensitivity to light (photophobia)
Severe headache
Neck stiffness (meningism)
Other manifestations that can occur with this disease
Agitation
Bulging fontanelle
Refusal of food or irritability in children under 2 years
High-pitched cry
Rapid breathing
Unusual posture. Head and neck arched backwards (opisthotonos)

Table 12. Symptoms of meningitis and septicaemia

	Septicaemia	Meningitis
Fever and/or vomiting	●	●
Severe headache		●
Pain in the limbs or joints or muscles*	✚	
Cold hands and feet, chills	✚	
Pale or blotchy skin	✚	
Fast breathing or shortness of breath		
Rash (in any part of the body)	●	● ‡
Stiff neck (less common in children under 2 years)		●
Intolerance to bright light (less common in children under 2 years)		●
Sleepy, absentminded, difficulty staying awake	●	●
Confused or delirious	●	●
Seizures		●

*: Sometimes stomach pain or diarrhoea
‡: Not given in all cases.

Please remember:‡

Symptoms marked with a red cross (✚) usually occur before the symptoms of meningitis (such as stiffness, photophobia) and before more severe symptoms: red dot (●)

Other symptoms may be present in sepsis and/or meningitis (●)

Sepsis can occur with or without meningitis

Extracted and modified from: Meningitis Research Foundation 2007. Original version in Spanish.

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Appendix 2. Glossary

Adjuvant: medication administered in addition to a primary treatment (in our case, the primary treatment is antibiotic).

Attack rate: proportion of cases that occur in a closed population and in a very specific moment. It's a cumulative incidence. This terminology is generally used in the study of outbreaks. The secondary attack rate represents the probability an individual has of having the disease exposed to a primary case, the number of patients between the contacts of a case.

Band forms: the "band forms" or slightly immature neutrophils are characterized by having a non-segmented nucleus forming a continuous band. Usually less than 5% of peripheral blood neutrophils are "band forms."

Close contact: term that is not defined with absolute precision, but it is intended to include all individuals who have had prolonged contact (8 hours or more) and also near (35 inches is the general limit set for the dissemination of large droplets) with a case of IMD, or who have been directly exposed to the patient's oral secretions during the week before the start of the patient's symptoms and up to 24 hours after the start of the antibiotic treatment.

Close contacts of a patient with IMD are: members within the same household, day carers and contact people directly exposed to the patient's oral secretions (such as by kissing, mouth-to-mouth resuscitation, endotracheal intubation or operation thereof).

According to the SIGN CPG[6], close and prolonged contact is defined as that derived from living or sleeping in the same household, students within the same dormitory, boyfriends/ girlfriends or college students who share the kitchen in a hall of residence.

Colorimetric detection by hybridization: Hybridization of the amplified material with specific probes labelled and objective reading of the results using a spectro-photometer.

Confirmed case: that in which *N. meningitidis* is isolated from a normally sterile site (CSF, blood, etc.) in a patient with clinical symptoms compatible with IMD.

Co-primary case: two or more cases that occur in a group of close contacts with disease onset within 24 hours.

Fatality rate: proportion of deaths among the sick. Cumulative incidence of death in a group of patients.

Glass test: test to be carried out at home to detect a characteristic of sepsis: the appearance of petechiae or spots on the skin anywhere on the body. It is done by pressing a glass tumbler firmly against the rash spot or, if the stains do not go away and can be seen through the glass, it may be sepsis.

Invasive meningococcal disease (IMD) is a bacterial infection whose etiologic agent is *Neisseria meningitidis*. The IMD may occur with a clinical spectrum ranging from acute meningitis to rapidly progressive meningococcal septicaemia, or a combination of both. It usually occurs in three forms:

- Meningococcal septicaemia, characterized by fever, petechiae, purpura and impairment in the general condition. This presentation is associated with significantly worse outcomes.
- Clinical meningitis with fever, lethargy, vomiting, headache, photophobia, neck stiffness and positive signs of Kerning and Brudzinski. These are the common characteristics of bacterial meningitis established by any cause. Petechiae and purpura may also be associated. Some young patients may have less specific characteristics, such as poor appetite, irritability, high-pitched cry and a bulging fontanelle.
- Combination of both meningitis and septicaemia.

LAMP (*loop-mediated isothermal amplification*) is a variant of the recently developed PCR technique. This methodology employs multiple primers and isothermal conditions (60 °C to 65 °C) to amplify the target sequence in a relatively short time (30-60 min.) using *Bst*-DNA polymerase (*Bst*-ADNpol). LAMP does not require thermocycler to ensure denaturing-recoupling cycles for annealing of *primers* and the polymerase activity, as in conventional PCR.

Likelihood ratio: ratio between the probability of a particular outcome in an individual patient and the likelihood of the same result in an individual who is not sick.

Low-density microarray: an array is a collection of molecular probes (DNA or RNA) orderly fixed on a solid support. The term low density refers to the number of probes attached.

Odds ratio: the ratio between the probability of occurrence of an event and the probability that it does not occur. This ratio, which in English is called odds and for which there is no commonly accepted Spanish translation, indicates the more likely occurrence of the event is than its non-occurrence.

Open clinical trial: at least two meanings exist for this term:

- Clinical trial in which the researcher and participant know the intervention that is being applied to the participants (not blind). The randomisation may or may not be used in these trials. It is sometimes also referred to as *open label* designs.
- Clinical trial which uses an open sequential design whereby the decision or not to stop the trial depends on the magnitude of the effect, and there is no maximum finite number of participants in the trial.

Negative likelihood ratio: proportion of patients with a negative result (1-sensitivity) versus the proportion of non-sick patients who also have a negative result (specificity).

Negative predictive value: proportion of people with a negative test result and who really do not have the disease. It varies with the prevalence of the disease among the population.

Positive likelihood ratio: the proportion of patients who have a positive test result (sensitivity) versus the proportion of non-sick patients who also have a positive result (1- specificity).

Positive predictive value: proportion of people with a positive test result who actually have the disease. It varies with the prevalence of the disease among the population.

Primary Case: this case occurs in the absence of previous known close contact with other patients.

Primary prevention: a set of interventions that aim to prevent the onset or incidence of the disease; interventions aimed at susceptible individuals, which may or may not have risk factors to avoid suffering from the disease. Other actions include detection, assessment and reduction or control of risk factors among the population.

Probable cases: one in which the polysaccharide antigen is detected in the CSF (for example, latex agglutination reaction or polymerase chain immunohistochemistry) or presence of clinical purpura fulminans in the absence of a diagnosis by culture, in a patient with clinical symptoms compatible with IMD.

Public Health is the science and art of preventing diseases, prolonging life, promoting health as well as physical and mental efficiency through the organized efforts of the community in order to: a) clean up the environment, b) control infectious diseases; c) provide health education; d) organise medical and nursing services and e) develop social mechanisms that provide the individual and the community living standards adequate for the maintenance of good health.

Purpura fulminans: extensive or rapidly progressive bruising associated with DIC and shock.

Relative risk: measures the strength of the association between exposure and disease. It indicates the likelihood of developing the disease in those exposed to a risk factor compared to the unexposed group. It is calculated by dividing the estimated incidence of disease in those exposed between the incidence of the disease in those unexposed.

Resuscitation of sepsis: measurements performed in the first and following five hours of the treatment after 0 hour, aimed at restoring cardiovascular stability (standardise mental status, capillary refill < 2", palpable peripheral pulses with normal heart rate and blood pressure levels for age), normalize oxygenation and ventilation and correction of critical metabolic disturbances. It includes the removal of blood culture, start of antibiotics therapy and control of the infectious site, as well as determination of blood lactate levels.

Secondary case: one that takes place in close contact with a primary case 24 hours or more after the onset of symptoms in the primary case.

Secondary prevention: a set of interventions that aim to prevent the progression of the biological injury or illness in patients who are asymptomatic or show a reduced morbidity. The incidence of the disease cannot be reduced, as it has already started, but can reduce its prevalence.

Sensitivity: proportion of true sick patients who have a positive test result. It measures the ability of the diagnostic test to detect sick individuals.

Sepsis, severe sepsis and septic shock: sepsis is characterized by the presence of two or more systemic inflammatory responses following a documented infection:

1. Temperature > 38 °C or < 36 °C.
2. Heart rate > 90 beats/min.
3. Respiratory rate > 20 breaths/min or pressure or blood pressure CO_2 < 32 mmHg.
4. White blood cell count > 12,000 / mm 3, <4000/mm 3, or> 10% of immature types.

Septic shock: severe sepsis subgroup defined as the persistence of sepsis-induced hypotension despite adequate fluid resuscitation.

Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension. Disorders due to hypoperfusion may include lactic acidosis, oliguria, or acute mental status disorder.

Severity scoring system: system used to identify changes in clinical conditions; widely used can improve results.

Specificity: proportion of true healthy people who have a negative result in the test. It measures the ability of the diagnostic test to detect healthy individuals.

Tertiary prevention: a set of interventions that aim to prevent disability in patients with a disease at a symptomatic stage. It includes measures to postpone or delay the progression of the disease and prevent complications, as well as the rehabilitation of patients.

Transmission Precautions: all those measures to separate the infected patients from the healthy patients, in order to avoid transmission.

- **Precautions against standard transmission:** includes washing of hands, gloves, goggles, mask and gown and preventing any biological accident. **Precautions against air transmission:** includes individual room with a negative pressure system, HEPA filters and enough daily air replacements. Respiratory protection by wearing a mask to enter the room or limit transportation of the patient around the hospital. If it is indispensable, it will be carried out using a surgical mask.
- **Precautions against contact transmission:** individual room or with another patient suffering from the same infection. Hand washing and use of gloves when entering the room. When leaving, dispose of gloves and wash hands again. Use a gown and limit transportation of the patient around the hospital as much as possible.

- **Precautions against droplet transmission:** the measures to take be taken into account in the case of a patient with meningococcal meningitis are the following:

  – The patient will not be sharing the bedroom.

  – People who have close contact with the patient will use disposable masks.

  – The use of disposable gloves and gowns is not recommended.

Appendix 3. Abbreviations

AGREE	*Appraisal of Guidelines for Research & Evaluation*
APC	Activated protein C
CT	Cranial computed tomography
CI	Confidence interval
CPG	Clinical practice guideline
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
ECDC	*European Centre for Disease Prevention and Control*
EDTA	Ethylenediaminetetraacetic acid
GDG	Guideline development group
ICP	Intracranial pressure
ICU	Intensive Care Unit
IMD	Invasive meningococcal disease
LP	Lumbar puncture
LR-	Negative likelihood ratio
MIC	Minimum inhibitory concentration
MISS	Meningococcal septic shock
NICE	*National Institute for Health and Clinical Excellence*
NPV	Negative predictive value
OR	Odds ratio
PCR	*Polymerase chain reaction*
LR+	Positive likelihood ratio
PPV	Positive predictive value
RCT	Randomized
RR	Relative risk
SIGN	*Scottish Intercollegiate Guidelines Network*

Appendix 4. Declaration of interest

The following members of the development group have declared no conflict of interests: José Cristóbal Buñuel Álvarez, Alejandro Eguilleor Villena, Patricia Gavín Benavent, Juan Manuel García-Lechuz Moya, Juan Antonio Guerra de Hoyos, Pedro Martín Muñoz, Juan Ignacio Martín Sánchez, Jorge Miguel Megías Carrión, Purificación Robles Raya, Juan Ruiz Canela Cáceres, Azucena Santillán García.

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