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Be vigilant for invasive meningococcal disease

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What are the different presentations?

INVASIVE MENINGOCOCCAL DISEASE (IMD) IS POTENTIALLY DEVASTATING, CAUSING DEATH AND permanent disability, mainly, but not exclusively in young children.

Justifiably, therefore, fear of this disease has taken the place in the consciousness of parents and medical practitioners alike, which was once occupied by infections such as smallpox, polio and diphtheria. Few therapeutic advances have been made in the management of these diseases, but in most parts of the world, vaccination has confined all three to history.

Similarly, despite public awareness campaigns, and advances in intensive care, mortality rates from meningococcal disease have altered little since the millennium. However, the development of vaccines with the potential to cover the majority of meningococcal strains, now brings the prospect of eradication much closer.

What are the red flags for referral?

CAUSES

Neisseria meningitidis is an encapsulated Gram-negative diplococcus which colonises the upper respiratory tract without causing symptoms in up to 25% of the population. Carriage is more common in teenagers, smokers, and in those living in overcrowded conditions.[1,2]

At least 13 different serogroups cause invasive disease. In the UK serogroup B causes more than 80% of cases of invasive disease. This was not always so. Serogroup A was common in the early part of the 20th century, and though now rare in Western Europe, still causes epidemics in sub-saharan Africa. Serogroup C caused about half the cases in the UK before the conjugate vaccine was introduced. Serogroup Y is seen in the USA, and increasingly in the UK. W135 is the strain associated with the Haj pilgrimage.[3]

INCIDENCE

Although the annual incidence of IMD in the UK has halved in the past 20 years, it is still 25/100,000 children, or 2.05/100,000 population i.e. around 1,000 cases per year. There are more cases in the winter and early spring, often mirroring the influenza season.

More than 75% of cases occur in the under 5s, reflecting the lack of ability of the immature immune system to »

How can cases be prevented?

mount an effective response to the polysaccharide capsule of the organism. There is also a peak around adolescence, attributed to high rates of nasopharyngeal carriage. Risk of development of invasive disease also varies with socioeconomic status, contributed to by overcrowding and passive smoking.

However, even in areas with higher than average incidence, a GP would not expect to see cases commonly enough to hone diagnostic skills. A high index of suspicion and a low threshold for referral is therefore essential if children are to be given the maximum chance for morbidity-free survival.

CLINICAL FEATURES

Meningococcal disease can present with features of septicaemia, fever, purpura, and rapidly progressive shock, or with meningitis (fever, headache, photophobia, neck stiffness, seizures, altered level of consciousness), which can occur without a rash. Many cases have a mixed picture.[1,2]

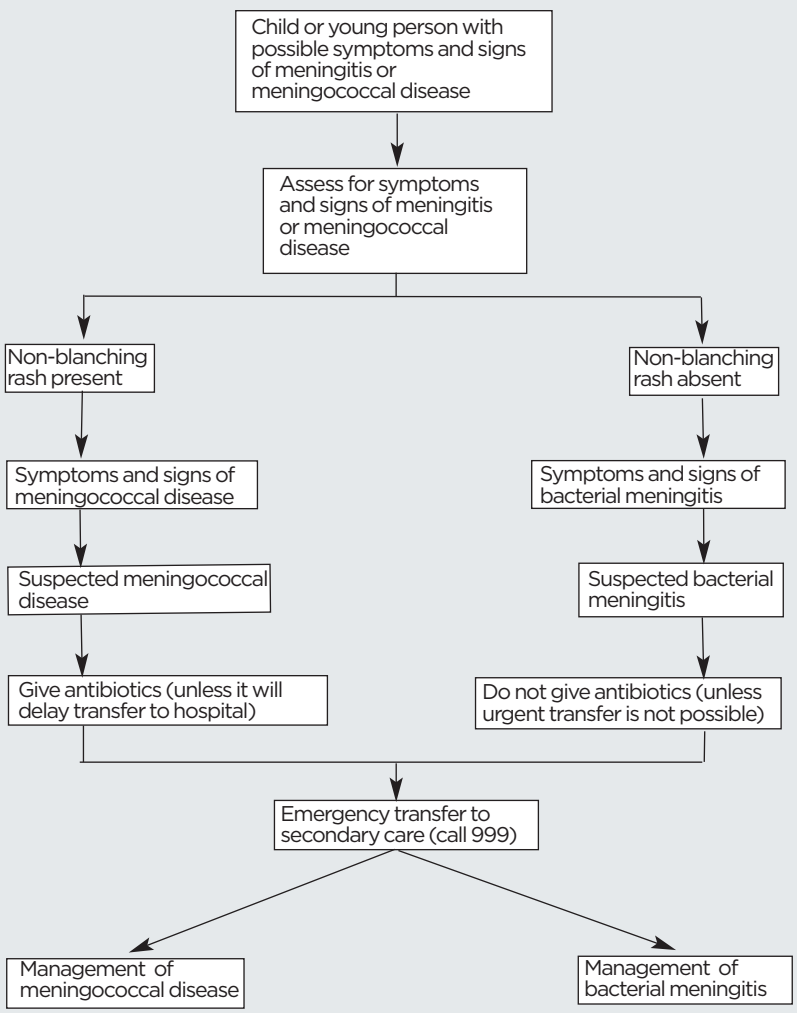
Early in its course, symptoms and signs may be indistinguishable from other more common intercurrent infections in childhood. Young infants with meningitis may not display the classical signs, but appear unwell, lethargic and floppy. Furthermore, the rash may initially appear as a blanching eruption, with an irregular moth-eaten appearance, which only later becomes purpuric.

The following features in a sick child should always raise the suspicion of IMD, particularly when found in combination:

- Non-blanching rash
- Altered mental state/reduced level of consciousness
- Cold hands and feet
- Extremity/leg pain
- Fever
- Headache
- Neck stiffness
- Focal neurological signs
- Skin mottling/prolonged capillary refill
- Signs of shock

Figure 1

Prehospital management for bacterial meningitis and meningococcal disease (adapted from the NICE pathway)[4]



GP ASSESSMENT

A focused history backed up by a thorough examination is vital. Individually, the features listed have a low positive predictive value for IMD, so it is important to put them in the context of an overall assessment.[4]

'A high index of suspicion and a low threshold for referral is essential'

The timescale of the evolution of symptoms is particularly important to establish. A rash which has been present and unchanged for days is unlikely to be caused by IMD, whereas a rapidly evolving rash is more concerning.

Similarly an ill, toxic-looking child, not interested in his or her surroundings will prompt immediate action, whereas a child sitting up smiling, and playing with toys is much more reassuring.

While we tend to think of non-blanching rashes as being particularly indicative of IMD, there are many other causes.

Pin-prick petechiae in association with a more generalised erythematous rash, tonsillitis and lymphadenopathy may indicate group A streptococcal disease, which has increased in incidence over the past decade. An afebrile child with purpura in extensor distribution of limbs, associated with joint swelling may suggest Henoch-Schönlein purpura. Petechiae in the distribution of the superior vena cava

may be associated with any vomiting illness. However, petechiae which start to spread, become pupuric, or occur in association with signs of shock or meningitis, or in any child who appears ill should always be treated as IMD until proven otherwise. The underlying principle is: if in doubt treat.

IMMEDIATE ACTION

Any child with symptoms and signs suggestive of IMD and a non-blanching rash should be transferred to hospital as an emergency immediately. Give IM (or IV) benzylpenicillin (or ceftriaxone) at the earliest opportunity, but do not let treatment delay transfer, see figure 1, opposite.

A vague history of penicillin allergy (e.g. rash developing during a treatment course) does not contraindicate treatment. Only withhold treatment if there is a clear history of anaphylaxis.

'Any child with symptoms and signs suggestive of IMD and a non-blanching rash should be transferred to hospital as an emergency immediately'

If you suspect meningitis in a child with no rash, do not give antibiotics unless there is likely to be significant delay (hours) before transfer is possible, e.g. in remote and rural settings.

If the child does not have features suggestive of IMD at the time of initial assessment it is important to give parents advice regarding symptoms and signs which may suggest deterioration, and make sure they know how to access emergency care. In moderately ill children with non-specific signs, arrange a further review in 4-6 hours.

PREVENTION

Antibiotics

Antibiotics to eliminate nasopharyngeal carriage are given to close contacts, who may transmit infection to other susceptible individuals.[5]

Until 2012, rifampicin was the agent of choice. However, ciprofloxacin is now given to all age groups including pregnant women. Its advantages are that it is a single dose, is more readily available in community pharmacies, and does not interfere with the oral contraceptive pill, or stain contact lenses. Traditionally, ciprofloxacin has not been used routinely in pregnancy or childhood because animal studies associated it with arthropathy. This has not proved significant in humans.

Vaccination

The first vaccines to be developed for meningococcal disease were polysaccharide vaccines, which gave some protection against serogroups A, C, W135 and Y. These were used for travellers to endemic areas, for secondary prophylaxis in outbreaks, and in those at increased risk such as asplenic patients. However, children under two years do not respond to this vaccine, and even in older children and adults, the protective response is short lived (3-5 years), and it has no effect on nasopharyngeal carriage or herd immunity.[6]

A major advance in the prevention of meningococcal disease came with the development of conjugate vaccines, in which the polysaccharide antigen is coupled to a carrier protein, thus enabling a T cell dependent immune response achievable by infants, and induction of memory.

Following successful introduction of Hib conjugate vaccine to the routine childhood immunisation schedule in 1992, the group C conjugate vaccine was developed and introduced into the infant schedule in 1999-2000, with a catch up programme to protect susceptible adolescents.

A quadrivalent (A, C, W135 and Y) conjugate vaccine is now licensed, and has replaced the role of the polysaccharide vaccine, but is not deemed cost effective enough to supersede universal MenC vaccination in the UK. This may change if groups A, W135 or Y increase in prevalence.

Tackling group B meningococcal (MenB) disease has proved more challenging. Its capsule does not induce an effective immune response, even in adults, and it shares components in common with human glycoproteins, including those in fetal neural tissue. A vaccine directed against these antigens might therefore fail to produce protective immunity or even induce a harmful autoimmune response.[3]

The first vaccines to show efficacy in epidemics were directed against outer membrane vesicles (OMV), which contain proteins and lipopolysaccharide, specific to particular strains of MenB. They provided limited cross-protection against other strains, however. Following whole genome sequencing of MenB, candidate surface proteins were identified which were capable of inducing bacteriocidal antibodies.

'Give IM or IV benzylpenicillin or ceftriaxone at the earliest opportunity but do not let treatment delay transfer'

Three such proteins have been combined with the OMV from the New Zealand epidemic strain to produce the European Medicines Agency approved Bexsero vaccine. This is likely to induce immunity to an estimated 78% of circulating MenB strains. However, the exact efficacy will not be known unless the vaccine is introduced into the universal schedule. It is currently available to be given to high-risk patients, and following deliberations by the Joint Committee on Vaccination and Immunisation is likely to be introduced into the schedule at 2, 4 and 12 months, once a cost-effective price is negotiated.

Any change in the childhood vaccination schedule puts a considerable burden on those delivering the programme. Febrile reactions are common following this vaccination, so paracetamol will be given routinely, contrary to current practice. Primary care will be the first in line in the assessment of these febrile infants, and will have an invaluable role in reassuring parents that the benefits of vaccination far outweigh the risks from short-term sequelae. Parents of children who have lost life or limb through meningococcal disease will need no such convincing. »

key points

SELECTED BY
Dr Peter Saul
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***Neisseria meningitidis* is an encapsulated Gram-negative** diplococcus which colonises the upper respiratory tract without causing symptoms in up to 25% of the population. At least 13 different serogroups cause invasive meningococcal disease (IMD). In the UK serogroup B causes more than 80% of cases of invasive disease.

Although the annual incidence of IMD in the UK has halved in the past 20 years, it is still 25/100,000 children. There are more cases in the winter and early spring. More than 75% of cases occur in the under 5s, reflecting the lack of ability of the immature immune system to mount an effective response to the polysaccharide capsule of the organism. There is also a peak around adolescence, attributed to high rates of nasopharyngeal carriage. A high index of suspicion and a low threshold for referral is essential.

Meningococcal disease can present with features of septicaemia, fever, purpura, and rapidly progressive shock, or with meningitis which can occur without a rash. Many cases have a mixed picture. Young infants with meningitis may not display the classical signs, but appear unwell, lethargic and floppy.

A rash which has been present and unchanged for days is unlikely to be caused by IMD, whereas a rapidly evolving rash is more concerning. Petechiae which start to spread, become purpuric, occur in association with signs of shock or meningitis, or in any child who appears ill should always be treated as IMD until proven otherwise.

Any child with symptoms and signs suggestive of IMD and a non-blanching rash should be transferred to hospital as an emergency immediately. IM (or IV) benzylpenicillin (or ceftriaxone) should be given at the earliest opportunity, but treatment should not delay transfer. If the child does not have features suggestive of IMD at the time of initial assessment it is important to give parents advice regarding symptoms and signs which may suggest deterioration.

Ciprofloxacin to eliminate nasopharyngeal carriage is given to close contacts who may transmit infection to other susceptible individuals. Group C conjugate vaccine was developed and introduced into the infant schedule in 1999-2000. A vaccine active against MenB is likely to be added to the childhood schedule at 2, 4 and 12 months, once a cost-effective price is negotiated.

Bacterial meningitis caused by Haemophilus B is rare, and cases caused by pneumococcus have markedly reduced since the 13-valent vaccine was introduced. Once the vast majority of meningococcal strains are prevented by vaccination, the chances of seeing — and of missing — a case of bacterial meningitis or meningococcal septicaemia within routine practice will become exceptionally small.

'Primary care will have an invaluable role in reassuring parents that the benefits of vaccination far outweigh the risks from short term sequelae'

However, the sting of the disease when it occurs will remain even when the incidence tails off. We need to make sure that we remain vigilant to recognise IMD and administer prompt treatment.

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The Meningitis Research Foundation
Support for patients and families affected by meningitis and septicaemia
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Information, counselling and home visits for families affected by meningitis and septicaemia
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