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Review Article

Meningococcal Disease Section 3: Diagnosis and Management

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CLINICAL ASPECTS OF THE DISEASE

In a career lifetime, an average GP is likely to see only a handful of cases of meningitis. Despite this, at early presentation, meningococcal disease and in particular, meningitis, can have very non-specific symptoms, especially in children and may not demonstrate the tell-tale signs of non-blanching rash, neck stiffness, bulging fontanelle (in babies) etc. For this reason, GPs see many children with vague symptoms and in order to avoid missing a case, there can be precautionary hospital admissions, following a low threshold for reviewing a young child with symptoms.

Acute illness caused by *N. meningitidis* can result in meningitis and/or septicaemia. A mixed picture of invasive septicaemia and meningitis occurs in approximately 12% of cases, and the remainder include alternative sites of infection, including meningococcal pneumonia, monoarthritis, pharyngitis, as well as relatively mild meningococcaemia[1].

The classical clinical symptoms and signs of meningitis due to meningococcal infection include acute headache, photophobia, neck stiffness, nausea and vomiting and a petechial rash and typically only occur in older children and adults[2]. Elderly patients are less likely to present with neck stiffness and are more likely to present with altered consciousness compared to those aged <30 years[3]. As well as septicaemia, cause of death from meningitis may be related to raised intracranial pressure. When septicaemia is present either at the outset or as a complication the disease may advance very quickly with circulatory shock and reduced level of consciousness.

In infants and young children, who are most commonly affected by meningococcal disease, the features are less classic and meningitis and septicaemia may occur together. Features include fever, poor feeding, vomiting, irritable on handling, drowsiness, staring or vacant expression, bulging fontanelle and seizures. Cases of septicaemia will have increasingly poor circulation with cold mottled peripheries, prolonged capillary refill time, increased work of breathing and eventually unresponsiveness and death. The purpuric rash which aids diagnosis may be present early but often develops as the child is deteriorating.

Early diagnosis of meningococcal disease is very important given that it can lead to death in a healthy person within 6-12 hours of the first appearance of symptoms. Its course typically starts with non-specific vague features with fever but often then rapidly evolves. These early prodromal symptoms are non-specific, such as those typically found in common viral respiratory tract infections, including fever, headache, sore throat and coryza, as well as irritability, loss of appetite, nausea, vomiting. Early warning red alert signs include limb pain, skin discolouration, increased work of breathing and cool peripheries[4]. Because the early prodromal features are non-specific the National Institute for Health and Care Excellence (NICE) Guidance on Fever in under 5s [CG160] strongly recommends that when febrile children are being discharged parents should be given information on when to seek further help[5].

Recently, there have been several seminal publications on the diagnosis, treatment, prevention and control of meningococcal disease. Most notable have been two sets of guidelines published in 2016, namely the "*Global Meningococcal Initiative (GMI) Guidelines for the diagnosis and confirmation of invasive meningococcal disease*"[6] and the "*The UK Joint specialist societies guidelines on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults*"[7]. These comprehensive guidelines are an excellent reference resource for clinicians and microbiologists alike.

MICROBIOLOGICAL DIAGNOSIS

Conventional microbiology workup on peripheral blood and/or CSF for the diagnosis of meningococcal disease is performed at the major hospitals in Northern Ireland, as detailed in Table 1. Recently, the UK Standards for Microbiology Investigation issued an update on the investigation of cerebrospinal fluid and this forms the cornerstone for laboratory diagnosis[8].

Gold standard culture methods for meningococcal diagnosis are too slow and frequently compromised by prior antibiotic treatment. The development and application of sensitive quantitative Polymerase Chain Reaction (qPCR) assays has significantly improved laboratory detection rates and has reduced the time required to confirm invasive meningococcal disease[9-11]. Typically, molecular testing protocols follow a

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TABLE 1:

Laboratory microbiology workup on peripheral blood and/or CSF for the diagnosis of meningococcal disease as performed at the major hospitals in Northern Ireland

Site	Primary Culture*				Latex	Sens	ID	PCR
AAH	CBA	35 - 37°C	5 - 10% CO_2	48Hrs	Wellcogen antigen test	ETest	MALDI-TOF	Manchester (Confirmation, typing and sensitivities)
	Choc	35 - 37°C	5 - 10% CO_2	48Hrs	(if adult non blood stained WBC count > 5 /mm^3)			
					(if neonate non blood stained WBC count >30)			
RVH	CBA	34 - 38°C	5 - 10% CO_2	48Hrs	Pastorex Meningitis Kit	ETest	MALDI-TOF or Vitek2	Regional Virus Laboratory (RVL) [Confirmation, serogroup type]**
	Choc	34 - 38°C	5 - 10% CO_2	48Hrs	(if WBC count abnormal)			
CAH	CBA	35.5°C	5 - 10% CO_2	48Hrs	None	Etest	API NH	Manchester (Confirmation, typing)
	Choc	35.5°C	5 - 10% CO_2	48Hrs				RVL Virology if PCR requested on form
UH	CBA	35 - 37°C	5 - 10% CO_2	48Hrs	Pastorex Meningitis Kit	Etest	Vitek2	RVL [Confirmation, serogroup type]
	Choc	35 - 37°C	5 - 10% CO_2	48Hrs	(if WBC count > 50 /mm^3)			

Abbreviations:
AAH=Antrim Area Hospital, CAH=Craigavon Area Hospital, RVH = Royal Victoria Hospital, UH=Ulster Hospital, CBA = Columbia Blood Agar, Choc = Chocolate Agar

* HSC Clinical Microbiology Laboratories in Northern Ireland base their SOPs off the UK Standards for Microbiology Investigations, Investigation of Cerebrospinal Fluid (SMI B27) which is produced in association with several groups including the Northern Ireland Microbiology Forum And Audit Group.

** Current practice is for qPCR testing (ctrA TaqMan) to be performed in Belfast. Positives are all typed by qPCR (siaD TaqMan) with ctrA LAMP also used for confirmation, especially of "discrepant" results

two stage process (i) confirmation of infection using specific qPCR detection of *N. meningitidis ctrA* gene (capsule transport gene) (ii) identification of meningococcal serogroup by qPCR analysis of specific conserved regions within *N. meningitidis* capsular biosynthesis (*cps)* locus[9]. A positive qPCR result for a normally sterile site specimen e.g., blood and/or CSF is regarded as definitive for meningococcal diagnosis[12]. Despite concerns regarding detection of carriage strains, molecular testing of respiratory specimens in clinical context is increasingly recognised as a valuable adjunct[13-15]. NICE acknowledge the proven clinical utility of molecular assays (qPCR) for meningococcal diagnosis, but also note that such assays are not available in most NHS hospitals due to resource limitations[12]. Currently, qPCR remains the preserve of a limited number of centralised reference laboratories who possess the necessary infrastructure, equipment and technical skills to routinely deliver an effective service. The time required to transport samples to centralised laboratories ultimately means that molecular detection of meningococci has little or no impact on patient management, whereby such testing merely confirms an initial clinical diagnosis and provides epidemiological data on circulating strains[16,17]. Recently, the Regional Virus Laboratory at the Royal Victoria Hospital has developed a Loop-Mediated Isothermal Amplification (LAMP) molecular assay, comprising a high activity strand displacing enzyme, nucleotides and Mg^{2+} and a minimum of four or a maximum of six primers targeting a total of six or eight specific regions on target sequence, resulting in an assay with stringent specificity. This assay offers performance equivalent to reference laboratory qPCR testing and this LAMP technology has opened up the ability to perform rapid detection of *N. meningitidis* in any health care setting in less than 60 minutes[15,18,19]. Compared to qPCR, LAMP offers several advantages including simplified methodology, quicker reaction time and lower instrument costs combined with visual detection of positive reactions. LAMP is also highly resilient to inhibition and is capable of being applied to crude specimen preps which increases their potential for use in resource limited environments[20].

Testing of respiratory specimens (i.e. nose, throat or nasopharyngeal swabs) to detect meningococci using conventional culture methods is often discouraged, unless the objective is to detect meningococcal carriage. Indeed, throat and nasopharyngeal swab cultures have been used for decades to recover both pathogenic capsular strains and non-pathogenic non-capsular strains in carriage studies[21]. However, there is growing evidence that direct molecular testing of respiratory specimens is useful for diagnosis of meningococcal disease in children[14,16]. Carriage rates are very low in young children and employment of the sensitive LAMP assay to specifically detect capsular strains has shown very high positive and negative predictive values in a recent clinical study[15]. Rapid molecular testing of non-invasive

respiratory specimens could help clinicians to identify the many children with meningococcal disease who are not diagnosed when they first present to healthcare[4]. In addition to improving diagnosis of disease, molecular testing of respiratory swabs has also been useful to detect carriage in adolescents. Currently a meningococcal carriage study is being undertaken of undergraduate students in Belfast, employing direct molecular testing of self-collected throat swabs using real-time PCR and LAMP to identify carriers of serogroups B, W and Y.

CLINICAL MANAGEMENT

(i) *Paediatric intensive care*

Paediatric intensive care unit (PICU) management of meningococcal disease is extremely challenging. Patients suffering from the same infection differ in host response to the infection ranging from a mild influenza-like illness to fulminant sepsis with multiple organ failure[22]. Children with meningococcal disease usually present to the district general hospital where the initial resuscitation and administration of antibiotics takes place. Thereafter those with evidence of on-going shock will be transferred, usually ventilated, to the PICU. A paediatric retrieval team based in the Royal Belfast Hospital for Sick Children undertakes the majority of these transfers.

Fig 1. Continuous Veno-venous Haemofiltration (CVVH) has been introduced as a treatment option in Northern Ireland and has been available in the PICU, RBHSC since 2013.

Treatment of meningococcal disease follows well defined principles of managing severe sepsis in children[23]. In brief this consists of aggressive intravenous fluid resuscitation with administration of crystalloid boluses of up to 60ml/kg in the first fifteen minutes of presentation, antibiotic therapy and frequent reassessment of response to therapy. This is followed by intubation and controlled ventilation. This requires the administration of anaesthetic drugs and muscle relaxants and is frequently associated with haemodynamic instability. This can be minimised with cautious dosing, fluid loading and use of peripheral intravenous adrenaline as an inotrope. Goals of controlled ventilation include reduced oxygen demand and tighter control of arterial carbon dioxide levels. The latter is important in regulating cerebral blood flow in children with meningitis and raised intracranial pressure. Pragmatically, ventilation also allows easier placement of arterial and central venous lines and may assist in preventing pulmonary oedema, secondary to capillary leak and massive volume resuscitation. Some children with severe sepsis will require in excess of 200ml/kg of resuscitation fluid in the first 24 hours, despite concomitant use of inotropic therapy. To put this in context, this volume is almost three times the circulating blood volume.

Whilst the meningococcal bacterium is usually killed by the administration of a cephalosporin, the inflammatory process triggered by this contributes to the morbidity and mortality associated with this disease. As the sickest children are looked after in the PICU, it is usually here that

TABLE 2:

Definitions of cases requiring public health action[11]

Cases requiring public health action
Confirmed case
Clinical diagnosis of meningitis, septicaemia or other invasive disease (e.g. orbital cellulitis, septic arthritis)
AND at least one of:
• *Neisseria meningitidis* isolated from normally sterile site
• Gram negative diplococci in normally sterile site
• Meningococcal DNA in normally sterile site
• Meningococcal antigen in blood, CSF or urine.
NB: Although not meeting the definition of a confirmed case, meningococcal infection of the conjunctiva is considered an indication for public health action because of the high immediate risk of invasive disease.
Probable case
Clinical diagnosis of meningitis or septicaemia or other invasive disease where the consultant in health protection, in consultation with the physician and microbiologist, considers that meningococcal infection is the most likely diagnosis. Some microbiological tests (e.g. rising antibody levels) that are not considered sufficient to confirm the diagnosis of meningococcal disease may change the case category from 'possible' to 'probable'.
Cases not requiring public health action
Possible case
Clinical diagnosis of meningitis or septicaemia or other invasive disease where the consultant in health protection, in consultation with the clinician and microbiologist, considers that diagnoses other than meningococcal disease are at least as likely. This category includes cases who may have been treated with antibiotics but whose probable diagnosis is viral meningitis. In such cases, prophylaxis for contacts is not indicated, but giving out information about meningococcal disease may be helpful.

the feared complications of limb-loss and brain injury are manifest. Whilst fluid loading is recognised as lifesaving, the development of severe fluid overload with capillary leak syndrome and severe tissue oedema can compromise the blood supply to the limbs. This is compounded by the use of vasoconstrictive agents used in order to maintain an adequate blood pressure and support vital organ perfusion. Early fasciotomies may be needed to relieve compartment pressures in the hope of salvaging the limbs. Fluid overload is increasingly recognised in the intensive care literature as contributing to the morbidity associated with intensive care[24]. This, coupled with acute kidney injury, secondary to sepsis, has led to the use of modified forms of dialysis instituted on the PICU. Recently, Continuous Veno-venous Haemofiltration (CVVH) has been introduced as a treatment option in Northern Ireland and has been available in the PICU, RBHSC since 2013 (Figure 1). This therapy uses a haemofilter to allow precise control of fluid removal from the plasma. Removed ultrafiltrate contains cytokines and starting this therapy often allows a reduction in the vasopressor requirements for that patient. This "dirty" ultrafiltrate is replaced with a balanced electrolyte solution to maintain haemodynamic stability. By not fully replacing small amounts of the ultrafiltrate, very precise fluid balances may be achieved in order to reduce tissue oedema.

(ii) *Local antibiotic management*

Current local antibiotic treatment recommendations for meningitis were consulted through publically available web-based guidelines. Three HSC Trusts, namely Belfast, South Eastern and the Western Trusts utilised the 'Microguide' app and the Northern Trust used the 'RxGuidelines' platform.

All guidelines recommend the use of an IV Cephalosporin as first line treatment for adult meningitis, with the Western Trust recommending Cefotaxime 2g qid IV, the Belfast and South Eastern Trusts both recommending Ceftriaxone 2g bd IV and the Northern Trust recommended either of these two cephalosporins first line. These two antibiotics have been described as' two peas in a pod' as they are third generation cephalosporins with very similar activity against meningococci, pneumococci and *Enterobacteriacae*. All four Trust apps recommend the addition of Amoxicillin 2g four hourly IV, if the patient is immunocompromised or pregnant.

All four guidelines recommend Choramphenicol 25mg/kg qid IV in severe penicillin allergy with the addition of Cotrimoxazole 1.44g bd IV in patients who are immunocompromised, pregnant or aged over 55/50 as previously outlined above. The Northern Trust guideline alone advised that pregnant cases where Co-trimoxazole was been considered should first be discussed with microbiology as treatment choice would then be based on risk benefit and could include Cotrimoxazole, Meropenem and Vancomycin.

Advice on the use of steroids in adult meningitis was outlined by two trusts. The Northern Trust advised that steroid therapy was only indicated for patients with meningitis but not septicaemia and that steroids should not be utilised in those with impaired consciousness level, focal or lateralised neurological signs, markedly raised opening pressure at LP or evidence of cerebral oedema on brain scan. The Belfast Trust guideline advise that steroids should be given when pneumococcal meningitis is suspected, for example in recent ear infection, age over 65 and in people with underlying health problems. This guideline also advises that steroids should be continued if there is frankly purulent CSF with Gram positive cocci on Gram stain or if pneumococcal infection is confirmed, but that steroids may be discontinued if CSF analysis is not consistent with bacterial meningitis, i.e. CSF is not purulent, the WCC is less than 1000, CSF protein is less than 1gm/L. It states that steroids should also be stopped if another pathogen other than pneumococcus is found and that steroids are contraindicated following recent neurosurgery or in immunosuppression.

Full prescribing details for the antibiotic and clinical management of meningococcal disease in adults have recently been published by the UK Joint Specialist Societies, entitled "*The UK Joint Specialist Societies Guidelines on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults*"[7]. These may be freely obtained at the following link:-

http://www.journalofinfection.com/article/S0163-4453(16)00024-4/fulltext

Similarly, for children under 16 years, NICE have recently (February 2015) updated their previous Clinical Guideline (CG102) on "*Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management*"[12], which may be found at the following link:-

https://www.nice.org.uk/guidance/cg102

Accurate diagnosis can influence the duration of treatment in children and young people. If meningococcus is identified, e.g. using qPCR or LAMP testing (confirmed meningococcal disease), NICE guidance recommends treatment with IV Ceftriaxone for 7 days[12]. If no specific bacterial pathogen is identified (unconfirmed bacterial meningitis) NICE recommends IV Ceftriaxone for at least 10 days. Duration of IV antibiotic treatment for other (confirmed) causes of bacterial meningitis may be significantly longer; 21 days or more, depending on the pathogen identified[12].

PUBLIC HEALTH MANAGEMENT

Acute bacterial meningitis or meningococcal septicaemia are on the lists of statutory notifiable diseases in Northern Ireland. All doctors have a legal responsibility to notify the Public Health Agency if they suspect that a patient is suffering from one of these diseases. The Public Health Agency duty room (0300 555 0119) should be contacted and the cases assessed and categorised as detailed in Table 2: If a case is categorised as "confirmed" or "probable" meningococcal disease, then the Public Health Agency will arrange for antibiotic prophylaxis to be given to close contacts. These contacts are usually

defined as anyone who had an overnight stay in the same household as the case in the seven days prior to the onset of symptoms. The first line antibiotic choice is now ciprofloxacin in most cases[13].

Although the overall risk to household contacts is low, if prophylaxis is not given, the absolute risk to an individual in the same household, one to 30 days after disease onset in the index case, is about one in 300 of also developing disease. Chemoprophylaxis aims to reduce the risk of invasive disease by eradicating carriage of meningococci in the close household contacts. Chemoprophylaxis acts by eradicating carriage from established carriers who pose a risk of infection to others and also to eradicating carriage in those who have newly acquired the invasive strain and who may themselves be at risk of developing disease.

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