Meningococcal disease in children: a clinical review

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Meningococcal disease is a global burden and remains one of the leading infectious causes of death in children, with an estimated annual death rate of 170,000 worldwide. Despite these figures, the management of children with severe meningococcal sepsis and septic shock remains suboptimal. This review presents an overview of this condition including the epidemiology, pathogenesis, clinical manifestations, complications, management, and prediction.

Key words: meningococcal disease, epidemiology, pathogenesis, prevention, Neisseria meningitidis, meningococcemia, meningitis, children.

1. Neisseria meningitidis

Meningococcal disease (MCD) is caused by a bacterial microorganism called *Neisseria meningitidis*, a member of the genus Neisseria, which is an obligate human-specific pathogen that preferentially colonizes the mucous membrane of the nasopharynx[1]. Neisseriae are gram-negative diplococci with two pathogenic members: *N. meningitidis* (meningococcus) and *N. gonorrhoeae* (gonococcus). These are very similar in their morphological and cultural characteristics[2]. In pus from inflammatory exudates, pathogenic neisseriae are usually found inside polymorphonuclear pus cells, and they appear, in gram-stained specimens, as kidney-shaped pairs with the opposed surfaces flat or slightly concave[2,3]. Other members of the genus Neisseria are common commensals of the nasopharynx. These include *N. lactamica, N. polysaccharea, N. subflava* and *N. sicca*, which are of low pathogenicity[2,4]. Colonies of pathogenic neisseriae (*N. meningitidis* and *N. gonorrhoeae*) are identified by their ability to produce acid from glucose. On the other hand, they do not ferment lactose or sucrose, and therefore, they could be differentiated from low or non-pathogenic neisseriae[4]. Despite their similar morphological and cultural characteristics, meningococcus and gonococcus are associated with two entirely different diseases: meningococcal disease and gonorrhea.

Neisseria meningitidis has five major serogroups that are pathogenic for humans: A, B, C, W135, and Y. Serogroups A, B, and C account for more than 90% of all invasive MCD, while less than 10% of clinical isolates are from serogroups W-135 and Y[1]. The classification of serogroup is determined by the meningococcal lipopolysaccharide (LPS) capsular antigen[4]. Serotyping and subtyping are used to further classify meningococcal strains by the variations in outer membrane proteins (OMP)[2]. These are classified according to electrophoretic mobility into five major classes including PorA (class 1 protein) and PorB (class 2 and 3 proteins)[1]. OMP act as cation- or anion-selective porins controlling the influx of water-soluble molecules through the outer membrane and are linked to the severity of the disease[5].

2. Epidemiology

Meningococcal disease (MCD) is a global burden, with an estimated annual death rate of 170,000 worldwide[6]. The disease has an overall mortality greater than 10%[7] and is even higher in the developing world, reaching 26%.[8] Invasive disease is most common among young children, with a slightly higher incidence in males (55% of cases) than females[3,9]. Up to 10% of the population may be asymptomatic carriers with nasopharyngeal colonization, but higher rates among children can be seen in crowded conditions[3]. Meningococcal carriage rates are expectedly higher in institutions such as universities, schools, prisons, and military institutions. A study by Neal et al.[10] showed a dramatic increase in carriage rates among students in their first year at a British

university. This was, particularly, in the first week of the academic year, with meningococcal carriage rates increasing rapidly from 6.9% (day 1) to 23.1% (day 4).

Meningococcal disease (MCD) occurs sporadically and in epidemics throughout the world with seasonal variations. As mentioned above, there are five major pathogenic organisms that cause invasive MCD, and their prevalence varies with time and geographical location (Fig. 1). Areas such as sub-Saharan Africa from Ethiopia to Senegal (known as the meningitis belt), Nepal and India are endemic for serogroup A, which caused large epidemics during the nineties, whereas serogroups B and C tend to be the commonest in Europe and most of the Americas[8,9,11,12]. In 2009, the meningitis belt area struggled to cope with another large epidemic affecting thousands of people, with a case fatality of up to 11.4%. Most of these cases were reported from one epidemic focus including Northern Nigeria and Niger, which is again characterized by the predominance of serogroup A[13]. In contrast to serogroup A, MCD due to serogroup W-135 occurs in smaller numbers and has been associated mainly with outbreaks during the Hajj (pilgrimage to Mecca) season.[4]

In the United Kingdom (UK), about two-thirds of cases were due to group B, one-third to group C and less than 5% to other groups[14]. However, the epidemiology in the UK has changed in recent years. This is explained by the dramatic decline in the number of cases caused by serogroup C following the implementation of a new meningococcal serogroup C conjugate (MCC) vaccination program, which has successfully reduced the morbidity and mortality rate from serogroup C disease[15]. As in other parts in the world, in Turkey, the epidemiology of *N. meningitidis* is also changing. Previously, carriage rate due to serogroups A and C accounted for most isolates[16,17]. Nonetheless, recent studies show that W-135 and B are currently the commonest serogroups causing meningococcal meningitis[18,19]. This current trend may be attributed to pilgrims travelling to Saudi Arabia for the Hajj.

Fig. 1. Distribution of predominant *N. meningitidis* serogroups before meningococcal serogroup C conjugate vaccination.

3. Pathogenesis

Nasopharyngeal carriage is the reservoir of pathogenic meningococci in 5-20% of the general population, and man is the only known reservoir[11]. Nasopharyngeal colonization usually remains asymptomatic and does not progress further[14]. However, following colonization of the nasopharyngeal area of the upper airway tract by meningococci, bloodstream spread may ensue. This type of invasion is typically seen following upper respiratory tract infections[11]. The development of invasive MCD is dependent upon a wide variety of bacterial, host and environmental factors.

3.1. Bacterial Factors

Some meningococcal strains (virulent strains) are more likely to cause invasive MCD[4]. Virulence of the meningococci is determined by the ability to release endotoxins and adhere to and invade nasopharyngeal epithelium. This is achieved through the presence of surface-expressed proteins, such as pili and OMP[1], polysaccharide capsule[3] and lipooligosaccharide (LOS)[5,20]. Type IV pili expressed by *N. meningitidis* are essential for selective adherence to host non-ciliated epithelia[3], and this gives the meningococci their ability for colonization and transmission[5]. Meningococcal LOS (endotoxin) is another factor implicated in meningococcal interaction with host epithelial cells and constitutes up to 50% of the outer membrane of pathogenic neisseriae. LOS is biochemically similar to LPS of gram-negative bacteria, in that it contains a lipid A subcomponent[5]. In addition to interaction with host epithelial cells, it is also a major factor contributing to the human proinflammatory response to meningococci[20]. LOS may alter the permeability of the blood-brain barrier, which is important for the invasion of the central nervous system. Furthermore, it causes the activation of macrophages and

release of tumor necrosis factor, a primary mediator of meningococcal septic shock[5]. This outlines the importance of LOS as a virulence component involved in multiple steps in the pathogenesis of both meningococcal meningitis and meningococcemia. OMP that act as cation- or anion-selective porins (PorA and PorB), controlling the influx of water-soluble molecules through the outer membrane, are linked to the severity of the disease[5]. The surface-exposed loops of PorA are greatly involved in activating the human immune system by inducing the production of bactericidal and opsonophagocytic antibodies[1]. Once through the epithelium, *N. meningitidis* enters into the bloodstream, where the capsular polysaccharide enhances the survival of meningococcus by resisting phagocytic killing[3].

3.2. Host Factors

Age is an important factor, which is evident by the variation in incidence of MCD in different age groups. The peak incidence of the disease is in the first year of life[4], which could be explained by the loss of maternal antibody[5]. Moreover, it seems that asymptomatic carriage contributes to increasing the immunity against the disease in older populations[4]. Host factors are still not fully understood. Older patients with hereditary complement deficiencies are more likely to acquire MCD and have more severe infection than others. For example, patients who have deficiencies in the terminal component C5 to C9 of the complement cascade will usually suffer from recurrent infection with gram-negative bacteria, caused almost solely by meningococci[1,3,5], whereas absent or malfunctioning properdin results in an increase in both risk[21] and severity of MCD[1]. Also, there is an increased risk among persons with acquired complement deficiencies, such as nephrotic syndrome, systemic lupus erythematosus and hepatic failure[3]. This highlights the importance of the complement system in defense against MCD. Anatomical or functional asplenia are other recognized factors predisposing to MCD[5]. Other host factors that may affect the outcome and severity of MCD include protein C or protein S deficiency and decreased endothelial expression of thrombomodulin and protein C receptors, which are linked to the severity of the disease and development of purpura fulminans[4].

3.3. Environmental Factors

The transmission and development of invasive MCD has been associated with many environmental factors. Crowded living conditions, low socioeconomic status and antecedent viral infections, particularly influenza, are recognized factors with increased risk of MCD[3]. Other factors include both active and passive smoking[3]. Maternal smoking has been demonstrated to be a significant risk factor for the development of invasive MCD in infants[22,23]. The effect of smoking is presumed to be due to disrupting the respiratory epithelium with a decrease in mucociliary function and hence reduced bacterial clearance[24]. During outbreaks, other factors that are associated with higher risk of acquiring invasive MCD include intimate kissing with multiple partners, being a university student and preterm at birth[25], binge drinking[26], marijuana-related activities[27], bar patronage[28], and attendance at a party of adolescents or young adults[29]. The increased risk of invasive MCD associated with these activities may be explained by a combination of factors that could facilitate transmission, including overcrowding, intimate contact with carriers, poor ventilation, sharing of drinking glasses and cigarettes, active and passive smoking, and smoking-associated coughing.

4. Prevention

Natural immunity against *N. meningitidis* frequently develops after repeated colonization with different serogroups or serotypes. Additionally, enteric bacteria that express cross-reactive antigen and non-pathogenic neisseriae contribute to the development of natural immunity against meningococcal infection[3]. Immunity can also be induced artificially by vaccination. Prevention includes primary prevention by vaccination and secondary prevention with chemoprophylaxis for close contacts of patients with MCD.

4.1. Primary Prevention

Vaccines against groups A, C, W135, and Y meningococci have been licensed in the United States of America (USA), the UK and other countries[9,14,30]. Polysaccharide vaccines including the tetravalent vaccine (Menomune®) against serogroups A, C, W-135, and Y were

first developed 30 years ago, and research studies showed that in adults, the vaccine induced the production of suitable levels of bactericidal antibodies, which were maintained for up to one year following immunization[31]. The limitation of these polysaccharide vaccines is that they are ineffective in young children and induce only short-term protection[20]. However, a new approach to improve the immunogenicity of these polysaccharide vaccines was achieved by chemical conjugation to a carrier protein, which transformed the vaccine to a T-cell-dependent antigen inducing long-term immunity[32,33]. A promising phase 2 study provides evidence for the efficacy of a novel tetravalent meningococcal (MEN-ACWY) vaccine in infants by using a nontoxic mutant of diphtheria toxin as the carrier protein and aluminium phosphate as an adjuvant[34]. An earlier successful attempt led to the development of the MCC vaccine, which changed the healthcare practice in the UK with the implementation of a new vaccination program in November 1999.

The UK was, in fact, the first country to start mass vaccination with the MCC vaccine, which was integrated into the routine immunization schedule for infants, administered as one dose for those under 5 years of age, and as a catch-up school-based immunization campaign for adolescents[35]. The benefits of the new MCC vaccine have been demonstrated in many research studies[36-38]. These included high levels of herd immunity and reduced morbidity and mortality from laboratory-confirmed serogroup C disease in England and Wales[11,15]. MCD due to serogroup C in different age groups is almost nonexistent after five years of the MCC vaccination program[39]. An effective vaccine against serogroup B is not yet available for routine use in young children[30,39,40]. The major challenge in developing a vaccine targeting the serogroup B capsular polysaccharide is its poor immunogenicity in humans. This could be explained by the cross-reactivity with human neural antigens that express structurally similar antigens[41,42]. Several attempts have been made to develop a reliable vaccine against serogroup B. For example, a nine-valent meningococcal B PorA vaccine (NonaMen®) has been developed with promising results inducing suitable anti-PorA antibodies[43].

4.2. Secondary Prevention

Meningococcal meningitis and septicemia are both notifiable diseases[5]. Protection of close contacts is possible via administration of effective chemoprophylaxis, which includes rifampicin, ceftriaxone or ciprofloxacin[3,14,44]. The rationale of antibiotic prophylaxis is to eliminate nasopharyngeal carriage in close contacts and thus prevent the development and transmission of pathogenic strains. Although evidence suggests that other antibiotic regimens such as azithromycin[45] or a combination of rifampicin and erythromycin[46] may be effective in eradicating nasopharyngeal carriage, only rifampicin, ciprofloxacin and ceftriaxone are currently recommended for the chemoprophylaxis of MCD in the UK national guidelines[47,48] and the USA[49].

4.3. Other Measures

Other preventive measures include public education, reducing overcrowding in living quarters and workplaces, and isolation of patients for 24 hours after start of antibiotics with concurrent disinfection of discharges[9]. Good communication and involvement of parents, school, nursery, and college are other measures that may reduce any unnecessary concerns and contain the disease at the time of epidemics. Additionally, all risk factors such as smoking, binge drinking, and attending of overcrowded places should be addressed, especially during outbreaks of the disease.

5. Clinical Manifestations

Following colonization of the nasopharyngeal area by meningococci and then bloodstream spread, invasive MCD may manifest in various infectious syndromes. The spectrum of MCD ranges from occult bacteremia, which is self-limited, to severe sepsis resulting in death within a few hours. Invasive MCD tends to manifest mainly in two major forms, meningitis and septicemia, with the predominant features of cardiovascular collapse and cutaneous manifestations of clotting disorder. In Europe, the commonest presentation is actually a mixed picture of both meningitis and septicemia (60-66%), followed by septicemia alone (22-25%) and lastly meningitis alone[50,51]. The septicemia only presentation tends to have a greater mortality rate than the meningitis

only presentation[52]. A large retrospective study between 1977 and 1993[53] reported a 19% mortality rate for children with meningococcal septicemia, 11% for those with mixed picture of sepsis and meningitis and 1.2% for meningitis only. About half of the patients who die of MCD do so within 24 hours of admission[54]. Data from the developing world showed a higher proportion of fatalities, with more than 70% dying within 24 hours of admission[8,55]. This high mortality rate may be explained by the poorly developed healthcare system, limited resources, late presentation, and difficulties accessing immediate healthcare, in addition to differences in socioeconomic and environmental conditions.

5.1. Meningococcal Septicemia (Meningococcemia)

This syndrome results from the systemic release of various mediators in response to bacteria endotoxins leading to generalized increase in capillary permeability[56]. Meningococcemia is characterized by shock and disseminated intravascular coagulation (DIC)[54]. Diagnosis is not always straightforward because classic clinical features may be absent or non-specific at initial presentation. Initially, there may be a prodrome of an upper respiratory tract infection followed by high fever, poor feeding, lethargy, malaise, headache, and nausea. Then, within a few hours, the toxic picture of septic shock and DIC becomes apparent. Cold hands and feet, leg pains and abnormal skin color (skin mottling or pallor) were reported to be early signs of MCD, which precede the typical symptoms by several hours[51]. These findings attracted public attention and were included in the recently published guidelines by the Scottish Intercollegiate Guidelines Network (SIGN)[57]. However, no data are available about the predictive values of these non-specific symptoms. Should these be low, this would unnecessarily increase the workload of emergency and primary care physicians and the burden on the healthcare system by unnecessary admissions. Hence, more research in this area is clearly justified to give a precise answer. Skin rash is another characteristic feature of this syndrome, which may begin as a non-blanching rash (erythematous macules) or petechiae progressing to purpuric lesions and large hemorrhagic areas[58]. However, the interpretation of non-blanching rash should be done in the context of the overall picture. Only a small percentage of children with non-blanching rash will have MCD, whereas the rest are likely to have viral illnesses[59]. An important feature to differentiate meningococcal rash is that it is unlikely to be confined to the distribution of the superior vena cava[59]. Thompson et al.[51] reported petechial rash as being the first and most common (42–70% of cases) classic symptom to emerge and that parents are usually alerted to act by this symptom. This is expected following the intense public education campaigns about MCD quoting non-blanching rash as an important warning sign. Cases of fulminant meningococcemia can also be complicated by massive adrenal hemorrhage (Waterhouse-Friderichsen syndrome), which is characterized by a rapidly progressive course of irreversible shock and DIC with massive mucosal and skin hemorrhages[60].

Diagnosis of meningococcemia is confirmed by cultures from blood, cerebrospinal fluid (CSF) or skin lesion aspirate[51]. Detection of meningococcal DNA by polymerase chain reaction (PCR) is another useful test to confirm the diagnosis, particularly for patients who received prior antibiotics[54]. A quick detection of meningococci is possible with Gram stain of buffy coat preparations of blood, CSF[60] or skin lesion biopsy/aspirate[61].

5.2. Meningococcal Meningitis

The invasion of the meninges and crossing of the blood-brain barrier with the sequential liberation of endotoxins and activation of pro- and anti-inflammatory cytokines are the underlying pathophysiological processes of the clinical picture from meningococcal meningitis[54]. This may also result in brain edema and high intracranial pressure. Patients presenting with meningitis share similar symptoms and signs of other types of meningitis. These include fever, headache, neck stiffness, nausea, vomiting, impaired consciousness, photophobia, and seizures. The classic meningeal signs such as Kernig sign, Brudzinski sign and fever may be absent in neonates and small infants[62,63], and therefore the threshold to admit to hospital and treat should be lower. In contrast to meningococcemia, meningococcal meningitis is usually straightforward to diagnose; however, atypical presentation with focal neurology

without the characteristic rash may make the diagnosis of MCD more difficult[54]. Children with meningitis are generally better than those with meningococcemia alone[60], and as mentioned earlier, have a relatively good prognosis[51,53]. When meningitis is associated with septicemia, it may present with sudden onset and rapidly progressive manifestations of shock, purpura and reduced level of consciousness. The prodrome of meningitis resembles that of meningococcemia including symptoms of upper respiratory tract infection[52], but the course is more insidious[54].

The diagnosis of meningococcal meningitis is confirmed by examining the CSF including culture. Biomedical analysis shows a low CSF: blood glucose ratio and high protein, whereas microscopy shows high neutrophils and gram-negative intracellular diplococci[64]. Other possible tests include those mentioned earlier under meningococcemia such as PCR and Gram-stain.

5.3. Rare Presentations

Meningococcal disease (MCD) may rarely present in other forms such as upper respiratory tract infection, tonsillitis, pneumonia, septic arthritis, pericarditis, peritonitis[65], osteomyelitis, conjunctivitis, endophthalmitis, or chronic meningococcemia[39].

Chronic meningococcemia is a rare clinical manifestation of MCD presenting as recurrent attacks of fever, arthralgia and maculopapular rash with normal periods in the interim when symptoms may disappear completely[1,60]. The nature of this condition makes it more difficult to diagnose, and it is commonly misdiagnosed as collagen or autoimmune disease such as Henoch-Schönlein purpura[5]. The diagnosis of chronic meningococcemia is usually confirmed by blood culture taken during febrile episodes, but several blood cultures may need to be performed, as false-negative results are high[1,5]. The course of this condition is variable, ranging from spontaneous recovery to progression to systemic complications. Generally, it has an excellent prognosis for patients treated with appropriate antibiotic therapy, with a cure rate approaching 100%[66].

6. Complications

The rates of complications and sequelae were linked to the severity of MCD associated with a specific strain of *N. meningitidis:* serogroup C serotype 2a[67]. These complications include skin infarction, adrenal hemorrhage, reactive arthritis, endocarditis, myocarditis, renal infarction, lung abscess, subdural effusion or empyema, and brain abscess[3]. Another fatal complication is basilar artery occlusion secondary to intracerebral purpuric lesions, which manifests with collapse and respiratory arrest in an apparently improving patient[5]. Most patients who survive the disease fully recover; however, a significant number of patients will suffer permanent neurological sequelae such as intellectual impairment and cranial nerve deficits including deafness[4,8,55] and peripheral amputations[68,69]. Other recognized but rare complications are avascular necrosis with growth disturbances and late skeletal deformities, seizures, blindness, hemiparesis or quadriparesis, and obstructive hydrocephalus[3]. Cataract and uveitis are reported as well[55]. All these complications are assumed to be related to vasculitis, DIC and hypotension of severe MCD[3]. As these pathophysiological processes are mostly associated with septicemia, this may explain the higher morbidity and mortality rates from meningococcemia rather than from meningitis.

7. Definitions

This review utilizes the published definitions of systemic inflammatory response syndrome (SIRS), severe sepsis and septic shock defined by Goldstein and the Members of the International Consensus Conference on Paediatric Sepsis[70]. Table I presents the categorization of these syndromes in line with the published consensus and Figure 2 illustrates these various syndromes and their overlap.

8. Clinical Management: Therapeutic Goals

Meningococcal disease (MCD) is a medical emergency. Early recognition of invasive MCD is crucial to successful disease management. Management requires immediate treatment of the underlying infection and its systemic manifestations. If there is any suspicion of meningococcal infection, antibiotic therapy should be initiated immediately. A benefit

Table I. Definitions of SIRS, Sepsis, Severe Sepsis and Septic Shock*

	Syndrome	Definition
1	SIRS	Presence of at least two of the following criteria: core temperature of >38.5°C or <36°C, tachycardia, tachypnea, and elevated or depressed white blood cell count (all corrected for age)
2	Sepsis	SIRS in the presence of or as a result of infection
3	Severe Sepsis	Sepsis and one of the following: Cardiovascular dysfunction, acute respiratory distress syndrome, or two or more other organ dysfunctions
4	Septic Shock	Sepsis and cardiovascular dysfunction defined as hypotension, need for vasoactive drug, or presence of at least two signs of hypoperfusion (unexplained metabolic acidosis, high lactate, oliguria, prolonged capillary refill time: >5 seconds, and temperature gap >3°C) despite administration of intravenous fluid bolus ≥40 ml/kg in one hour

*Adapted from Goldstein et al.[70]

of general practitioners (GPs) immediately administering antibiotic (e.g. parenteral benzylpenicillin) to patients with suspected meningococcal septicemia was demonstrated, showing that these patients are 2.5 times less likely to die than those not given penicillin[71]. Many other studies support the early use of antibiotics, showing a higher mortality rate from delays in administrating antibiotics[72-74].http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WJT-4TWFH1W-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=ed29c1a9d410fcade5759ef13a8b608a - aff3#aff3 In contrast, however, a controversial study suggested that antibiotic therapy in the community increased mortality[75]. In that study, the average Glasgow Meningococcal Septicaemia Prognostic (GMSP) score for patients who received penicillin was noticeably higher than for those who did not. Since the severity of the disease correlates well with poor outcome, it is important to consider the confounding potential of severity on the findings of that study. Also, most GPs justified their decision when penicillin was not given as being due to uncertainty in the diagnosis, and hence this is another potential source of bias. The authors recommended conducting a randomized controlled trial to provide a definitive answer. However, this would be unethical unless stronger evidence is available from large prospective studies that control for any possible biases. Hence, GPs should continue giving antibiotics in line with the recommendation from national health agencies such as SIGN[57] and the Health Protection Agency[47]. Penicillin, chloramphenicol and third-generation cephalosporins are all antibiotics recognized in the treatment of MCD. Resistance to both penicillin and chloramphenicol has been reported[76,77], and hence, third-generation cephalosporins (cefotaxime and ceftriaxone) are currently the mainstream antibiotics used, with proven good CSF penetration[78].

Following admission to the hospital, the main target of therapy is to maintain adequate microcirculation. Therefore, volume resuscitation to restore the intravascular compartment and inotropes to support the myocardium are the main approaches to the management of meningococcal septic shock[79]. Failure to administer adequate fluids or inotropes was associated with an increased risk of death in MCD[80]. An audit recently conducted in the UK showed failure in more than 60% of cases to follow a consensus guideline on emergency management of children with severe sepsis and septic shock, with most children

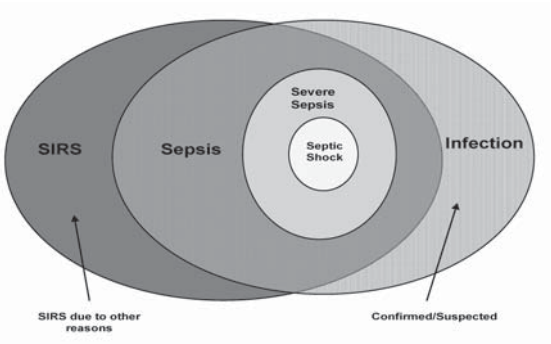

Fig. 2. The overlap of various syndromes.

receiving inadequate fluid resuscitation and inotropic support during the golden hours following presentation[81]. This failure mainly affected children presenting with shock, and may have resulted in a higher mortality rate. A previous study showed similar results with hospital treatment being suboptimal in 71% of patients, with higher fatalities in patients with longer times from illness onset to treatment[82].

As with any other patient with severe sepsis, the management of these patients may also include, subject to severity, ventilatory support, hemofiltration, steroid therapy, administration of activated protein C, and administration of blood and blood products[83]. The instigation of these therapies should be considered without delay within the framework of goal-directed therapy. This implies stepwise management with certain therapeutic endpoints being achieved within a specific time interval. The guidelines published by the American College of Critical Care Medicine[84] recommended the therapeutic endpoints presented in Table II.

Despite increasing awareness of the concept of goal-direct therapy since the mid-eighties[85], it was not linked to outcome and reported until the late 1990s[84]. Subsequently, a substantive change in the management of septic patients was applied with studies reporting a decrease in mortality rate both in children[86] and adults[87] following this management approach. The Surviving Sepsis Campaign[88] is a global initiative aiming to improve the management of sepsis based on the concept of early goal-directed therapy or evidence-based goals. This provides guidelines (adult and pediatric) and sepsis management bundles, which are accessible via the internet from anywhere in the world.

9. Outcome and Prediction

Several investigators have identified unfavorable prognostic features in patients with MCD using clinical and laboratory parameters. Many studies have been undertaken to generate prognostic scores using these parameters as predictors of a patient's outcome and risk of mortality[89-91]. All available scoring systems were primarily developed to predict death, either specifically in MCD[90,92-94], or generically in a critically-ill pediatric population[89,91,95]. More than 25 specific scoring systems have been developed for prediction in MCD[55,90,92-94,96-100]. However, not all of these scores are widely used. The GMSP score is the most well-known (Table III). Children presenting with a GMSP score of ≥8 are at an increased risk of death[90,101]. There are two other generic scores widely used that have been validated for use in MCD. These are the Pediatric Index of Mortality (PIM) and Pediatric Risk of Mortality (PRISM). Some of these scores were developed on the basis of an extended period of time (e.g. values over 24 hours) rather than at a single point on first medical contact[89]. Others were calculated from the information collected at the time of the first face-to-face contact, or one hour after, between the patient and a doctor from the pediatric intensive care unit (PICU)[91,95].

Despite the extensive research done about prediction in MCD, there is a scarcity of work about predicting the level of supportive therapy (fluid and inotrope therapy) required. Hence, there is a need for more research to identify the important predictors of management requirements. This would improve the management of MCD, with the ultimate goal of increasing the survival rate and decreasing complications.

Table II. The Therapeutic Goals In and Beyond the First Hour of Presentation

First hour	Beyond the first hour
CRT < 2 seconds	The same goals as for the first hour and the following:
Normal pulses with no differential between peripheral and central pulses	ScvO2 ≥70%
Warm extremities	Normal perfusion pressure (MAP-CVP or MAP-IAP)
Urine output >1 ml/kg/h	CI between 3.3 and 6.0 l/min/m^2
Normal mental status,	
Normal blood pressure for age	

CRT: Capillary refill time. ScvO2: Mixed oxygen venous saturation. MAP: Mean arterial pressure. CVP: Central venous pressure. IAP: Intra-abdominal pressure. CI: Cardiac index.

Table III. Glasgow Meningoccoccal Septicaemia Prognostic (GMSP) score[90]

Variables	Score
Hypotension: SBP < 75 mmHg for age < 4 years SBP < 85 mmHg for age > 4 years	3
Skin / rectal temperature difference >3°C	3
Modified coma score <8 or deterioration of ≧3 at any time	3
Absence of neck stiffness	2
Deterioration in the last hour (by asking parents or nurses)	2
Base deficit > - 8	1
Widespread ecchymoses or extending lesions on review	1

10. Conclusion

Meningococcal disease continues to be one of the main infectious causes of childhood mortality. In spite of modern therapies, mortality is 5-10% in developed countries and much higher in the developing world[6,8,55]. Early recognition, aggressive resuscitation and normalization of all physiological parameters, with prompt referral to a specialist PICU for severe cases, may lead to a significant reduction in the case fatality rate[79]. This overview of MCD has identified a number of key issues relating to improving the management of this condition. However, many studies identified a failure of recognition and management of severe sepsis and septic shock despite the availability of evidence-based published guidelines. There is insufficient published work addressing this issue to date. There is therefore a need for more research to explore these shortcomings.

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