Review

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Two centuries of meningococcal infection: from Vieusseux to the cellular and molecular basis of disease

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Scientific knowledge of meningococcal infection has increased greatly since the epidemic nature of the illness was first described by Vieusseux at the dawn of the nineteenth century. In fact, revolutionary advances have been made in public-health measures, antimicrobial therapy, diagnostic procedures, anti-inflammatory drugs and supportive care facilities. Based on the knowledge accumulated to date, it is generally accepted that the pathogenesis of meningococcal infection involves multiple links that interconnect in a complex web of phenomena from *Neisseria meningitidis* attachment to meningococcal sepsis or meningitis. In fact, a myriad of strongly interacting inflammatory molecules and cells have been implicated in neisserial infection, illustrating the complexity of meningococcal pathogenesis. In addition, many of these signalers are critically involved in outcomes in the human host. Deciphering the pathogenesis of meningococcal infection could expand our knowledge and provide important clues to the host–pathogen interaction, as well as leading to the development of new therapeutic tools. Herein, we review the history of the discovery and characterization of meningococcal disease, epidemiological features of the disease with an emphasis on recent developments in Brazil, the cellular and molecular basis of disease, and discuss diagnosis and therapy.

Introduction

Meningococcal disease is an infection caused by *Neisseria meningitidis*. The disease can have catastrophic consequences in individuals and can become epidemic in developed and developing countries (Buysse *et al.*, 2008). In Brazil, neisserial infection is endemic and presents a cyclic pattern, the majority of cases occurring during the winter. At the Emílio Ribas Institute of Infectology, located in the city of São Paulo, the incidence of meningococcal disease is approximately 100 cases per year (de Souza *et al.*, 2007a). We have observed a broad range of clinical presentations of *N. meningitidis* infection, including atypical complications and dramatic manifestations such as purpura fulminans (de Souza *et al.*, 2006a, 2007b; Marotto *et al.*, 1997). In fact, this malady has been linked to a constellation of pathophysiological phenomena: euthyroid sick syndrome (Joosten *et al.*, 2000), acute renal failure (Marotto *et al.*, 1997), acute respiratory distress syndrome (Eisenhut *et al.*, 2006), cerebrovascular disease (de Souza *et al.*, 2008a, b), brain abscess (Rothbaum *et al.*, 2006), atrioventricular-node inflammation (Robboy, 1972), primary meningococcal conjunctivitis (Barquet *et al.*, 1990), intrauterine meningococcal infection (Bhutta *et al.*, 1991), electrolyte and acid-base disturbances (Holland *et al.*, 2002; Kornelisse *et al.*, 1997), peritonitis

(de Souza *et al.*, 2006b), pericarditis (de Souza *et al.*, 2006c), cellulites (Kennedy *et al.*, 2006), myocardial dysfunction (Pathan *et al.*, 2004), endocarditis (Arias *et al.*, 2007), urethritis (Urre *et al.*, 2005) and rhabdomyolysis (van Deuren *et al.*, 1998).

Historical background

The classic discovery that various diseases are caused by micro-organisms occurred in the twilight of the nineteenth century and symbolised a milestone in the history of infectious diseases. In 1879, Louis Pasteur demonstrated the link between microbiological organisms and puerperal sepsis. In 1887, an equally novel discovery was made by the Austrian pathologist Anton Weichselbaum, who clarified the aetiological nature of meningococcal disease by showing, for the first time, that there was a connection between *N. meningitidis* (then known as *Diplococcus intracellularis meningitidis*) and ‘epidemic cerebrospinal meningitidis’ (Weichselbaum, 1887). In Europe, meningococcal disease was first reported by Vieusseux in the city of Geneva in 1805 (Vieusseux, 1805). Vieusseux provided a striking clinical picture of meningococcal sepsis and baptised the malady ‘fièvre cérébrale maligne non contagieuse’ (non-contagious malignant cerebral fever).

Interestingly, during the epidemic of cerebrospinal fever in Geneva, Vieusseux hypothesized that meningococcal infection, rather than being transmitted through direct person-to-person contact, was spread by 'bad air': '*le mal parut tenir à une constitution particulière de l'air, et non à une contagion se communiquant de proche en proche* (the illness seemed to be linked to a particular property of the air rather than a contagion passed from individual to individual).' In fact, Vieusseux did not fully understand the nature of neisserial disease transmissibility, because he was unaware of a certain epidemiological link, the asymptomatic carrier state, which would only be described at the close of the nineteenth century (Kiefer, 1896). Across the Atlantic, the first reported cases of this 'singular and very mortal disease' occurred in Medfield, MA, USA (Danielson & Mann, 1806).

In the first decade of the twentieth century, the mortality rate for untreated meningococcal disease was 75–80% (Swartz, 2004). In 1906, Simon Flexner succeeded in producing a meningococcal antiserum that appeared to protect animals against meningococcal disease (Flexner, 1906). The serum was prepared by injecting live and killed bacteria into horses. In 1913, Flexner conducted the first human trials of the meningococcal antiserum, and reported that the mortality rate among the subjects receiving the antiserum was approximately 30% (Flexner, 1913). During World War I and II, meningococcal disease had a profound effect on military forces, although, with the introduction of sulfonamides in the 1930s, mortality from meningococcal infection decreased to approximately 15% (Swartz, 2004). Nevertheless, until the introduction of meningococcal antiserum and antimicrobial agents, neisserial infection was often fatal. Since then it has become a curable illness, although the rates of morbidity and mortality vary by geographical region.

In Brazil, meningococcal disease was historically spread by military operations, pilgrimages and social disturbances, causing four epidemic events during the twentieth century (de Moraes & Barata, 2005). The first confirmed case of meningococcal infection in Brazil was reported in 1906 by Godinho (Godinho, 1906) in the city of São Paulo at the Emílio Ribas Institute of Infectology. In 1971, a severe epidemic of sulfonamide-resistant serogroup C meningococcal meningitis broke out in São Paulo. Notably, an atypical phenomenon occurred in the period from 1972 to 1974, when there was an overlapping of two epidemic waves in São Paulo, one caused by serogroup C and another, larger epidemic caused by serogroup A. Initially, 91% of all meningococcal infection was caused by *N. meningitidis* serogroup C strains, while in 1974, 90% of the strains were serogroup A (Sacchi *et al.*, 1992). In fact, it was one of the most widespread meningococcal epidemics in history. During the tragic 1 year period of 1974, nearly 1 in every 300 inhabitants of São Paulo developed meningococcal infection (Anderson *et al.*, 1998). In 1975, mass vaccination of millions of Brazilians with vaccine A plus C put an end to this brutal epidemic, which was responsible for thousands of deaths.

Epidemiology and transmission

After routine vaccination of infants with the *Haemophilus influenzae* type B capsular conjugate vaccine was introduced, *N. meningitidis* became the leading cause of bacterial meningitis, and continues to be a major public-health problem, not only in Brazil but also in the United States and worldwide. The World Health Organization estimates that at least 500 000 new cases of meningococcal infection occur every year, resulting in more than 50 000 deaths (Brandtzaeg & van Deuren, 2002). Although the disease has a more severe impact on children and young adults, all age groups are susceptible to infection.

The bacterial pathogen *N. meningitidis* typically spreads from person to person by airborne droplets or via direct physical contact, such as kissing. However, in recent decades, there have been remarkable changes in the epidemiological behaviour of *N. meningitidis*, and the human nasopharynx is no longer the only recognized primary site of the initial stage of meningococcal infection (Anderson *et al.*, 1998; Barquet *et al.*, 1990; Faur *et al.*, 1975; Judson *et al.*, 1978; Lourenco *et al.*, 2006). In fact, the pathogen has been found in unexpected locations, such as the mucous membranes of the endocervix (Fiorito *et al.*, 2001), anus (Judson *et al.*, 1978), urethra (Faur *et al.*, 1975) and conjunctiva (Barquet *et al.*, 1990). The ability of meningococci to colonize mucous membranes other than the nasopharynx is critically linked to direct inoculation of *N. meningitidis* into the mucous from an exogenous source, via orogenital sex (Urra *et al.*, 2005) or vertical transmission (Fiorito *et al.*, 2001). In addition, inoculation can occur via airborne micro-organisms or through manual contact with the conjunctival sac (Barquet *et al.*, 1990). Orogenital sex has become a potential pathway for the transport of meningococci from the natural nasopharyngeal habitat to the genital organs (Fiorito *et al.*, 2001), and has posed a new epidemiological challenge. Therefore, although meningococcal pathogens have been implicated in various genitourinary, anal and conjunctival disturbances, they have typically been overlooked and unexplored as possible aetiological factors in such disturbances.

Colonization and invasion

Meningococci are found in the airways of 10% of the healthy population (Yazdankhah & Caugnant, 2004), and the rate of colonization might exceed 50%, especially in individuals with viral respiratory tract illness (Musher, 2003). Meningococcal bacteria typically exist as harmless commensal inhabitants of the human nasopharynx, their pathogenic form being less common. Damage to the integrity of the ciliated columnar epithelium in the nasopharynx caused by active or passive smoking, as well as by viral infections, might represent the first step in colonization (van Deuren *et al.*, 2000). In fact, colonization and invasion of the nasopharyngeal mucosa are the primary events in the pathogenesis of meningococcal infection. One challenge in unravelling the puzzle of

meningococcal pathogenesis is deciphering how and why some strains of *N. meningitidis* overcome the immune system of the mucosal cells and disseminate from their natural habitat into the intravascular compartment and subarachnoid space. This process is undoubtedly dependent on a variety of bacterial, environmental and host factors, since the introduction of the identical strain into different schools can be associated with very different rates of attack (Musher, 2003). Recent studies of meningococcal infection have shown that a phage can contribute to this enigmatic switch from commensal organism to infectious pathogen (Bille *et al.*, 2005). A phage DNA was present in 100 % of the strains isolated from individuals with invasive infection and absent from 90 % of the non-invasive isolates.

Cell and molecular biology

Meningococcal pathogenesis involves multiple links that interconnect in a complex web of phenomena from *N. meningitidis* attachment to meningococcal sepsis or meningitis. In fact, there are a multitude of molecular/cellular receptors and mediators that are involved in the outcome of host–meningococcal interactions (Emonts *et al.*, 2003; van der Flier *et al.*, 2003). These factors work in concert with various strongly interacting pathways within the vascular tree and in the subarachnoid space (van Amersfoort *et al.*, 2003). Some of these crucial factors and pathways are as follows: the complement cascade (Brandtzaeg *et al.*, 1989a; Emonts *et al.*, 2003); the haemostatic system (Brandtzaeg *et al.*, 1989b; Faust *et al.*, 2001; Weisfelt *et al.*, 2007); the cytokine network (Brandtzaeg *et al.*, 1992a; Waage *et al.*, 1987, 1989); the neuroendocrine system (Joosten *et al.*, 2000; den Brinker *et al.*, 2005); Toll-like receptor (TLR) 2, TLR-4 and TLR-9 (Mogensen *et al.*, 2006); the CD46 receptor (Johansson *et al.*, 2003); endotoxins (Brandtzaeg *et al.*, 1989a, b, c, 1992b; DeVoe, 1982); nitric oxide (Baines *et al.*, 1999; Constantin *et al.*, 2004; Visser *et al.*, 1994); oxidant species (Scheld *et al.*, 2002; van der Flier *et al.*, 2003); as well as cholesterol and lipoproteins (Vermont *et al.*, 2005).

A key factor in neisserial pathogenesis is the ability of the bacteria to attach to human host cell receptors known as CD46 receptors (Johansson *et al.*, 2003). Adhesion of the meningococci to eukaryotic cells is a complex phenomenon that involves different adhesive factors depending on the environment that meningococci encounter within the human host (Serruto *et al.*, 2003). The primary attachment is mediated by type IV pili (Rytönen *et al.*, 2004). Type IV pili recognize the CD46 receptor, a cell surface glycoprotein, and establish a critical communication link between the bacteria and target cells during the initial phase of infection (Nassif, 2000). In fact, pili structures act as ‘meningococcal sensory organs’, establishing the primary cellular communication between pathogen and host target cells (Nassif, 2000). Meningococcal attachment can directly trigger cortical actin changes within the epithelial cell, such

as cytoskeletal rearrangements, leading to neisserial uptake (Rytönen *et al.*, 2004). Therefore, meningococci gain access to the epithelial cells through engulfment into vacuoles, which are transported to the basolateral surface of the cell via a transcellular pathway (Nassif *et al.*, 2002; Rytönen *et al.*, 2004). One intriguing aspect is that this phenomenon is thwarted by the presence of a capsule, an element that is critical for the survival of meningococci within the vascular compartment (van Deuren *et al.*, 2000). Similarly, meningococci penetrate the central nervous system through direct interaction with the luminal side of the cerebral endothelium, which constitutes the blood–brain barrier (Nassif *et al.*, 2002). Indeed, meningococci adhere primarily to endothelial target cells via their type IV pili and then promote the local formation of membrane protrusions that surround meningococcal cells, leading to internalization of bacteria within vacuoles and, subsequently, transcytosis to the subarachnoid space (Nassif *et al.*, 2002).

Endotoxins

The cellular and molecular mechanisms of meningococcal sepsis and meningitis are not fully understood. In fact, the clinical phenomena preceding the development of meningococcal sepsis or meningitis are highly complex. Inflammatory and immune responses are crucial for the containment of meningococcal bacteria but at the same time have the potential to cause cardiovascular collapse in the human host. Therefore, the final outcome of meningococcal infection depends on a delicate balance between the pathogen and the human host response. It has been shown that a biologically active product of *N. meningitidis* known as lipooligosaccharide (LOS), an endotoxin, is released from multiplying meningococcal cells (DeVoe, 1982). Meningococcal LOS (Fig. 1) is released in profusion during meningococcal sepsis and meningitis, and comprises, in part, the lipid A moiety, which is a powerful trigger of the inflammatory cascade either within the intravascular environment or in the central nervous system (Brandtzaeg *et al.*, 1992a, b). In fact, the rates of morbidity and mortality in meningococcal sepsis are correlated with levels of circulating meningococcal LOS (Brandtzaeg *et al.*, 1989c, 1992a, b). However, the LOS molecules are not toxic when they are incorporated into the bacterial outer membrane (van Amersfoort *et al.*, 2003). Various studies have demonstrated that LOS-deficient *N. meningitidis* also induce cytokine activation, via the TLR-2 signalling network (Brandtzaeg & van Deuren, 2002). However, the inflammatory power of such LOS-free mutants was found to be less than that of the LOS-containing meningococci.

Within the intravascular environment, LOS can bind to the LOS-binding protein synthesized by hepatic cells, thereby forming a complex. This complex is recognized, via the CD14 receptor, by various immunological cells. However, the CD14 receptor itself does not have an intracellular domain and therefore cannot directly transduce the LOS

Fig. 1. Electron-microscopy image showing meningococcus releasing many outer membrane vesicles ('blebs') (indicated by arrows) known to harbour endotoxin (lipooligosaccharide) (magnified $\times 65\,000$).

signals (van Amersfoort *et al.*, 2003). Recently, it was revealed that TLR-4 and its cofactor, myeloid differentiation factor 2 (MD-2), are critical to the process of LOS signal transduction (Emonts *et al.*, 2003). The TLR signalling networks are evolutionarily conserved proteins that recognize the pathogen-associated molecular patterns produced by various microbes, and these networks are responsible for the innate immune response (Mogensen *et al.*, 2006; van Amersfoort *et al.*, 2003). For example, *Streptococcus pneumoniae*, *H. influenzae* type b and *N. meningitidis*, the three major causes of bacterial meningitis, use distinct sets of TLRs to trigger the inflammatory response (Mogensen *et al.*, 2006). TLRs are characterized by an extracellular leucine-rich repeat domain and a cytoplasmic Toll-interleukin-1 receptor domain that shares considerable homology with the interleukin-1 receptor cytoplasmic domain (Annane *et al.*, 2005). Although TLRs are expressed by most cell types, the most important TLR-expressing cell types are believed to be dendritic cells, macrophages and B lymphocytes (Mogensen *et al.*, 2006). Subsequently, the signal is conducted via different intracellular signal pathways leading to activation of nuclear factor κ B (NF κ B), which is a key transcription factor first recognized for its role in the immune system. Various anti-inflammatory drugs, including corticoids and anti-inflammatory cytokines, such as interleukin-10, inhibit the NF κ B pathway (van der Flier *et al.*, 2003). Finally, NF κ B migrates to the cell nucleus and initiates transcription of genes coding for various inflammatory mediators (Stephens *et al.*, 2007). So, in general, the TLR-4/MD-2 interaction initiates the LOS-induced cell response via multiple signalling pathways in the intracellular

domain, leading to gene transcription and the synthesis of cytokines. However, *N. meningitidis* is also able to activate TLR-2 and TLR-9 (Mogensen *et al.*, 2006). The receptor TLR-9 recognizes double-stranded bacterial DNA, modulating cytokine expression (Stephens *et al.*, 2007).

Cytokines

During meningococcal sepsis and meningitis, a myriad of cells release cytokines within the intravascular environment and subarachnoid space. In fact, cytokine production is a prominent feature of meningococcal pathogenesis. Cytokines are key molecular messengers of the immune and inflammatory systems, and this 'cytokine storm' can be devastating in its inflammatory force. These molecular messengers are produced by a variety of cell types within the vascular tree: macrophages, polymorphonuclear neutrophils, dendritic cells and endothelial cells (Kolb-Maurer *et al.*, 2001; van Amersfoort *et al.*, 2003; van der Flier *et al.*, 2003). In the central nervous system of individuals with meningococcal meningitis, cytokines, as well as chemokines, are produced and released into the cerebrospinal fluid by the following cell types: microglia, astrocytes, ependymal cells, endothelial cells and infiltrating blood monocytes (Brandtzaeg *et al.*, 1992a, b; Kolb-Maurer *et al.*, 2001; Scheld *et al.*, 2002; van der Flier *et al.*, 2003). The cerebrospinal fluid contains few humoral and cellular defences, thus meningococcal bacteria multiply freely before being detected, releasing toxic components such as LOS, which evokes a strong inflammatory response via cytokines (van der Flier *et al.*, 2003).

In addition, cytokines play key roles in orchestrating and mediating the metabolic, endocrine and coagulation responses to meningococcal infection (Emonts *et al.*, 2003; Weisfelt *et al.*, 2007). In fact, the morbidity and mortality rates of meningococcal sepsis are directly correlated with cytokine levels (Brandtzaeg *et al.*, 1992a, b; Waage *et al.*, 1987, 1989). Cytokines are also involved in the genesis of various conditions: myocardial dysfunction (Pathan *et al.*, 2004), euthyroid sick syndrome (den Brinker *et al.*, 2005), rhabdomyolysis (van Deuren *et al.*, 1998), pericarditis (de Souza & Seguro, 2007; de Souza *et al.*, 2006a) peritonitis (de Souza *et al.*, 2006b), stroke (de Souza *et al.*, 2008a, b; Weisfelt *et al.*, 2007), metabolic derangements (den Brinker *et al.*, 2005; Joosten *et al.*, 2000), degradation of albumin (Holland *et al.*, 2001), hypocalcaemia (Holland *et al.*, 2002), hypokalaemia (Kornelisse *et al.*, 1997), hypomagnesaemia or hypophosphataemia (Nadel & Kroll, 2007), purpura fulminans (de Souza *et al.*, 2007b), and acute respiratory distress syndrome (Eisenhut *et al.*, 2006). It is of note that the levels of cytokines, although increasing significantly during meningococcal sepsis, decline rapidly after the initiation of antibiotic therapy, suggesting that the mechanism of clearance is quite efficient (van Deuren *et al.*, 2000). Interestingly, patients with septic shock induced by Gram-positive bacteria, including *Streptococcus pneumoniae* and

Staphylococcus aureus, present with significantly higher plasma concentrations of gamma interferon than patients with meningococcal septic shock, whereas *N. meningitidis* induces more interleukin-10 synthesis than *Streptococcus pneumoniae* (Bjerre *et al.*, 2004). Therefore, there is a different pattern of cytokines between these Gram-positive bacteria and *N. meningitidis* (de Souza & Seguro, 2008).

In patients with meningococcal sepsis, albumin undergoes proteolytic degradation (Holland *et al.*, 2001). Albumin levels appear to be related to clinical severity, as well as to the degree of hypocalcaemia (Brandtzaeg & van Deuren, 2002). In addition, when levels of tumour necrosis factor alpha (TNF- α) are elevated, adrenal adrenocorticotropin hormone receptor binding can decrease, leading to suppressed synthesis of cortisol (Joosten *et al.*, 2000), which has been shown to be associated with refractory meningococcal septic shock. High cytokine levels have also been implicated in disseminated intravascular coagulation, which is characterized by a breakdown of the endothelium, and coagulation homeostasis, leading to overexpression of adhesion molecules on the surface of the endothelium, together with fibrin precipitation in vessels (de Souza *et al.*, 2007b). These prothrombotic disorders can progress to intravascular thrombus formation and subsequent ischaemic phenomena, as illustrated in the clinical profile of meningococcal purpura fulminans. In addition, the kallikrein-kinin system leading to formation of bradykinin is activated in parallel with other plasma mediators in systemic neisserial infection (Stephens *et al.*, 2007). Bradykinin contributes to the capillary leak syndrome and to the production of nitric oxide by endothelial cells, leading to vasodilation. Nitric oxide is produced constitutively in blood vessel walls by the enzyme nitric oxide synthase, at which point it acts to control vascular tone. Higher levels of nitrates and nitrites (nitric oxide metabolites) were seen in cerebrospinal fluid and plasma of patients with meningococcal meningitis (Visser *et al.*, 1994) and meningococcal disease (Baines *et al.*, 1999), respectively. In fact, nitric oxide production in meningococcal disease is directly related to disease severity (Baines *et al.*, 1999).

Myocardial cell

Myocardial involvement is widely recognized as playing a role in the pathophysiology of meningococcal sepsis and can be a critical factor for patient outcomes (Hardman & Earle, 1969; Pathan *et al.*, 2004). In fact, myocardial dysfunction during meningococcal sepsis can cause vascular collapse, leading to impaired tissue perfusion and multiple organ failure. Pathan *et al.* (2004) reported that interleukin-6 induced a dose-dependent myocardial depression, and that TNF- α had no significant effect on myocyte contractility. The authors also found that adding TNF- α to the interleukin-6 did not increase the myocardial depressant effect. In another study, 5 out of 22 patients with meningococcal sepsis showed signs of myocardial

ischaemia with increased levels of troponin I (Brandtzaeg & van Deuren, 2002). Furthermore, fatal cases can unexpectedly arise from asystole caused by inflammation of the conduction system (Robboy, 1972).

Diagnosis

Early recognition, proof of aetiological diagnosis and initiation of appropriate therapy can, in many instances, spare patients unfortunate sequelae such as permanent impairment. Only with scientific knowledge of the early clinical clues and laboratory features of this distressing illness can the medical practitioner achieve these targets. For instance, the gold standard for the definitive diagnosis of meningococcal infection is isolation of meningococci from a normally sterile body fluid, such as pericardial fluid, cerebrospinal fluid or blood. In addition, the phenotypic characterization of *N. meningitidis* is of paramount importance, not only to confirm meningococcal infection, but also to perform antibiotic susceptibility testing, epidemiological surveillance and development of meningococcal vaccination strategies. Although the search for early biomarkers of meningococcal sepsis has been successful, useful early clinical clues toward detecting meningococcaemia have typically been unexplored. At the beginning of the twentieth century, the pioneer Herrick, in his classic article entitled 'Extramenigeal meningococcus infections' (Herrick, 1919), stated, correctly, that 'The meningeal picture resulting from meningococcus infection has so fixed the attention of clinicians and pathologists that possibilities of extramenigeal infections by the organism have had scant notice'. In addition, he stated that 'This has resulted in a general failure to recognise the fundamental nature of the disease as a meningococcus septicemia, which has in turn had important consequences in the fields of diagnosis and treatment'. Archetypal clinical profiles of neisserial infection, such as impaired consciousness and petechial skin lesions, emerge relatively late in the course of the infection (Thompson *et al.*, 2006). In fact, petechial skin lesions are not always included in the clinical presentation of meningococcal disease. Furthermore, lesions analogous to petechial skin lesions can be seen in various conditions: sepsis caused by *Streptococcus pneumoniae*, group A streptococci or *Staphylococcus aureus*; infections caused by rickettsiae or viruses; and illnesses such as heatstroke (de Souza *et al.*, 2006d). Severe muscle tenderness of the lower extremities is one of the earliest clinical signs of neisserial sepsis (Thompson *et al.*, 2006). Recognizing these symptoms can help identify some patients with otherwise unsuspected meningococcal sepsis (Inkelis *et al.*, 2002). Nevertheless, myalgia is frequently overlooked as a potential early clinical clue.

Therapy

The prognosis of meningococcal infection was dramatically changed by the introduction of meningococcal antiserum

Fig. 2. Meningococcal purpura fulminans can progress to extensive tissue necrosis of the limbs, leading to dramatic physical sequelae such as skin scars and amputations, which have a critical impact on quality of life.

(Flexner, 1906, 1913) and antimicrobial therapy (Swartz, 2004). However, despite significant improvements in supportive care, as well as treatments involving modulation of the inflammatory and coagulation cascades, the mortality rate has changed little in recent years. In fact, clinical research studies involving modulation of the host inflammatory cascade have produced controversial results, demonstrating that the intricacies of the pathogenesis of meningococcal disease continue to preclude predicting the benefit of any given intervention (Brandtzaeg & van Deuren, 2002; Nadel *et al.*, 2007; van der Flier *et al.*, 2003).

In the management of meningococcal disease, the emphasis must still be placed on early diagnosis (Thompson *et al.*, 2006) and prompt initiation of antibiotic therapy, which continue to be the cornerstones of the successful management of this dramatic illness, reducing morbidity and mortality rates. In fact, all meningococci in cerebrospinal fluid are killed within 3–4 h after intravenous treatment with an adequate dose of antibiotic, and concentrations of endotoxin in plasma fall by 50 % within 2 h (Stephens *et al.*, 2007). It has been reported that the monitoring of systolic blood pressure in children is insufficient to detect the development of meningococcal septic shock (van Deuren *et al.*, 2000). The key diagnostic indicators are as follows: urinary output $<0.5 \text{ ml kg}^{-1}$ for at least 1 h, capillary refilling time $\geq 3 \text{ s}$, a change in mental status, cold extremities and tachycardia (Annane *et al.*, 2005; van Deuren *et al.*, 2000). In our experience, virtually all patients show some evidence of coagulopathy, and coagulation status can be assessed by observing the size and number of skin lesions, together with the platelet counts (van Deuren *et al.*, 2000). There are other measures that are equally vital to the management of meningococcal sepsis (Nadel & Kroll, 2007; van Deuren *et al.*, 2000): early and aggressive correction of hypovolaemia and electrolyte disorders, administration of vasoactive drugs, the establishment of central venous access in order to perform fluid resuscitation and to assess cardiovascular function (by measuring central venous oxygen saturation), treatment of coagulopathy, as well as early mechanical ventilation and renal replacement therapy as necessary. In fact, the treatment of meningococcal sepsis can be extremely complex. Therefore, treatment should be given in a facility

capable of administering the critical medical care. Such capacity is defined as follows: having dialysis and mechanical ventilation equipment available; having physicians and nurses that are skilled in intensive care medicine; and having orthopaedic, vascular and plastic surgeons who take a multidisciplinary approach to treating patients with ischaemic tissue damage (Fig. 2).

Conclusions

Scientific knowledge of meningococcal infection has increased greatly since the epidemic nature of the illness was first described by Vieusseux. The significant milestones along the way have included many remarkable discoveries: the epidemic and aetiological nature of meningococcal disease, the asymptomatic carrier state, serum and antimicrobial therapies and vaccines. In addition, there were significant discoveries of the endotoxin molecule, the cytokine cascade and TLR signalling networks, as well as the mapping of the meningococcal genome and host genetics. Deciphering the pathogenesis of meningococcal disease could expand our knowledge and provide important clues to the host–pathogen interaction, as well as leading to the development of new therapeutic tools.

For two long centuries, this complex and dramatic war has been waged within the arena of the human body. Although the end of this war is not yet in sight, many battles have already been won, and there will certainly be more victories in the future.

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