Changing the diagnostic framework of meningococcal disease

In today’s Lancet, Matthew Thompson and colleagues show that leg pain, cold extremities, and abnormal skin colour, which are symptoms and signs of sepsis and shock, are seen in the first 12 h of meningococcal disease, whereas the classic features of haemorrhagic rash—meningism, and impaired consciousness—are relatively late signs with a median onset of 13–22 h. The authors recommend that the diagnostic framework is changed to emphasise recognition of the early symptoms of sepsis (panel). Thompson and colleagues’ study pioneers the description of the presentation and time course of meningococcal disease in children and adolescents before admission to hospital.

Few infections can cause the tremendous stress that occurs when meningococcal disease enters a community. The rapid onset of disease, the fulminant course of some infected patients, and the mortality and morbidity are all reasons why this infection is so dreaded. Meningococcal disease continues to be a major worldwide health problem and is the most common infectious cause of death in children in many developed countries. Studies have shown improved outcomes in children who receive aggressive treatment in paediatric intensive care units, but initial misdiagnosis often delays appropriate treatment. A multivariate analysis showed that not receiving care from a paediatrician, insufficient supervision of junior staff, and failure of staff to administer adequate inotropes were all independently associated with an increased risk of death. Those authors concluded that suboptimum health-care delivery significantly reduces survival in children with meningococcal disease. Also, it is important that parents recognise when to seek medical assistance for their children so that appropriate treatment can be started as quickly as possible.

Early diagnosis can be challenging because the initial features of the patients in Thompson and colleagues’ study are similar to many common, self-limiting viral illnesses seen in primary care. These include the misleading features of coryza and sore throat, and this non-specific phase lasted about 4 h in younger children and 8 h in adolescents. Nonetheless, most of the sepsis symptoms arose before the first contact with a physician. Changing the diagnostic framework is crucially important to enable doctors to recognise serious illness. However, two important items are missing: the ability to determine positive and negative predictive values of leg pain, cold extremities, and abnormal skin colour for the diagnosis of meningococcal disease. This information could be provided by a study of children presenting with the common viral illness signs and symptoms whether or not they are subsequently diagnosed as having meningococcal disease. Until this information is available, doctors should be encouraged to schedule clinical review within 4–6 h if early meningococcal disease cannot be ruled out at the first contact. Our experience is that delay in providing appropriate treatment is common in children who die of meningococcal disease. This delay is sometimes caused by parents’ unawareness of their child’s condition.

To wait for the late signs of meningitis, such as neck stiffness, photophobia, and bulging fontanelle, is a glaring mistake if meningococcal disease is to be promptly diagnosed, because those signs usually arise as late as 12–15 h after onset of illness. In our experience, this is an important factor in the delay in the diagnosis of meningococcal disease. The recognition of early signs of meningococcal disease could reduce subsequent mortality.

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In today’s Lancet, Daniel Hackam and co-authors’ report that statin therapy in patients with cardiovascular disease is associated with a reduced rate of sepsis, severe sepsis, and fatal sepsis. Statins are well established as lipid-lowering drugs. Cardiovascular morbidity and mortality are significantly reduced by primary and secondary prevention with statins, as well as by acute therapy with a statin.

While lipid lowering itself was initially thought to be responsible for the beneficial effects of statins in cardiovascular disease, more recent findings have suggested that pleiotropic effects of statins—eg, anti-inflammatory and antioxidative properties, modulation of cellular immunity, improvement of endothelial function, or increased bioavailability of nitric oxide—might contribute. Notably, most of these effects are independent of lipid lowering, and seem to be mediated by interference with isoprenoid synthesis and subsequent geranylation of membrane proteins. For instance, blockade of the isoprenoid pathway modulates immune-cell responses by inhibiting the expression of coagulation factors, chemokines, MHC II, and adhesion molecules. Some statins directly antagonise adhesion receptors independently of isoprenoid metabolism. Statins have also been shown to exert direct antichlamydial effects during pulmonary infection with Chlamydia pneumoniae in mice. The benefit of the drugs might also extend to fungal and viral pathogens. They might even hold promise against the potential threat of an influenza pandemic.

Among many clinical and experimental approaches undertaken to curb the lethal toll of sepsis, activated protein C and low-dose hydrocortisone have, to date, emerged as the only inflammation-modulating substances to benefit patients with severe sepsis. In view of their strong effect on inflammation, statins may represent a desirable enforcement in the battle against the increasing incidence and morbidity of severe sepsis and septic shock in developed countries. Indeed, studies in animals and observational reports provide evidence in support of this notion. In a prospective cohort study in 361 patients with acute bacterial infections, previous treatment with statins was associated with a substantially reduced rate of severe sepsis and admission to the intensive care unit. However, this study was not powered to detect differences in mortality.

Benefiting from the unique medical infrastructure with linked administrative databases in Ontario, Hackam and colleagues have produced an impressive observational study by initial evaluation of 141,487 patients with cardiovascular disease, resulting in a well-paired and homogeneous study cohort of 69,168 patients after propensity-based matching. To minimise the risk inherent to any observational study of the conclusion being based on selection bias in the treatment group, the investigators carefully scrutinised and adjusted the data for several possible confounders. Furthermore, to exclude significant bias favouring statin users, they have analysed tracer outcomes (eg, the association between statin therapy and cataract extraction was assessed to check for the lack of

Figure: Overlapping benefit of statins in patients with atherosclerosis at risk for recurrent acute cardiovascular events, severe sepsis, or both. Cells in background are activated platelets.