Multiple organ dysfunction syndrome due to tropical infections

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There is as yet no precise definition of the multiple organ failure syndrome, or what is today more appropriately termed the multiple organ dysfunction syndrome (MODS). Clinically MODS can be considered as a sequential or concomitant occurrence of a significant derangement of function in two or more organ systems of the body, against a background of a critical illness. Organ dysfunction may be mild, moderate or severe, and multiple organs may show varying degrees of dysfunction. There is no universally acceptable classification system which defines parameters of organ specific failure. An ACCP/SCCM Consensus Conference which was held in 1991, defined MODS as “the presence of altered function in an acutely ill patient such that homeostasis cannot be maintained without intervention”.1 This concept is clinically acceptable as it has a practical bearing on management.

MODS is really an extension or rather a further evolution of the systemic inflammatory response syndrome (SIRS) defined at the same ACCP/SCCM conference in 1991. The systemic inflammatory response syndrome (SIRS) is said to be present when any two or more of the features listed below are encountered in a patient. 1. Temperature > 38°C or < 36°C; 2. Respiratory rate > 20/min or a respiratory alkalosis, PCO2 < 32 mm Hg; 3. Tachycardia > 90/min 4. Leucocytosis > 12,000/mm3 or < 4,000/mm3 or > 10% band forms

SIRS due to infection is termed sepsis. The criteria laid down by the ACCP/SCCM consensus conference in defining SIRS are of little practical use in our part of the world. If followed, most patients in a general ward of a teaching hospital would be termed as SIRS and many of these would be dubbed as ‘sepsis’. In our setting these criteria therefore need to be far more stringent, suitably altered or perhaps abandoned. The concept of SIRS is however important, as it emphasizes that SIRS with its evolution into a state of shock or into MODS can result not only from infection (sepsis) but equally from non-infectious causes (e.g. trauma, burns, pancreatitis, multiple transfusions and several other causative factors).

Sepsis (which is SIRS due to infection), trauma, and shock from any cause, remain the most important causes of MODS all over the world. We are in a way unfortunate in that we see not only the usual causes of sepsis and MODS encountered in the West, but also special infections peculiar to tropical and developing countries. These special infections to which we are exposed are not just related to geography or climate, but are significantly related to environmental and socioeconomic conditions that prevail in our part of the world.

Unquestionably the commonest cause of sepsis and MODS all over the world (including the tropics) is bacterial infection, chiefly caused by Gram-negative bacteria, though Gram-positive infection by staphylococci (including MRSA) is assuming increasing importance. In our unit the site of bacterial sepsis is most often intra-abdominal, followed by pulmonary infection, post-surgical infection, urosepsis, and nosocomial infection. The important infections peculiar to tropical and developing countries that can cause MODS include fulminant Pl falciparum infections, fulminant tetanus, disseminated haematogenous tuberculosis, B typhosus and salmonella

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infections, Gram-negative infections caused by ingestion of contaminated food, fulminant amoebic infection, severe leptospiral infections, haemorrhagic fevers and hyperinfection due to strongyloidosis. The following discussion centers on a few basic aspects of important fulminant tropical infections that can lead to MODS.

Plasmodium falciparum infection is responsible for about one million deaths every year. Life-threatening malaria is invariably due to the intra-erythrocytic asexual form of the Pl falciparum parasite. Almost every organ in the body can be affected, due to:

1. Sequestration of parasitised red blood cells caused by cytoadherence of RBCs to the endothelial cells of the capillary and post-capillary venules in all tissues and organs of the body. The parasitised red blood cells induce the formation of protein-rich ‘knobs’ on the cell surface which in turn promote adherence to microvascular endothelial cells, through proteins such as thrombospondin, intracellular adhesion molecules and CD36. A partial or complete blockage of these vessels results, leading to ischaemia and consequent dysfunction of various organ systems.

2. Production and liberation of cytokines (e.g. tumor necrosis factor alpha and interleukins) and of other potentially toxic or pharmacologically active compounds (induced by parasitised RBCs) that damage endothelial cells, increase capillary permeability, damage other tissue cells and produce various toxic effects.

3. Activation of complement and the evolution of varying degrees of disseminated intravascular coagulopathy.

The similarity to the pathogenesis of bacterial sepsis is clearly evident. Fulminant Pl falciparum infection like bacterial sepsis initially results in a hyperdynamic circulatory state, characterized by tachycardia, high cardiac output, hypotension and a reduced systemic vascular resistance. Terminally or in very fulminant cases, the haemodynamic state is characterized by a high systemic vascular resistance, a low cardiac output with an imperceptible pulse and a very low arterial blood pressure – exactly as in terminal bacterial sepsis.

The central nervous system is most frequently involved (> 70% of patients). This takes the form of cerebral encephalopathy, manifested by disturbed consciousness, hyperpyrexia, coma, seizures. Yet fulminant Pl falciparum infection may kill through severe involvement and dysfunction of other organ systems with little or no involvement of the CNS. The co-existence of severe acute respiratory distress syndrome (ARDS) and severe disseminated intravascular coagulopathy invariably spells disaster. There are certain important points to note with reference to Pl falciparum infections. Though a high parasitic index (> 20%) in the peripheral blood often points to a severe infection, the most fulminant forms are sometimes characterized by few or undetectable parasites in the peripheral blood. Such patients are generally in severe shock – cold, clammy, pulseless with a barely recordable blood pressure. The parasites in these patients are sequestrated within the capillaries and post-capillary venules of different organ systems. A definite diagnosis may be impossible; empiric treatment with quinine is mandatory when suspicion of fulminant malaria is strong in an endemic area. The next important point to note is that in some patients organ system dysfunction may develop and evolve even after parasites have been eradicated from the blood by specific therapy. It appears that the immunoinflammatory processes set into motion by the fulminant infection may at times be self-perpetuating even when parasites have been destroyed by treatment. The scenario in fulminant Pl falciparum infection can be complicated further by secondary bacterial infection which adds both to morbidity and mortality.

Management is through the appropriate use of quinine and perhaps also the use of arteseminin in fulminant disease. Exchange transfusions in appropriate situations where the parasite index is very high (30% or more) may be lifesaving. Exchange transfusions have also been recommended in patients with a lower parasitic index (> 10%) who fail to respond to specific therapy. Support to all organ systems is mandatory and is frequently rewarded by success even in what appear to be hopeless cases. Good ventilator support is crucial for survival in patients with ARDS or in those who manifest respiratory muscle fatigue.

Fulminant tetanus if treated early and expertly has in our experience a mortality of 6.25%. Multiple organ dysfunction is frequently observed. It is however debatable as to what extent this is related to nosocomial or superadded bacterial infection, or related to the direct effect of tetanus toxin. Acute lung injury or ARDS occurring very early in the natural history of severe tetanus (unassociated at that point in time with other complica-
tions) is almost certainly directly related to tetanus per se; ARDS occurring late in the natural history of fulminant tetanus is most likely due to nosocomial infection. Myocardial dysfunction in spite of a markedly increased cardiac index and a hyperdynamic circulation has been attributed to a direct effect of tetanus toxin on the myocardium. The hyperdynamic, high output circulatory state in severe tetanus and evidence of myocardial dysfunction are again very similar to that observed in early bacterial sepsis.

Severe miliary tuberculosis and disseminated haematogenous tuberculosis chiefly involve the lungs, causing acute lung injury and ARDS. There is also often a varying degree of dysfunction of other organ systems. Miliary tuberculosis with densely packed miliary lesions is easily recognizable. It can cause acute hypoxaemic respiratory failure necessitating ventilator support. Disseminated haematogenous tuberculosis can however present in an unusual form. The clinical picture is that of a pyrexia of unknown origin for 2 or more weeks. The patient becomes increasingly ill. The Xray chest shows bilateral blotchy shadows in both lungs as in ARDS, with increasing hypoxaemic respiratory failure. There is progressive impairment of function of other organ systems. Diagnosis can be only established by demonstrating acid fast bacilli in bronchoalveolar lavage fluid and by detecting tuberculous granulomas on a transbronchial biopsy. Investigations often reveal tubercle in other organ systems. This clinical presentation is more often observed in immunosuppressed individuals but can occur in immunocompetent patients as well. Early diagnosis and the use of anti-TB drugs can help to salvage these patients.

Fulminant infection with B typhosus or salmonella can cause multiple organ dysfunction. This can set in with frightening abruptness and intensity. ARDS is the most common extra-intestinal manifestation. Hepatic dysfunction, shock, renal dysfunction and even CNS dysfunction with low Glasgow coma scores can occur. Again prompt diagnosis, use of specific antibiotic therapy, ventilator support and support to all other organ systems sharply reduces mortality.

Fulminant amoebic infections are due to single or multiple hepatic abscesses that leak into the pleural space, the lung or into the peritoneal cavity. Severe hepatic dysfunction with deep jaundice can result from multiple hepatic abscesses, particularly in malnourished individuals or in alcoholics. Multiple organ dysfunction generally arises in those diagnosed late or in those with a poor response to specific therapy. Septic shock due to severe cardiovascular dysfunction is the usual cause of death. Ulcerative amoebic colitis can cause paracolic abscesses or a peritonitis which again leads to MODS. Associated bacterial sepsis is an important contributory factor.

Severe leptospiral infections can again cause death from multiorgan dysfunction. CNS dysfunction, liver cell dysfunction and renal failure are commonly observed. However acute lung injury can also occur and worsen prognosis. Lung involvement can take the form of an extensive intra-alveolar bleed that can cause death from overwhelming hypoxia. Though anecdotal, our experience strongly suggests that the use of 1 g methyl prednisolone intravenously for 3 days is life-saving in severe intra-pulmonary bleeds caused by leptospiral infections, suggesting that immune mediated reactions are probably involved in the pathogenesis of the condition.

Haemorrhagic dengue can cause death from uncontrollable bleeding or from multiorgan dysfunction caused by bleeds into various organs of the body. Severe haemorrhagic fevers like the Ebola virus and the Hanta virus fevers are fortunately confined to specific areas in Africa. They are often fulminant and can lead to death from widespread tissue necrosis, haemorrhage and severe organ dysfunction.

Strongyloidosis, a nematode infection, is endemic in tropical Asia, Africa and Latin America. Hyperinfection in immunocompromised individuals (such as HIV positive patients) can lead to MODS with lesions in the lungs, liver, colon and other organs. ARDS is the presenting feature. Severe lung injury can be caused directly by the parasites, by associated bacterial sepsis, and by the inflammatory response triggered by the destruction of parasites following the use of specific therapy. Mortality is high in spite of specific treatment and support to all organ systems.

It is rather amazing is that in our small experience with fulminant infections (leading to MODS) peculiar to our part of the world, the mortality with severe three or more organ dysfunction was not as horrendous as with fulminant bacterial sepsis. We have observed that patients
with fulminant tropical pulmonary infections with a SOFA score of 16 have a mortality of 50%. In contrast to this, a study by Vincent and colleagues, in which 74% of subjects with four organ failure had bacterial sepsis, found that a SOFA score of 16 was associated with a greater than 80% mortality. More patients with severe tropical infections need to be studied to confirm this impression. Again, the present impression rests on a ‘mix’ of a small number of fulminant tropical infections with different aetiologies. A larger number of patients in each aetiological group need to be prospectively studied before definite conclusions are drawn. Improved mortality in MODS due to fulminant tropical infections could well be related to prompt critical care after onset of symptoms and to the fact that specific therapy is available in many tropical infections – quinine for malaria, a proven successful protocol for the management of fulminant tetanus, anti-TB drugs for disseminated tuberculosis, ceftriaxone and quinolones for typhoid, specific drugs for amoebic infection and for leptospirosis.

The pathogenesis of MODS due to sepsis caused by bacterial infections observed all over the world is probably very similar to MODS caused by infections peculiar to our part of the world. MODS results from immunoinflammatory, metabolic, vascular, neural, endocrine responses to a causative agent. These responses are dynamic, variable, interconnected and according to current concepts, perhaps non-linear in nature. They vary not only in different hosts, but probably vary at different time intervals in the same host. The responses form an ever-changing, interconnecting network or non-linear system, so that an analytical approach would fail to evaluate the emergent properties of this network or system. Simplistically summarized, the overall host response in MODS, whatever the cause, is unorchestrated, poorly directed and characterized by an exaggeration of the proinflammatory cytokines, mediators and mediator products, so that more harm than good is perpetrated on the host. In reality, the problem of MODS is far more difficult, complex, and is as yet unsolved. If the host response is indeed a variable, complex, interconnecting non-linear system, lack of response to various specific anti-mediator therapies (observed in numerous clinical trials) is understandable. It appears that organs do not work in splendid isolation. They ‘talk’ to each other, and cells within them do likewise at the molecular level. It is also likely that they communicate in more than one language. It is probably this communication system which preserves the balance between health and disease. We need to decipher this communication system if we are to comprehend and find means to arrest the frequent downward spiral of severe multiple organ dysfunction.

References