ABERRANT CELLULAR SIGNALLING IN MULTIPLE ORGAN FAILURE: MECHANISMS, CONSEQUENCES AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Objective: To review multiple organ dysfunction syndrome with respect to: 1) clinical and preclinical measurement systems; 2) Interventions/ Model system used 3) pathophysiology and 4) Various therapeutic implications.

Methods: The Medline, Pubmed, Pubmed Central and Science Direct, conference proceedings, bibliographies of review articles were searched for relevant articles. Key index words were multiple organ failure, multiple system organ dysfunctions, sepsis, septic shock, shock, systemic inflammatory response syndrome. Outcomes prospectively defined were death and physiological reversal of end organ failure.

Results: Multiple organ dysfunction/failure (MODS) is very colloquial cause for death in intensive care units. With early resuscitation, it was possible to save life otherwise it would have been hard to save one. It occurs due to the unconstrained systemic inflammation and varied etiologies. As of now, there is no therapy which can prevent or improve MODS with dramatic favourable outcomes.

Conclusion: Multiple organ dysfunction may serve as a useful way to check disease severity for improved quality of care and therapy. Shock patient treated by Anesthesiologists will take into consideration subsequent development of MODS in the critical care unit and may be required to provide anesthetic support to these patients.

Keywords: Aberrant Cellular Signalling, Multiple Organ Failure

INTRODUCTION:

Multiple organ dysfunction syndrome (MODS) is a continuum, with incremental degrees of physiologic derangements in individual organs; it is a process rather than a single event. Alteration in organ function can vary widely from a mild degree of organ dysfunction to completely irreversible organ failure. It is the unwanted outcome of successful shock resuscitation. Shock is an insufficient perfusion of organ, inspite of adequate fluid resuscitation, usually prevent a steady hypotension or require vasoactive drugs to raise blood pressure.

MODS is widely considered to be the leading cause of morbidity and mortality for patients admitted to an ICU. However, despite its immediate and infinitely recognizable manifestations in the critically ill patient, its characterization as a discrete syndrome with a common and measurable pathologic basis has been problematic. First, patients admitted to an ICU frequently have some degree of preexisting physiologic impairment, so that it may be difficult to differentiated rangements that are acute and potentially reversible from those that are chronic and irreversible. Second, the spectrum of disorders that lead to ICU admission commonly includes diseases that cause direct organ injury, for example, pneumonia or trauma producing acute lung injury, or mesenteric vascular ischemia causing liver dysfunction. Finally, the challenge in characterizing organ dysfunction in biochemical terms has been not a lack of definable abnormalities, but a surplus of it. Literally hundreds of biochemical and cellular abnormalities have been described in patients with MODS, and their very number has made it difficult, if not impossible, to define a single common underlying event or process as the pathogenic basis of the disorder. In fact, it is not yet clear whether MODS is a single pathologic process with highly variable clinical expression or simply the limited phenotypic expression of a large number of pathologically divergent processes. This paper will review the more prominent theories about the pathogenesis of MODS, recognizing that the mechanisms that have been proposed are by no means exclusive and are often best viewed as differing perspectives on common pathologic processes.
Figure 1. Illustrates the basic pathway involved in multi organ dysfunction, infected with an pathogen.

It is also defined as the presence of altered organ function in an acutely ill patient such that homeostasis could not be maintained without intervention. It also was recognized that the initial injury may produce direct organ system injury or be accompanied by hemodynamic alterations, such as hypotension and/or decreased cardiac output, which could result in organ dysfunction/failure. This condition has been termed primary MODS. Secondary MODS is the term used to describe the onset of organ failures that develop later in the course of illness and is frequently related to shock and sepsis.

It is a progressive condition normally characterized by combined failure of several major organ systems in a critically ill individual that can make it impossible to maintain homeostasis without some type of medical intervention and which is normally a complication of sepsis and is also a major factor in predicting mortality. It normally involves the collapse of at least two organ systems. MODS may include any of these listed vital systems:

- Respiratory
- Renal
- Cardiovascular
- Neurologic
- Hepatic
- Hematologic

The signs and symptoms of end-organ dysfunction in the above organ systems consist of:

**Lung or respiratory system** – will show a dysfunction of normal exchange of gas, revealed mainly in “arterial hypoxemia” which is insufficient oxygen getting into the blood system. Many pathologic features add to this impaired gas exchange.

**Kidney or renal system** – is revealed in the impairment of the normal selective excretory function first in oliguria or low output of urine despite adequate intravascular volume, but later in a rising creatinine level and electrolyte and fluid problems of sufficient magnitude that in some cases dialysis may be required.

**Heart and cardiovascular system** – dysfunction of this system consist of abnormalities predisposed to impaired delivery of oxygen and therefore contribute to the injury of other organ systems.

**Hepatic system** – dysfunction of the hepatic system is reflected in excess bilirubin circulating in the blood as well as lack of bile flowing from the liver.

**Neurologic system** – there is an altered level of consciousness, which is reflected in the reduction in the Glasgow Coma Score which is the scale of consciousness of a individual due to multiple causes.

**Hematologic system** – the most widely cited manifestation of dysfunction of the blood system consist of thrombocytopenia which in critical illness is cause by a multiple of factors.
Criteria for Organ Dysfunction:

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Mild Criteria</th>
<th>Severe Criteria</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>Hypoxia or hypercarbacia necessitating assisted ventilation for 3-5 days</td>
<td>ARDS requiring PEEP &gt; 10 cm H₂ O and F₁ O₂ ≤ 0.5</td>
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<tr>
<td>Hepatic</td>
<td>Bilirubin 2-3 mg/dL or other liver function tests &gt; 2 × normal, PT elevated to 2 × normal</td>
<td>Jaundice with bilirubin 8-10 mg/dL</td>
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<tr>
<td>Renal</td>
<td>Oliguria (&lt; 500 mL/day) or increasing creatinine (2-3 mg/dL)</td>
<td>Dialysis</td>
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<tr>
<td>Gastrointestinal</td>
<td>Intolerance of gastric feeding for more than 5 days</td>
<td>Stress ulceration with need for transfusion, acalculouscholecytis</td>
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<tr>
<td>Hematologic</td>
<td>aPTT &gt; 125% of normal, platelets &lt; 50-80,000</td>
<td>DIC</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Decreased ejection fraction with persistent capillary leak</td>
<td>Hyperdynamic state not responsive to pressors</td>
</tr>
<tr>
<td>CNS</td>
<td>Confusion</td>
<td>Coma</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Mild sensory neuropathy</td>
<td>Combined motor and sensory deficit</td>
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</table>

*aPTT = activated partial thromboplastin time; ARDS = acute respiratory distress syndrome; CNS = central nervous system; DIC = disseminated intravascular coagulation; F₁ O₂ = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PT = prothrombin time.*

The aggregate score can then be interpreted as a likelihood of predicted mortality based upon the observed mortality in those study patients used to construct the original scoring system. Ideally, scoring systems should be simple, demonstrate good inter and intra observer reliability, be generalizable over time and in different intensive care units, and be independent of therapy provided.

**INCIDENCE AND EPIDEMIOLOGY**

Given the difficulties with accepted definitions, it is not surprising that the actual incidence of MODS/MOF is unknown. In part, this uncertain incidence is related to lack of a uniformly accepted definition, but there also is uncertainty concerning how to factor in pre-existing organ dysfunction/failure. Major risk factors include sepsis and the systemic inflammatory response syndrome (SIRS), shock and prolonged periods of hypotension, trauma, bowel infarction, hepatic dysfunction, increased age, and alcohol abuse. Nonetheless, MODS / MOF is currently recognized as a major cause of mortality in SIRS, trauma, sepsis, the acute respiratory distress syndrome (ARDS), and other critical illnesses.
CELLULAR MECHANISMS

The frequent association of MODS/MOF with sepsis, SIRS, ARDS, and other inflammatory processes suggests that there may be a causal link to the complex pathophysiologic processes that are characteristic of SIRS. Recent evidence has suggested that the SIRS response is rapidly followed in most patients by a compensatory anti-inflammatory response that limits the SIRS response so that it is not counterproductive. The subsequent balance between the proinflammatory (SIRS) and anti-inflammatory (CARS) response has been referred to as the mixed antagonistic response syndrome or MARS. Typically, this delicate balance is difficult to achieve and there is a predominance of either the inflammatory response or the anti-inflammatory response. Does excessive inflammatory reaction, organ dysfunction is likely to ensue? when there is an excessive anti-inflammatory response, the patient is at risk for opportunistic or secondary infections? Development of subsequent infections may serve as an additional insult to again trigger the SIRS response.

There are a variety of potential mediators for the injury process seen in sepsis and other causes of SIRS. A number of the potential humoral, cellular, and exogenous mediators are listed below:

Potential Humoral Mediators:
- Complement
- Arachidonic Acid
- Metabolic products
- Lipooxygenase products
- Cyclooxygenase products
- Tumor Necrosis Factor
- Interleukins (1-13)
- Growth Factors
- Adhesion Molecules
- Platelet Activating Factor
- Procoagulants
- Polymorphonuclear Leukocytes
- Monocytes/Macrophages
- Endotoxin
- Toxic Oxygen Free Radicals
- Endogenous Opioids
- Neuroendocrine Factors
- Vasoactive Polypeptides and Amines
- Bradykinin and Other Kinins
- Platelet Activating Factor
- Coagulation Factors and Their Degradation Products

Cellular Inflammatory Mediators
- Platelets
- Endothelial Cells
- Complement
- Arachidonic Acid
- Metabolic products
- Lipooxygenase products
- Cyclooxygenase products
- Tumor Necrosis Factor
- Interleukins (1-13)
- Growth Factors
- Adhesion Molecules
- Platelet Activating Factor
- Procoagulants
- Polymorphonuclear Leukocytes
- Monocytes/Macrophages
- Endotoxin
- Toxic Oxygen Free Radicals
- Endogenous Opioids
- Neuroendocrine Factors
- Vasoactive Polypeptides and Amines
- Bradykinin and Other Kinins
- Platelet Activating Factor
- Coagulation Factors and Their Degradation Products

Exogenous Mediators
- Endotoxin
- Exotoxin and Other Toxins

The humoral mediators include components of the complement system, products of arachidonic acid metabolism (both lipoxygenase and cyclooxygenase metabolites), tumor necrosis factor (TNF), interleukins (IL 1-15), various growth factors, adhesion molecules, platelet activating factor (PAF), nitric oxide, procoagulants, fibronectin and opsonins, toxic oxygen free radicals, endogenous opioids (endorphins), vasoactive polypeptides and amines, bradykinin and other kinins, neuroendocrine factors, myocardial depressant factor, and coagulation factors and their degradation products. The fact that there is no single pathway for organ system dysfunction/failure makes treatment extremely difficult and has generated the current enthusiasm toward defining methods of prevention.

Figure 2: Elaborates the role of various mediators involved and final outcome as multi organ failure.
Comprehensive Interventions studied and various mechanisms involved

<table>
<thead>
<tr>
<th>S.no</th>
<th>Model name</th>
<th>Intervention studied</th>
<th>Pathway Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Altered chemokine response in an animal model of multiple organ dysfunction syndrome induced by zymosan</td>
<td>Role of Chemoattractants</td>
<td>Elevated MCP-1, locally and systematically</td>
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<tr>
<td>2.</td>
<td>The zymosan-induced generalized inflammation (ZIGI) model</td>
<td>Role of TNF-α, LT-α</td>
<td>Generalised Inflammation</td>
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<tr>
<td>3.</td>
<td>Elucidation of the early events contributing to zymosan-induced multiple organ dysfunction syndrome using MIP-1alpha, C3 knockout, and C5-deficient mice</td>
<td>Role of Macrophage inhibitory protein, complement system in Multiple organ failure</td>
<td>Zymosan induced inflammation</td>
</tr>
<tr>
<td>4.</td>
<td>Protective effect of N-acetylcysteine on multiple organ failure induced by zymosan in the rat.</td>
<td>Anti-inflammatory role of N-acetylcysteine</td>
<td>Regulates pro-inflammatory profile via NF-KB signalling</td>
</tr>
<tr>
<td>5.</td>
<td>Protective effect of poly(ADP-ribose) synthetase inhibition on multiple organ failure after zymosan-induced peritonitis in the rat.</td>
<td>Aminobenzamide, Nicotinamide</td>
<td>PARS inhibitor</td>
</tr>
<tr>
<td>6.</td>
<td>Classical corticosteroids and new lipid peroxidation inhibitors in the therapy of multiple organ failure (MOP).</td>
<td>Dexamethasone, Antioxidants</td>
<td>Inhibition of Lipid Peroxidation reaction</td>
</tr>
<tr>
<td>7.</td>
<td>Protective effect of melatonin in a non-septic shock model induced by zymosan in the rat.</td>
<td>Role of Melatonin, an antioxidant hormone</td>
<td>Scavenger of hydroxyl radicals, peroxynitrate, inhibition of NO production</td>
</tr>
<tr>
<td>8.</td>
<td>Study on delay two-phase multiple organ dysfunction syndrome.</td>
<td>Study of injury factors, pathogenic process and clinical features of delay two-phase multiple organ dysfunction syndrome (MODS)</td>
<td>Inflammatory processes</td>
</tr>
<tr>
<td>9.</td>
<td>A pathological study of goat multiple organ failure model.</td>
<td>Inflammatory cell infiltration, spotty parenchyma</td>
<td>LPS mediated endotoxemia</td>
</tr>
<tr>
<td>10.</td>
<td>Animal model of non-bacterial multiple organ dysfunction syndrome in the elderly</td>
<td>Importance of Lungs in zymosan induced MODS compared to other organs like brain, heart, liver and kidney.</td>
<td>Activation of Compliment and Macrophage leading to inflammation</td>
</tr>
</tbody>
</table>

Inflammation has become the most current etiological explanation of MODS. It is the activation of circulating cells (leukocytes), the endothelium, the liver, and multiple mediator networks that are normally held in balance by corresponding anti-inflammatory mediators. Chemotactic agents attract, adhesion molecules focus, and cytotoxic agents assist these cells in driving the process. MODS (see Figure 2) occurs when either the host's inflammatory or anti-inflammatory response to injury (or both) are excessive; death may occur if the host response to injury is either excessive or insufficient. In broad terms, following a noxious insult there is an initial response mediated by liver, neutrophils, macrophages and the endothelium. Hepatic inflammatory proteins such as C reactive protein are opsonins of degraded proteins and nucleic acids derived from injured cells which would be potentially metabolized to more toxic substances. The macrophage response includes the release of a variety inflammatory mediators (e.g., Tumor Necrosis Factor [TNF], Interleukin 1, Interleukin 6); these mediators then up regulate receptors on neutrophils (e.g., L. Selectin) and endothelial cells (e.g., P Selectin, E Selectin, Intercellular Adhesion Molecule 1, Vascular Cell Adhesion Molecule 1Cellular) and stimulate transmigration. Adhesion molecules can be considered as aids to the retention of neutrophils as these large cells are transiently retained in the microvasculature by purely mechanical factors. With transmigration other effect or molecules (reactive free radical species, endopeptidases) are released that cause organ damage and further recruit activated neutrophil to the site of injury.

Cytokines are important inflammatory mediators with the following actions: 1) directing a T lymphocyte response; 2) inducing enzyme production in distant sites (e.g., endothelium: nitric oxide, liver: C reactive protein); and 3) altering cell surface adhesion molecules.

The theoretical intervention points for MODS therapy

1) Cell adhesion retardation 2) inflammatory mediator reduction (translation/transcription inhibition); 3) neutralizing (polyclonal or monoclonal) antibodies directed at cytokine/ vasoactive/coagulation/complement mediators; 4) cytokine/vasoactive/
complement / coagulation mediator receptor inhibitors: 5) anti-inflammatory protein induction (preconditioning, substrates, products, or genes); and 6) anti-oxidants and anti- proteases. 

CONCLUSION

Initiation of inflammation has been the key role in sepsis. Its prolongation is often associated with other biological cascade. Early recognition and measures to prevent it, will be vital. Otherwise, dramatic sequential events will occur, ultimately causing rise in mortality. A strong stand is required in the development of sepsis mimicking models. Since the initiated inflammation associated sepsis may or may not lead to multiple organ dysfunction and the death of the animal might be the result of some miscellaneous reasons. Over the past years, considerable amount of efforts have been put in, to comprehend the pathophysiology of sepsis and subsequently multiple organ dysfunction. So, I would like to conclude that new therapies to the existing therapies and new multiple organ dysfunction model systems are need of the hour.

REFERENCES: