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

Heena Agarwal*, [2]Santosh Reddy, [1]Komal Sharma

[1]Bhupal Nobles Institute of Pharmaceutical Sciences, Udaipur, Rajasthan, INDIA – 313001

[2]Lalitha College of pharmacy, Hyderabad, A.P., INDIA-500001

*Corresponding Author's Email: agarwal.pharma18388@gmail.com

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 dysfunctionmay serve as a useful way to check disease severity for improved quality of care and therapy. Shock patient streated 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[1-4].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 arechronic 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.
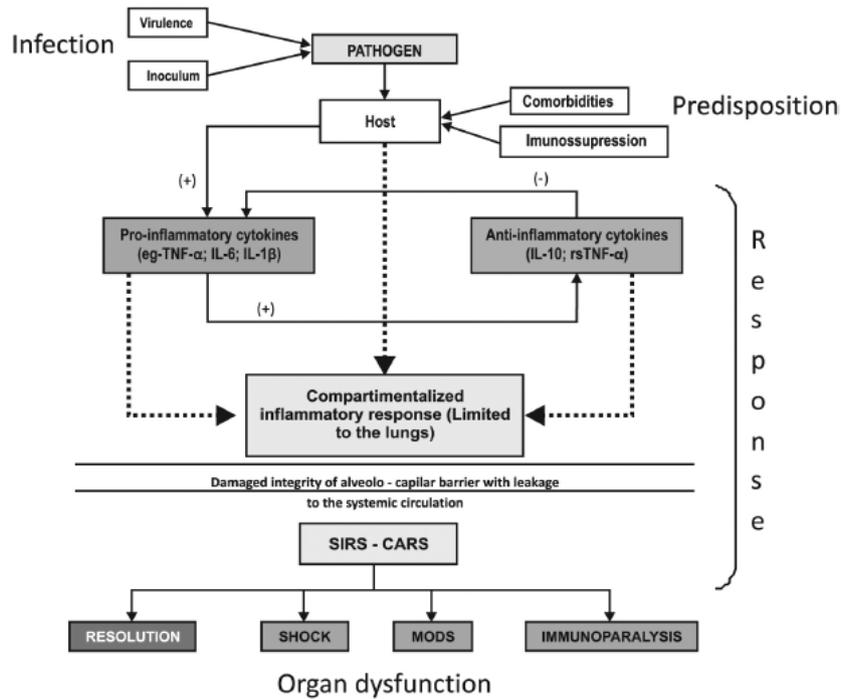
SIRS - Systemic Inflammation Response Syndrome; CARS - compensatory anti-inflammatory response syndrome; MODS - Multiple Organ Dysfunction Syndrome.

Figure1. 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[5]. This condition has been termed primary MODS. Secondary MODS is the term used to describe the onset of organdies function/failure that develops later in the course of illness and is frequently related to shock and sepsis[5].

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:

Organ System	Mild Criteria	Severe Criteria
Pulmonary	Hypoxia or hypercarbia necessitating assisted ventilation for 3-5 days	ARDS requiring PEEP >10 cm H_2O and $F_IO_2 < 0.5$
Hepatic	Bilirubin 2-3 mg/dL or other liver function tests $>2 \times$ normal, PT elevated to $2 \times$ normal	Jaundice with bilirubin 8-10 mg/dL
Renal	Oliguria (< 500 mL/day) or increasing creatinine (2-3 mg/dL)	Dialysis
Gastrointestinal	Intolerance of gastric feeding for more than 5 days	Stress ulceration with need for transfusion, acalculouscholecystitis
Hematologic	aPTT>125% of normal, platelets < 50-80,000	DIC
Cardiovascular	Decreased ejection fraction with persistent capillary leak	Hyperdynamic state not responsive to pressors
CNS	Confusion	Coma
Peripheral nervous system	Mild sensory neuropathy	Combined motor and sensory deficit

aPTT = activated partial thromboplastin time; ARDS = acute respiratory distress syndrome; CNS = central nervous system; DIC = disseminated intravascular coagulation; F_IO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; PT = prothrombin time.

Organ system	0	1	2	3	4
Respiratory[a] (PO$_2$/FIO$_2$ Ratio)	>300	226–300	151–225	76–150	≤ 75
Renal[b] (Serum Creatinine)	≤ 100	101–200	201–350	351-500	> 500
Hepatic[c] (Serum Bilirubin)	≤ 20	21–60	61–120	121–240	> 240
Cardiovascular[d] (R/P Ratio)	≤ 10.0	10.1–15.0	15.1-20.0	20.1–30.0	> 30
Hematologic[e] (Platelet count)	> 120	81–120	51–80	21–50	≤ 20
Neurologic[f] (Glasgow Coma Score)	15	13–14	10–12	7–9	≤ 6

a. The PO$_2$/FIO$_2$ ratio is calculated without reference to the use or mode of mechanical ventilation, and without reference to the use or level of PEEP.

b. The serum creatinine level is measured in μmol/liter, without reference to the use of dialysis.

c. The serum bilirubin level is measured in μmol/liter.

d. The R/P ratio is calculated as the product of the heart rate and right atrial (central venous) pressure, divided by the mean arterial pressure:

$$R/P \text{ Ratio} = \frac{\text{Heart rate} \times \text{RAP}}{\text{Mean BP}}$$

e. The platelet count is measured in platelets/mL 10^{-3}

MODS scoring systems can be classified using general physiological critical care scores i.e., Acute Physiological and Chronic Health Evaluation;(APACHE), Simplified Acquired Physiological Score (SAPS), Mortality Probability Model (MPM) [6] or specific organ score to describe dysfunction/failure (i.e., Multiple organ dysfunction score; MODS), Sepsis related Organ Failure Assessment (SOFA), Logistic Organ Dysfunction System CLODS). The specific organ dysfunction scores classify organs as failed (i.e., yes or no) or dysfunctional using an ordinal scale (i.e., graded score)[7,8]. The aggregate score quantitates severity in any one organ and the overall severity of organ dysfunction. 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 therapyprovided[9].

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[10-17].

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.[18-23], Recent evidence has suggested that the SIRS response is rapidly followed in most patients by a compensatory anti-inflammatory response limit the SIRS response so that it is not counterproductive[10]. The subsequent balance between the proinflammatory(SIRS) and anti-inflammatory (CARS) response has been referred to as the mixed antagonistic response syndrome or MARS[10].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[5,17,18,21,23-31]. A number of the potential humoral, cellular, and exogenous mediators are listed below:

Potential Humoral Mediators:

- ComplementArachidonicAcid Metabolic products
- Lipoxygenase products
- Cyclooxygenase products
- Tumor Necrosis Factor
- Interleukins (1-13)
- Growth Factors
- Adhesion Molecules
- Platelet Activating Factor
- Procoagulants
- Polymorphonuclear Leukocytes
- Monocytes/Macrophages

Exogenous Mediators

- Endotoxin
- Exotoxin and Other Toxins

- Fibronectin andOpsonins
- Toxic Oxygen Free Radicals
- Endogenous Opioids-Endorphins
- Vasoactive Polypeptides and Amines
- Bradykinin and Other Kinins
- Neuroendocrine Factors
- Myocardial Depressant Factor
- Coagulation Factors and Their Degradation Product

Cellular Inflammatory Mediators

- Platelets
- Endothelial Cells

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 opiods (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.
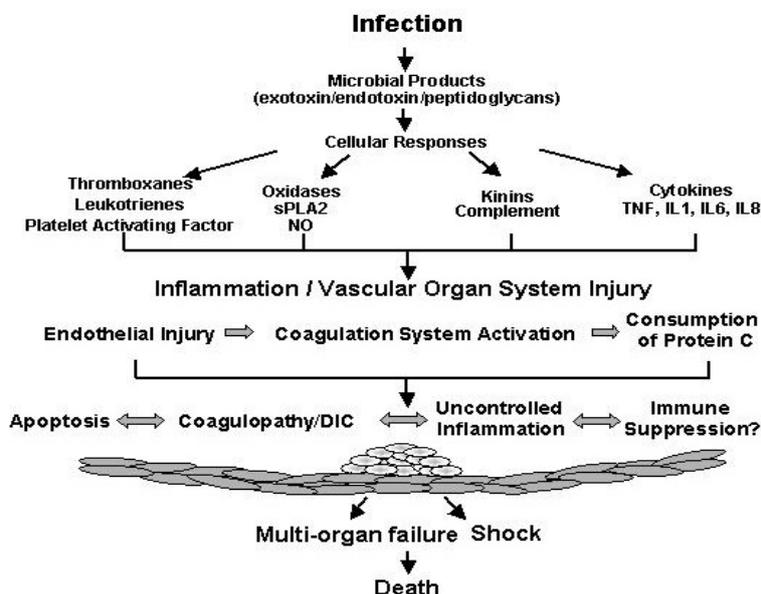

Figure 2: Elaborates the role of various mediators involved and final outcome as multi organ failure.

Comprehensive Interventions studied and various mechanisms involved

S.no	Model name	Intervention studied	Pathway Mechanism
1.	Altered chemokine response in an animal model of multiple organ dysfunction syndrome induced by zymosan[32]	Role of Chemoattractans	Elevated MCP-1, locally and systematically
2.	The zymosan-induced generalized inflammation (ZIGI) model[33]	Role of TNF-α, LT-α	Generalised Inflammation
3.	Elucidation of the early events contributing to zymosan-induced multiple organ dysfunction syndrome using MIP-1alpha, C3 knockout, and C5-deficient mice[34]	Role of Macrophage inhibitory protein, complement system in Multi organ failure	Zymosan induced inflammation
4.	Protective effect of N-acetylcysteine on multiple organ failure induced by zymosan in the rat.[35]	Anti-inflammatory role of N-acetylcysteine	Regulates pro-inflammatory profile via NF-KB signalling
5.	Protective effect of poly(ADP-ribose) synthetase inhibition on multiple organ failure after zymosan-induced peritonitis in the rat.[36]	Aminobenzamide, Nicotinamide	PARS inhibitor
6.	Classical corticosteroids and new lipid peroxidation inhibitors in the therapy of multiple organ failure (MOF) [37]	Dexamethasone, Antioxidants	Inhibition of Lipid Peroxidation reaction
7.	Protective effect of melatonin in a non-septic shock model induced by zymosan in the rat.[38]	Role of Melatonin, an antioxidant harmone	Scavenger of hydroxyradicals, peroxynitrate, inhibition of NO production
8.	Study on delay two-phase multiple organ dysfunction syndrome.[39]	Study of injury factors, pathogenic process and clinical features of delay two-phase multiple organ dysfunction syndrome (MODS)	Inflammatory processes
9.	A pathological study of goat multiple organ failure model[40]	Inflammatory cell infiltration, spotty parenchyma	LPS mediated endotoxemia
10.	Animal model of non-bacteriaImuItipIe organ dysfunction syndrome in the elderly[41]	Importance of Lungs in zymosan induced MODS compared to other organs like brain, heart, liver and kidney.	Activation of Compliment and Macrophage leading to inflammation

Inflammation has become the most current etiological explanation of MODS. It is the activation of circulating cells (leukocytes), the endotheliurm, 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[42]. 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[43].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 [44]. With transmigration other effect or molecules (reactive free radical species, endopeptidases) are released that cause organ damage and further recruit activated neutrophilsto the site of injury [45].

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[46].

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:

1. Deitch, E.A., *Multiple organ failure. Pathophysiology and potential future therapy.* Ann Surg, 1992. 216(2): p. 117-34.
2. Beal, A.L. and F.B. Cerra, *Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction.* Jama, 1994. 271(3): p. 226-33.
3. Marshall, J.C., et al., *Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome.* Crit Care Med, 1995. 23(10): p. 1638-52.
4. Vincent, J.L., et al., *Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine.* Crit Care Med, 1998. 26(11): p. 1793-800.
5. Bertleff, M.J. and H.A. Bruining, *How should multiple organ dysfunction syndrome be assessed? A review of the variations in current scoring systems.* Eur J Surg, 1997. 163(6): p. 405-9; discussion 410.
6. Bone, R.C., et al., *A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: results of a prospective, multicenter, randomized, controlled trial. The E5 Sepsis Study Group.* Crit Care Med, 1995. 23(6): p. 994-1006.
7. Bolton, C.F., *Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations.* Crit Care Med, 1996. 24(8): p. 1408-16.
8. Barton, R. and F.B. Cerra, *The hypermetabolism. Multiple organ failure syndrome.* Chest, 1989. 96(5): p. 1153-60.
9. Bone, R.C., et al., *Adult respiratory distress syndrome. Sequence and importance of development of multiple organ failure. The Prostaglandin E1 Study Group.* Chest, 1992. 101(2): p. 320-6.
10. Dorinsky, P.M. and J.E. Gadek, *Mechanisms of multiple nonpulmonary organ failure in ARDS.* Chest, 1989. 96(4): p. 885-92.
11. Fry, D.E., *Multiple system organ failure.* Surg Clin North Am, 1988. 68(1): p. 107-22.
12. Goris, R.J., et al., *Multiple-organ failure. Generalized autodestructive inflammation?* Arch Surg, 1985. 120(10): p. 1109-15.
13. Montgomery, A.B., et al., *Causes of mortality in patients with the adult respiratory distress syndrome.* Am Rev Respir Dis, 1985. 132(3): p. 485-9.
14. Regel, G., et al., *Pattern of organ failure following severe trauma.* World J Surg, 1996. 20(4): p. 422-9.
15. Tran, D.D., et al., *Risk factors for multiple organ system failure and death in critically injured patients.* Surgery, 1993. 114(1): p. 21-30.
16. Tran, D.D., et al., *Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit.* Crit Care Med, 1990. 18(5): p. 474-9.
17. Bone, R.C., C.J. Grodzin, and R.A. Balk, *Sepsis: a new hypothesis for pathogenesis of the disease process.* Chest, 1997. 112(1): p. 235-43.
18. Douzinas, E.E., et al., *The regional production of cytokines and lactate in sepsis-related multiple organ failure.* Am J Respir Crit Care Med, 1997. 155(1): p. 53-9.
19. Ertel, W., H.P. Friedl, and O. Trentz, *Multiple organ dysfunction syndrome (MODS) following multiple trauma: rationale and concept of therapeutic approach.* Eur J Pediatr Surg, 1994. 4(4): p. 243-8.

20. Hyers, T.M., M. Gee, and N.A. Andreadis, *Cellular interactions in the multiple organ injury syndrome.* Am Rev Respir Dis, 1987. 135(4): p. 952-3.
21. Jansen, M.J., et al., *Inflammatory cytokines in an experimental model for the multiple organ dysfunction syndrome.* Crit Care Med, 1996. 24(7): p. 1196-202.
22. Marshall, J.C., et al., *The microbiology of multiple organ failure. The proximal gastrointestinal tract as an occult reservoir of pathogens.* Arch Surg, 1988. 123(3): p. 309-15.
23. Casey, L.C., R.A. Balk, and R.C. Bone, *Plasma cytokine and endotoxin levels correlate with survival in patients with the sepsis syndrome.* Ann Intern Med, 1993. 119(8): p. 771-8.
24. Donnelly, S.C., et al., *Role of selectins in development of adult respiratory distress syndrome.* Lancet, 1994. 344(8917): p. 215-9.
25. Doughty, L., et al., *Plasma nitrite and nitrate concentrations and multiple organ failure in pediatric sepsis.* Crit Care Med, 1998. 26(1): p. 157-62.
26. Fink, M.P., *Adequacy of gut oxygenation in endotoxemia and sepsis.* Crit Care Med, 1993. 21(2 Suppl): p. S4-8.
27. Francois, B., et al., *Thrombocytopenia in the sepsis syndrome: role of hemophagocytosis and macrophage colony-stimulating factor.* Am J Med, 1997, 103(2): p. 114-20.
28. Mallick, A.A., et al., *Multiple organ damage caused by tumor necrosis factor and prevented by prior neutrophil depletion.* Chest, 1989. 95(5): p. 1114-20.
29. Pinsky, M.R., et al., *Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality.* Chest, 1993. 103(2): p. 565-75.
30. Schlag, G. and H. Redl, *Mediators of injury and inflammation.* World J Surg, 1996. 20(4): p. 406-10.
31. Symeonides, S. and R.A. Balk, *Nitric oxide in the pathogenesis of sepsis.* Infect Dis Clin North Am, 1999. 13(2): p. 449-63, x.
32. Thomas, N.J., T.M. Umstead, and D.S. Phelps, *Altered chemokine response in an animal model of multiple organ dysfunction syndrome induced by zymosan.* J Pediatr Surg, 2005. 40(3): p. 464-9.
33. Volman, T.J., T. Hendriks, and R.J. Goris, *Zymosan-induced generalized inflammation: experimental studies into mechanisms leading to multiple organ dysfunction syndrome.* Shock, 2005. 23(4): p. 291-7.
34. Mahesh, J., et al., *Elucidation of the early events contributing to zymosan-induced multiple organ dysfunction syndrome using MIP-1alpha, C3 knockout, and C5-deficient mice.* Shock, 1999. 12(5): p. 340-9.
35. Cuzzocrea, S., et al., *Protective effect of N-acetylcysteine on multiple organ failure induced by zymosan in the rat.* Crit Care Med, 1999. 27(8): p. 1524-32.
36. Cuzzocrea, S., et al., *Protective effect of poly(ADP-ribose) synthetase inhibition on multiple organ failure after zymosan-induced peritonitis in the rat.* Crit Care Med, 1999. 27(8): p. 1517-23.
37. Chiara, O., et al., *Classical corticosteroids and new lipid peroxidation inhibitors in the therapy of multiple organ failure (MOF).* Minerva Chir, 1997. 52(9): p. 1095-102.
38. Cuzzocrea, S., et al., *Protective effect of melatonin in a non-septic shock model induced by zymosan in the rat.* J Pineal Res, 1998. 25(1): p. 24-33.

39. Hu, S., et al., *Study on delay two-phase multiple organ dysfunction syndrome.* Chin Med J (Engl), 1998. 111(2): p. 101-8.

40. Lu, J., Y. Liang, and S. Hu, *[A pathological study of goat multiple organ failure model].* Zhonghua Wai Ke Za Zhi, 1996. 34(2): p. 117-9.

41. Li, J.S., et al., *[A model of multiple organ injury induced by Klebsiella pneumoniae pneumonia in aged rats].* Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 2009. 21(4): p. 226-9.

42. *HebeFt PC, DFummond A J, SingeF J, Bevnavd GR, Russell JA* A simple multiple system organ failure scoring system

predicts mortality of patients who have sepsis syndrome. Chest 1993; 104:230 5.

43. *Markos J, Hooper RO, Kavanagh Gray D, Wiggs BR, HoggJC.* Effect of raised alveolar pressure on leukocyteretention in the lung. J Appl Physiol 1990; 69:214 21.

44. *Bellingan G.* Inflammatory cell activation in sepsis. Br Ned Bull 1999; 55:12 29.

45. *Liu M, Slutsky AS.* Anti inflammatory therapies: application of molecular biology techniques in intensive caremedicine. Intensive Care Ned 1997; 23:718 31.

46. *Kotler DP.* Cachexia. Ann Intern Med 2000; 133:622 34.