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Review

Multiple organ failure in the newborn

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Proceedings

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The role of the clinical pathological dialogue in problem solving
Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken

Abstract

Multiple organ failure (MOF), or multiple organ dysfunction syndrome (MODS) as more recently known, is a clinical syndrome characterized by the failure of two, or more, organs which are unable to maintain homeostasis without intervention.

Described causative factors for MODS in the neonatal period are sepsis, shock due to any cause, tissue hypoperfusion, prematurity, hypoxic ischemic encephalopathy, necrotizing enterocolitis (NEC), surgery, congenital heart disease and others. MOF can be considered as the final common pathway of immunological, cytokine and hormonal changes, occurred as physiologic response to different infectious or non-infectious inflammatory insults, who lead to systemic inflammation, a procoagulant state and progressive organ dysfunction.

The clinical presentation of MODS can widely vary, depending on the primary causes, nature, number and severity of the organ systems involved. Pre-MODS conditions should be promptly identified and treated. In case of severe sepsis and septic shock, the available guidelines should be followed. When MODS already occurred, supportive care for single organ dysfunction should be provided and adequate oxygenation and organ perfusion maintained.

More studies in term and preterm infants (with the development of specific neonatal scoring systems) are needed, to further understand neonatal MODS and assess strategies for early prevention and treatment.

Keywords

Multiple organ failure, multiple organ dysfunction syndrome, newborn, sepsis, systemic inflammatory response syndrome.

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Background

Multiple organ failure (MOF) is a clinical syndrome characterized by the failure of two, or more, organs which are unable to maintain homeostasis without intervention [1].

It has been remarked that MOF is an entity that follows Osler's dictum: patients usually die of complications of their disease, rather than from the disease itself [2]. Indeed, MOF can be considered as the final common pathway of immunological, cytokine and hormonal changes, occurred as physiologic response to different infectious or noninfectious inflammatory insults, who lead to systemic inflammation, a procoagulant state and progressive organ dysfunction.

MOF is identified as the commonest cause of death in adult and pediatric patients admitted in intensive care unit [2, 3]. It is also likely that MOF could represent one of the leading cause of mortality for term and preterm infants admitted to neonatal intensive care unit (NICU), but, until recently, there was very little awareness of this syndrome among neonatologists. Therefore, neonatal deaths often attributed to prematurity, sepsis, disseminated intravascular coagulation (DIC), acute kidney injury (AKI) or other diagnosis, in some cases probably could have been better classified as MOF.

Hystorical perspective and terminology

MOF can be considered as a condition resulting from the recent advances in critical care, responsible for the increasing survival of patients with a single organ failure.

Baue, in 1975, described "multiple, progressive or sequential systems failure" as a new clinical syndrome and Eiseman, in 1977, first introduced the term MOF [2-4]. Since then, a number of different definitions have been used to describe this clinical syndrome.

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference suggested that multiple organ dysfunction syndrome (MODS) would have been the most appropriated term for this condition, emphasizing the dynamic state of the progression of the disease, rather than the final fail of the organs [5]. This view it is also supported by the fact that it is often arduous to trace a dividing line between organ dysfunction and organ failure; meanwhile the term MODS encloses a spectrum of conditions varying form mild organ dysfunction to irreversible organ failure.

Hayden, in 1994, redefined sepsis terminology in pediatrics and, in 2005, the International Pediatrics Sepsis Consensus Conference suggested definitions, for infection, systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and organ dysfunction, also for term neonates [6, 7].

In this paper we will adopt the terminology and definitions given by the Consensus Conference and by Marshall JC, as summarized in **Fig. 1** [7, 8].

The relationship between SIRS, sepsis, severe sepsis, septic shock and MODS is illustrated in **Fig. 2** [9].

MODS has also been classified as:

- primary (or early) MODS: where organ dysfunctions occur in the first 7 days of illness and can be directly attributable as a consequence of the primitive illness;
- secondary (or late) MODS: where organ dysfunctions develop after 7 days of illness as a consequence of the host responses.

Different scoring systems have been developed in adult, pediatrics and neonatal care to assess morbidity and response to treatment in MODS patients. Also physiologic systems affected by MODS (e.g. the hematologic system), not classically thought of as organs, have been included for evaluation in these scores. Scoring systems used in pediatric intensive care are the Pediatric Logistic Organ Dysfunction score (PELOD) and the Pediatric Multiple Organ Dysfunction score (PEMOD) [10, 11].

In 2001 Janota et al. established a new sequential scoring system (Neonatal Multiple Organ Dysfunction Score – NEOMOD) to describe the process of increasing physiologic derangements in the critically ill very low birth weight (VLBW) infants [12, 13]. However, the NEOMOD score has the limitations that can be used only on VLBW infants and it does not include in the scoring system the liver function and microvascular system evaluation. A European

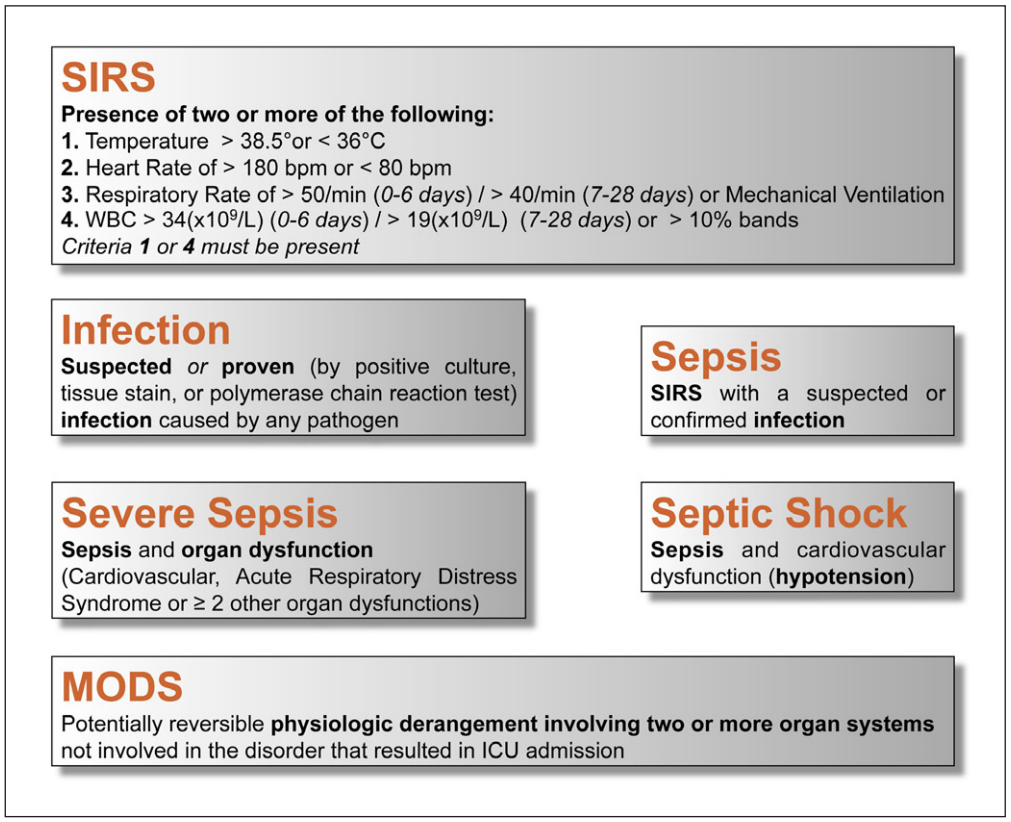

Figure 1. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS) in the newborn [7 , 8]. ICU: intensive care unit.

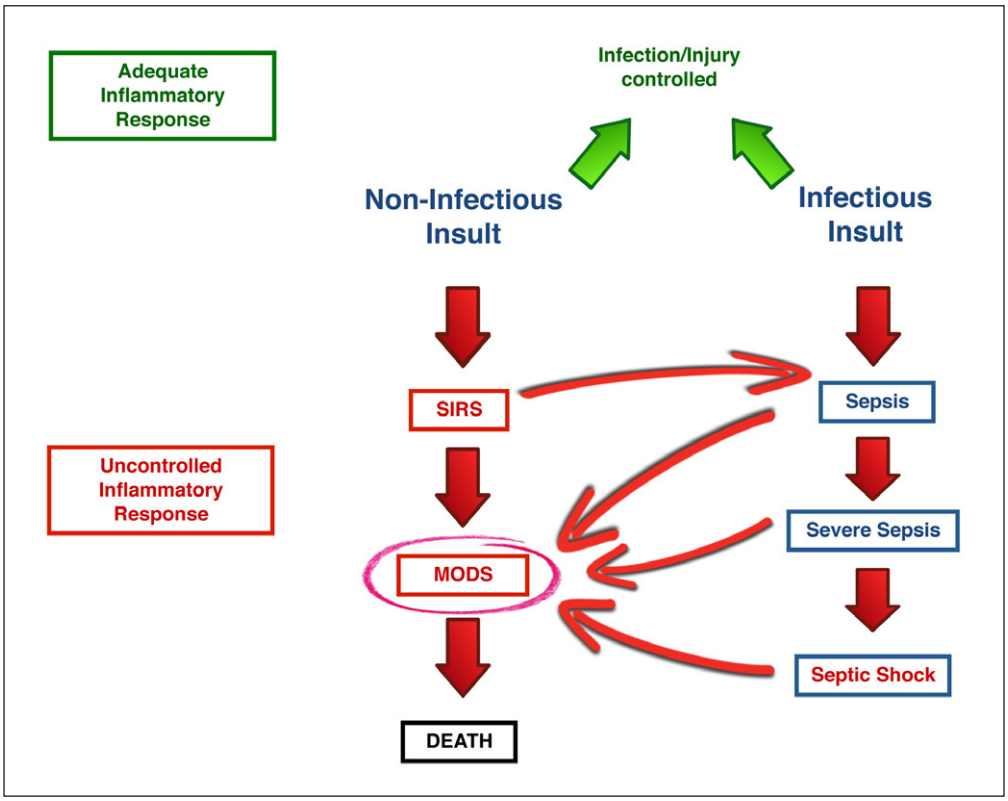

Figure 2. Relationship between systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS). Modified from Du Pont-Thibodeau et al., 2014 [9].

Medicines Agency expert panel in a meeting in 2010 stated that "no specific recommendation regarding the use of a specific organ failure score can be made for the neonatal population" and that new sequential organ failure scores targeting the specific aspects of neonatal sepsis (need for ventilatory support, need for inotropic and vasopressor support, need for renal replacement therapy, cholestatic icterus) are needed [14]. Other authors recently proposed a modified NEOMOD score systems, including microvascular system evaluation [15]. Criteria proposed by the PELOD, NEOMOD and modified NEOMOD scores, for determining specific organ dysfunction, are reported in **Tab. 1**.

Epidemiology

Most of researches on MODS have been conducted on adults and pediatric patients; thus, there are still limited data about the incidence of MODS in the neonatal period.

Described incidences of MODS, both in adult (11-40%) and pediatric patients (14-56 %) admitted in intensive care units, embrace wide ranges, reflecting differences in population, healthcare location and MODS definition [16].

A recent prospective, multicenter study, enrolling 1806 patients (of which 171 were term neonates), showed how, in pediatric intensive care units, the incidence of MODS was significantly higher in term neonates than in older children (14.6% vs 5.5%) [17].

Another recent study evaluating 198 preterm infants admitted in a Turkish NICU revealed incidence of MODS of 80.8% in this population [15].

Factors associated with the occurrence of MODS in critically ill neonates might vary, depending on prematurity, age, primitive conditions and interventions needed. Described causative factors for MODS in the neonatal period are sepsis, shock due to any cause, tissue hypoperfusion, prematurity, hypoxic ischemic encephalopathy, necrotizing enterocolitis (NEC), surgery, congenital heart disease and others [16, 18-21]. Recent studies in adult patients are also showing how certain genetic polymorphism involved in the inflammatory pathways increases significantly risk of MOF and mortality [22].

Pathophysiology

The exact pathophysiology of MODS has not yet completely defined and proposed pathways

Table 1. Comparison of multiple dysfunction scoring systems available for the neonatal period [10, 12, 15].

	PELOD	NEOMOD	Modified NEOMOD
Author, Year	Leteurte et al., 1999 [10]	Janota et al., 2001 [12]	Çetinkaya et al., 2012 [15]
Age	Newborn – Children	VLBW	VLBW
Validation	YES	NO	NO
Scoring system	0/1/10/20	0/1/2	0/1/2
Criteria established to determine organ dysfunction			
Neurological	Glasgow coma score, Pupillary reactions	Presence of IVH/leukomalacia	Presence of IVH/leukomalacia
Cardiovascular	Heart rate, Systolic blood pressure	Presence of Hypotension	Presence of Hypotension, Heart rate
Renal	Creatinine	Urine output	Urine output, Creatinine
Respiratory	PaO_2/FIO_2 ratio, $PaCO_2$, Mechanical Ventilation	Need for O_2, nCPAP or Mechanical Ventilation	Need for O_2, nCPAP or Mechanical Ventilation
Hematological	Platelet count, White blood cell count	Platelet count	Platelet count, White blood cell count
Hepatic	Aspartate transaminase, Prothrombin time	NA	Bilirubin, Alanine aminotransferase
Gastrointestinal	NA	Need for Parenteral Nutrition, Presence of NEC	Need for Parenteral Nutrition, Presence of NEC
Acid-Base Balance	NA	Base deficit	Base deficit
Microvascular	NA	NA	Presence of edema, Albumin

PELOD: Pediatric Logistic Organ Dysfunction score; NEOMOD: Neonatal Multiple Organ Dysfunction Score; NA: not available; NEC: necrotizing enterocolitis.

leading to organ dysfunction have been modified through the years and continue to be reshaped.

However, even if MODS is to be considered a complex, dynamic and heterogeneous syndrome, three common main pathogenic moments can be theoretically identified: 1) immune dysregulation; 2) failure of the gut barrier; 3) occurrence of a secondary (iatrogenic or nosocomial) insult.

Immune dysregulation

Innate immune response enables protection against infection since early life, even if immature in preterm and term infants [23, 24]. In MODS a dysregulate immune response occurs and plays a crucial role, with the lost of homeostasis between inflammatory and anti-inflammatory activities [25]. MODS traditionally was considered as the result of an excessive host inflammatory response to insults (SIRS in response of non-infectious insults; sepsis, severe sepsis and septic shock in response of infectious insults). However, in the past years many authors highlighted the importance of the compensatory antiinflammatory response, that causes a proper "immunoparalysis" [26]. Neutrophils recruitment, microthrombi formation, microvascular alteration and capillary leak with consequent tissue edema are some consequences of this disordered immune response that would subsequently lead to hypoperfusion, impaired oxidative metabolism, tissue damage, and multiple organ dysfunction. Thus, organ dysfunction is the final results of the loss of homeostasis between systemic inflammation and a counter-balancing anti-inflammatory response [27].

Mononuclear cells, pathogen-associated molecular pattern (PAMP), toll-like receptor (TLR); tumor necrosis factor (TNF); interleukins (IL1, IL 4, IL6, IL10), prostaglandins (PGE2), hormones (glucocorticoids) and complement system (C5a), among the others, play their role in the immune response in MODS, as already extensively described by many authors [16, 25-27].

Failure of the gut barrier

The role of the gut in the pathogenesis of MODS has been highlighted by many studies and some authors proposed bacterial translocation form gastrointestinal tract as the "motor" of MODS [28, 29]. The gastrointestinal system is characterized and regulated by the continuous crosstalking among three of its main components: the intestinal epithelium, the mucosal immune system and commensal intestinal bacteria [28].

As a consequence of the reperfusion mediated oxidative damage, the intestinal epithelium become hyperpermeable with disruption of tight junctions between the epithelial cells. The lipopolysaccarides can flow in the blood, stimulating production of TNFα causing endothelial damage, microthrombosis and capillary leak [30]. Histological findings of the colon and the ileum of two newborns with MOF, showing the loss of the epithelial layer, the increase of inflammatory cells in the mucosa and the submucosa and endothelial damage of vessels of submucosa, seem to confirm the presence of the hypothesized pathogenetic mechanism also in neonates [30].

Nutritional deficiency occurring during critical illness can cause a reduction in mucosal secretory IgA produced by B-lymphocytes in the gut-associated lymphoid tissue (GALT), predisposing to further infections [31]

The "bacterial translocation" was the originally proposed consequence of the loss of the intestinal barrier during MODS [28, 31]. Actually, instead, it is though that the main consequences of the intestinal epithelial damage are represented by the production and release into the mesenteric lymphatics of endogenous proinflammatory and tissue injurious factors that contribute to progression of MODS [32, 33].

During critical illness the immunoprotective function of normal gut microbiota get lost. Intestinal bacteria, try to adapt and survive, in response to hypoperfusion, lack of enteral nutrition, antimicrobial therapy and catecholamines, increasing their virulence [34, 35]. The increased bacterial virulence results in bacterial adherence to the epithelium that worsen and perpetuate the epithelial damage and the inflammatory response [29].

Occurrence of a secondary (iatrogenic or nosocomial) insult

It has been postulated a "two-hit" hypothesis in the pathogenesis of MODS.

The first severe insult ("first hit" can be infection or trauma), primes the host immune system so that a subsequent, apparently minor insult ("second hit"), generates an excessive inflammatory response which can lead to MODS

[36]. Iatrogenic and nosocomial factors that could represent a second "hit" are mechanical ventilation (volutrauma), nosocomial infection and blood transfusion, among the others.

Clinical features

The clinical presentation of MODS can vary widely, depending on the primary causes, nature, number and severity of the organ systems involved. Dysfunction in at least two organ systems is, by definition, diagnostic for MODS. The criteria proposed by the scoring systems reported in **Tab. 1** can be used for evaluation of organ dysfunction.

Meanwhile, in adult and pediatric patients, lungs are usually the first organ involved [16], renal and microvascular have been described as the first systems involved in MODS in term surgical newborns [21, 37]. Gastrointestinal and respiratory system are instead the earliest involved in preterm infants [15]. Cardiac function was reported to be always the latest involved in term infants [21, 37].

Treatment and prevention

MODS is less a syndrome to be treated than a complication to be prevented [8].

No specific treatments for all forms of MODS have been established and attempts to stop at early stages the immune response and "cytokine storm" failed.

Pre-MODS conditions should be promptly identified and treated. Guidelines for management of severe sepsis and septic shock specific for the neonatal period are available and should be followed [38]. When MODS already occurred, supportive care for single organ dysfunction should be provided and adequate oxygenation (superior vena cava O_2 Sat > 70%) and organ perfusion maintained. ECMO, when available, should be considered in neonates with refractory shock [38]. Continuous renal replacement therapy (CRRT) has been described in a recent paper to allow a rapid resolution of AKI and improvement of MOF in a neonatal patient with septic shock [39]. Recombinant human activated protein C, that seemed to be a promising treatment for severe sepsis in adults, has been withdrawn from the market in 2011, due to a higher mortality in a trial in adults, and should not longer be used in any age category [40, 41].

General measures that should be considered to reduce the progression of the inflammation and MODS are summarized in **Tab. 2**.

Prognosis

Mortality from MODS is high and varies widely among different studies, with reported rates in septic patients ranging from 44% to 50% in adults and from 11% to 54% in pediatric patients [16].

Probably this could be due to the fact that outcome of MODS patients depends from multiple factors, including primitive cause, genetic predisposition and availability of healthcare facilities (e.g. iNO, ECMO). Bestati et al. in 2010 showed how mortality for MODS, in a pediatric intensive care unit, was significantly higher among term neonates compared with older children (75.4% vs 50.9%) [17].

Meanwhile a relationship between number of failing organs and mortality has been reported in adults and in older children, there are still little data about MODS in neonates [15, 42, 43]. Neurological, cardiovascular, and hepatic dysfunctions seem to be the main predictors of death in term infants, whereas organs dysfunctions contributes equally to mortality in older children [17]. A NEOMOD score of ≥ 9 was associated with 100% mortality in VLBW [13].

Conclusions

MOF, or MODS as more recently known, nevertheless being one of the most challenging conditions to treat, is a syndrome poorly studied in its entire complex in the newborn infant. MODS features differ substantially among term infants, preterm infants, older children and adults. Scant is the literature on neonatal MODS and data and experiences obtained by researches in adults and children seems to be of little help. Therefore, more studies are needed, to further understand neonatal MODS and assess strategies for early prevention and treatment. But first, it is necessary to establish univocal criteria for defining single organs dysfunction and validated scoring systems for term and preterm infants.

Declaration of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper. This research received no specific grant from any funding agency in the public, commercial or not-for-profit-sectors.

Table 2. General measures that should be considered to reduce the progression of the inflammation and multiple organ dysfunction syndrome (MODS) in the newborn.

- Provide adequate initial resuscitation (ABCD)
- Treat shock: fluid resuscitation (up to 60 ml/kg of isotonic saline IV in the first hour, if necessary to attain normal capillary refill and blood pressure), inotropes (Dopamine ± Dobutamine) in fluid refractory shock, epinephrine, vasodilators, iNO, ECMO or CRRT
- Prevent and correct hypoxemia
- Treat infections: antimicrobial agents (early empiric followed by conversion to infection-specific, with best MIC, antibiotics), removal of known focus of infection, selective decontamination of the digestive tract
- Monitor organ functions: cardiac and pulmonary (pre- and post-ductal pulse oxymetry, invasive or non-invasive blood pressure, arterial blood gas analysis, continuous ECG, seriate Doppler echocardiography for evaluating PDA, ventricular function, cardiac output, PPHN, SVC flow), renal (urine output, eGFR/GFR, renal ultrasound), liver function, cerebral function (EEG, CFM, cerebral ultrasound, NIRS), metabolic (glucose, electrolytes, acid base balance), hemocoagulation
- Assess etiology for specific treatment (e.g. congenital heart disease, hypoxic ischemic encephalopathy, NEC, inborn errors of metabolism, adrenal insufficiency, hypothyroidism, primitive single organ failure)
- Avoid fluid overload: diuretics or renal replacement/dialysis
- Avoid lung overdistension: lung protective ventilation strategies (HFOV, volume guarantee with adequate tidal volumes)
- Avoid hyperglycemia/hypoglycemia: insulin, maintenance solution with D10
- Correct other metabolic imbalances
- Avoid malnutrition and microbial gut imbalance: early enteral nutrition, parenteral nutrition (to provide adequate caloric intake and nitrogen balance)
- Consider need for blood products: follow available guidelines for red packet cells (after resuscitation lower hemoglobin target could be considered), fresh-frozen plasma (bleeding due to DIC, liver failure or Vitamin K deficiency) and platelets transfusion
- Consider sedation/analgesia (in ventilated infant, to reduce metabolic expenditure)
- Monitor drug toxicity (drug clearances could be impaired during MODS)

ABCD: airway, breathing, circulation, drugs; CRRT: continuous renal replacement therapy; PDA: patent ductus arteriosus; PPHN: persistent pulmonary hypertension of the newborn; SVC: superior vena cava; NIRS near-infrared spectroscopy; NEC: necrotizing enterocolitis; DIC: disseminated intravascular coagulation.

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