CHAPTER 202

Multiple Organ Dysfunction in the Pediatric Intensive Care Unit

Emanuele Rossetti, Matteo Di Nardo, and Zaccaria Ricci

OBJECTIVES

This chapter will:

1. Describe the clinical manifestation of pediatric multiple organ dysfunction syndrome (MODS), including pathogenetic pathways and specific pediatric MODS causes.
2. Detail theoretic mechanisms of organ damage and current literature available in this field.
3. Present available therapeutic strategies for pediatric MODS management.

Multiple organ dysfunction syndrome (MODS), initially described as multiple systems organ failure in adult patients in 1960,[1] represents a critical state characterized by several clinical aspects (bleeding, sepsis, respiratory, hepatic, cardiac, and renal failure) that, if not controlled, can lead to a patient's death. In 1992 it was classified finally as a distinct syndrome by the American College of Chest Physicians/Society of Critical Care Medicine consensus conference.[2]

MODS is represented by a wide spectrum of organ dysfunction (two or more organ systems involved) with the inability to maintain the patient's metabolic need without any intervention. This syndrome currently is considered in adult and pediatric patients as the major cause of death in the intensive care unit.[3] In 2005 the International Pediatric Sepsis Consensus Conference delineated organ-specific diagnostic criteria for this dysfunction when triggered by a septic state.[4]

A dysregulated immune response, or immune paralysis, in which the homeostasis between the proinflammatory and antiinflammatory reaction is lost is thought to be key in the development of MODS. Lungs are usually the first organ involved in either adult or pediatric patients. Myocardial involvement follows closely, with neurologic involvement as the third most common system involved.

MODS has been classified as early or primary, which occurs in the first 7 days of illness, or late/secondary, which occurs after 7 days.

EPIDEMIOLOGY AND SCORING SYSTEMS FOR PEDIATRIC MULTIPLE-ORGAN DYSFUNCTION SYNDROME

MODS is more common in adults than in children and it is associated primarily with sepsis and trauma. This probably is because the functional organ reserve of the adult patient is reduced compared with children. In pediatric patients with sepsis, however, the incidence of MODS may reach up to 30% to 73% of cases,[5] whereas in patients admitted to the pediatric intensive care unit (PICU) with nonseptic diagnosis it shows a lower incidence ranging from 11% to 54%.[6]

Wilkinson et al.[7] showed that one fourth of children with MODS have chronic diseases in their pre-PICU clinical history. Most recently, a comorbid condition was noted among 64% of children admitted to the PICU.[8] Compared with previously healthy children, those with chronic health issues show a twofold increased risk of unscheduled admission to the PICU.[9]

The incidence of MODS, as defined by the International Pediatric Sepsis Consensus Conference[10] also independently increased the risk of death by 60% when controlling for the number of dysfunctional organs.

Such a wide range of clinical presentations reflects a broad variation in epidemiology, access to the healthcare system, and the differences in the definitions of MODS. The incidence rate of MODS is significantly higher in neonates compared with older children (14.6% vs. 5.5%) probably because of differences in organ response to injury between neonates and children.[11] Neurologic, cardiovascular, and hepatic dysfunctions are specific and independent predictors of death among neonates and deserve specific scoring systems.

Other important risk factors for the development of the pediatric MODS in PICU are hematopoietic stem cell transplantation, hypoxic-ischemic encephalopathy, hemophagocytic lymphohistiocytosis (HLH), and thrombocytopenia-associated multiple organ failure.

The two most widely used scoring system in pediatrics to describe and quantify the severity of MODS are the pediatric logistic organ dysfunction (PELOD) score and the pediatric multiple organ dysfunction score (P-MODS).[12,13] Both of these two scoring systems have been extrapolated by scoring systems used in the adults. However, only the PELOD score, which includes cardiovascular, neurologic, liver function, coagulation, respiratory, and renal variables, has been validated clinically.[12] In the neonatal period (first 28 days of life) the neonatal multiple organ dysfunction (NEOMOD) score is the only score that provides information on organ dysfunction in this selected population of patients.[14]

Pathophysiology

An unbalanced immune response in the homeostasis between proinflammatory and antiinflammatory mediators is thought to be the cause for the development of MODS. Failure of the antiinflammatory cascade to mitigate the initial inflammatory response in a timely manner propagates the organ damage. Furthermore, the gut is thought to play an important role in MODS. Because of a surplus of inflammatory mediators, intestinal walls become hyperpermeable, which in turn propagates the inflammatory response. In

addition, a decrease in mucosal immunoglobulin A (IgA), likely secondary to nutritional deficiency, predisposes to further infection.[15,16]

In general, all these aspects can induce a state of shock, which reduces the oxygen delivery to the organs affecting their functions and the coagulation cascade. If this state is left uncontrolled, MODS can lead patients to death. The lung is the first organ to be involved in MODS, and its involvement ranges from a mild form of acute lung injury to severe acute respiratory distress syndrome (ARDS), especially if a septic state is present. The involvement of the lung is due primarily to fluid overload associated with cardiac dysfunction or capillary leak syndrome, and surfactant deactivation.[17] The heart is the second organ involved after the lung: heart failure is due primarily to the cytokine storm that perpetrates MODS and in particular by the nitric oxide (NO) effect on myocardium. During sepsis-associated MODS the brain often is affected, and mechanisms for this involvement are multifactorial (alteration of the blood-brain barrier, cytokines, and toxic neuroamines). Hepatic and kidney dysfunction close the circle. Liver failure is due primarily to a low cardiac output state that often can be reversible using inotropic/vasoconstrictor support. Kidney dysfunction instead can be due to shock and cytokine-induced apoptosis.[18] Other distinctive diseases contribute to the development of pediatric MODS with mechanisms other than the ischemic hypoperfusion pathway. Thrombocytopenia-associated multiple organ failure (TAMOF)[19] is one of these. This complex syndrome presents with fever, thrombocytopenia, abnormal mental status and/or seizures, renal dysfunction, and microangiopathic hemolysis. Patients with TAMOF show systemic endothelial injuries that trigger an "uncontrolled" activation of the coagulation cascade. These endothelial injuries can be present in many clinical situations (e.g., acute phase of autoimmune diseases, cancer, transplantation, hemolytic uremic syndrome, use of drugs such as cyclosporine and tacrolimus, radiation therapy, chemotherapy). Currently, there has been a significant improvement in understanding this form of pediatric MODS, and it has been clarified that the activity of the von Willebrand factor (vWF) cleaving proteinase (called ADAMTS-13) is reduced (<10% normal activity) by the presence of unspecific antibodies. This leads to the inability to cleave the large multimers to the small isoforms of vWF, inducing intravascular thrombosis.

HLH is an often fatal disease of childhood with an estimated incidence of approximately 1.2 cases per million per year.[20] It is characterized by high fever, hepatosplenomegaly, cytopenia, hypofibrinogenemia, high triglyceride, and ferritin levels with nonmalignant infiltrates of macrophages with hemophagocytosis of the reticuloendothelial system. Primary (genetic form) and secondary (associated to infections, malignancy, systemic illness) HLH create defects in cytotoxic T lymphocytes and natural killer cells functions that result in prolonged antigenic stimulation (histiocytic infiltrates) and high cytokine levels. Thus all organ systems can be affected, and MODS can develop consequently. Other rare diseases can be associated with MODS. One of these is Kawasaki disease, which is considered generally as an acute self-limiting vasculitis.[21] Severe forms are associated with shock and managed in the PICU; these types of Kawasaki disease are unusual in terms of their hemodynamic, neurologic, intestinal, and renal profile. Many of these are unresponsive to immunoglobulin therapy and more frequently involve coronary artery anomalies. Shock is generally moderate in these situations as witnessed by the low lactate levels and inotropic and vasopressor doses. In those cases, MODS can be explained only by the intense and systemic inflammation that can lead to organ damage and failure.

The great impact on pediatric MODS incidence is provided from hematologic malignancies as associated infections with sepsis and ARDS patterns, treatment adverse reactions or complications, and drug overtreatment or intoxication, whose management may require extracorporeal support (ECMO) and extracorporeal blood purification or emergent organ transplantation at least, as proved by several case reports and case series in pediatric critical care literature.[22–25]

MANAGEMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME IN THE PEDIATRIC INTENSIVE CARE UNIT

Diagnosis

MODS in pediatric critically ill patients is manifested primarily as respiratory and cardiac failure. Neurologic impairment clinically occurs with loss of consciousness, agitation, and delirium. In a proportionally short time, renal failure with oliguria and fluid overload may appear early despite adequate cardiopulmonary support. Concurrent signs and symptoms may lead clinicians to challenge on differential diagnoses, particularly when liver failure and hemopoietic systems are affected. For instance, HLH requires differential diagnosis with macrophage activation syndrome (MAS), systemic inflammatory response syndrome (SIRS), and sepsis, therefore to tailor the best and specific treatment and avoid worsening of MODS. Many biomarkers have been explored, with efforts on early identification of renal failure (neutrophil gelatinase-associated lipocalin, cystatin C) or sepsis state (procalcitonin, presepsin, endotoxin activity assay). In our opinion, these biomarkers[26–34] require further clinical exploration before their widespread use can be recommended among pediatric MODS and critically ill children, because their costly application has not been associated with any specific therapeutic approach so far.

There is room for enhanced and more precise and advanced monitoring of MODS. Several candidate markers can be proposed to serve in this role. Various biomarkers are examples of promising candidates, such as the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) panel, which assigns a mortality probability for children with septic shock. PERSEVERE is based on classification and regression tree methodology and a panel of stratification biomarkers objectively selected through discovery-oriented transcriptomic studies. Using serum samples obtained during the first 24 hours of presentation with septic shock, PERSEVERE assigns a range of clinically meaningful mortality probabilities. The model was validated in a separate cohort, demonstrating excellent performance.[35] Patients with a high risk of PERSEVERE-based mortality, who actually survive, have a higher burden and duration of organ failure compared with those with a low risk of PERSEVERE-based mortality. Also proposed is monitoring of heart rate variability and/or respiratory rate variability as well as computational modeling: overall, the reduction of "biological chaos" has been considered as a pathologic sign of MODS severity. Other candidates merit some attention, such as biomarkers measured in sweat and many physiologic markers such as global oxygen delivery (Do_2) and/or oxygen consumption (Vo_2), intermittent or continuous central venous oxygen saturation ($Scvo_2$), near-infrared spectroscopy, blood lactate, global or peripheral oxygen extraction rate (O_2EXT, Po_2EXT),

plethysmographic variability, and gastric tonometry. If the reliability and added value of these candidate technologies could be established, they hold promise to enhance the understanding, monitoring, and perhaps treatment of MODS in children.[35]

Treatment

Multiple organ support of pediatric critically ill patients who experience MODS remains a challenge for pediatric intensivists, particularly in the light of the increasing number of cases with more than three involved organs. Of course, in case of septic MODS, the optimal management of antibiotic therapy and infection source control are mandatory for the resolution of the clinical syndrome.[36] Hemodynamic goal-directed therapy is aimed at optimizing circulatory dysfunction, and protective ventilation may be recommended in the attempt of reducing volo/baro/atelect-trauma of lungs.[36] Invasive and noninvasive devices for monitoring hemodynamics and perfusion indexes have been proving their synergic effect for the optimization of intensivists' practice. As a matter of fact, therapy is exploited to maintain the normal value of lactate, acidosis, arterial blood gases, electrolyte balance, coronary and peripheral perfusion, monitoring of cerebral and renal perfusion by controlling near infrared spectroscopy, PaO_2/FiO_2, oxygenation index, glycemic and electrolytes levels, and thermic gradient. The standard use of inotropic agents, blood components, surfactant treatment, immunoglobulin infusion, NO, and prone positioning often may represent effective treatment approach to MODS in the PICU.[36]

Many cases of sepsis-related MODS require a rescue dose of corticosteroid to "freeze" immunologic unbalance.[36] As stated previously, the occurrence of differential diagnosis among sepsis, SIRS, HLH, and MAS call in the PICU allow many pediatric specialties to reach a timely diagnosis. HLH is characterized by excessive immune activation, and the ideal form of immune suppression/antiinflammatory therapy remains unknown. Although somewhat responsive to corticosteroids and clearly responsive to etoposide or anti–T cell serotherapy (antithymocyte globulin or alemtuzumab), HLH remains difficult to treat. Generally, hemopoietic stem cell transplantation (HSCT) is recommended in the case of documented familial HLH, recurrent or progressive disease despite intensive therapy, and CNS involvement. In case of MAS, it usually responds to corticosteroid therapy and aggressive hemodynamic support.

Furthermore, patients affected from MODS after HSCT with severe graft versus host disease (GVHD) may require therapeutic plasmapheresis (TPA) or continuous renal replacement therapy (CRRT), according to specific indication after complications treatment. TPA also is indicated to support severe immune-mediated polyneuropathies that lead patients in the PICU for MODS with respiratory failure, neurologic impairment, and sepsis-related pattern with fever.[36]

Therapeutic hypothermia still is debated among pediatric intensivists in the management of hypoxic-ischemic encephalopathy; large prospective, multicenter, and randomized clinical trials are ongoing, but its role on pediatric MODS treatment is still far from being understood.[36] Great attention is provided carefully to prevent, protect, and manage renal function. Timely CRRT can be initiated to control fluid overload,[36] to remove excessive cytokine bloodstream spillover resulting from hyperinflammatory state secondary to infection,[37] and to promote drug clearance in case of intoxication, and endogenous toxic metabolites in case of inborn error of metabolism.[38]

A 2011 review of Extracorporeal Life Support Organization data[39] suggested that survival rates have increased significantly in cases of pediatric septic shock as compared with initial reports. Single-center experiences suggest more satisfactory outcomes in refractory MODS. The ACCM pediatric sepsis guidelines also were revised in 2009 to recommend consideration of ECMO in the event of refractory septic shock.[40]

A number of potential promising opportunities (although currently not confirmed consistently in clinical practice) include the need for a better understanding of the pharmacokinetics and pharmacodynamics of medications, the effect of early and optimized nutrition, and the impact of effective glucose control in the setting of MODS. In addition, anticytokine therapies, antitoxin treatments, antioxidant approaches, and multiple forms of exogenous steroids are currently under study.[41]

Pediatric MODS management surely benefits by multidisciplinary approach to tailor the best treatment on critically ill children. The concept of a multiorgan extracorporeal support should be made readily available in the near future in PICU, thanks to several technologic innovations,[42] to warrant timely support of pediatric MODS.

Key Points

1. Pediatric multiorgan dysfunction syndrome (MODS) has a blurred epidemiology, ranging from 10% to 50% of children admitted to the pediatric intensive care unit, mostly depending on critical illness diagnosis, the presence of sepsis, history of chronic diseases, and patients' age (the neonates being at highest risk).
2. An unbalanced immune response in the homeostasis between proinflammatory and antiinflammatory mediators is thought to be the cause for the development of MODS.
3. Lungs are most often the first organ initiating the MODS cascade. Heart, brain, kidney, and liver are the other typically involved components of MODS.
4. Specific pediatric MODS conditions are represented by thrombocytopenia-associated multiple organ failure (TAMOF), hemophagocytic lymphohistiocytosis (HLH), Kawasaki syndrome, and several pictures linked to hematologic malignancies' pathogenesis and management complications.
5. Management of pediatric MODS requires a multimodal approach and depends primarily on initial diagnosis. It includes aggressive ventilatory and hemodynamic support, prevention of renal damage, and the administration of immunosuppressive agents in selected cases.
6. The indications for ECMO and extracorporeal life support recently have increased, and more timely interventions may be suggested.

Key References

24. Maclaren G, Butt W, Best D, et al. Extracorporeal membrane oxygenation for refractory septic shock in children: One institution's experience. *Pediatr Crit Care Med*. 2007;8:447-451.

35. Typpo KV, Wong HR, Finley SD, et al. Monitoring Severity of Multiple Organ Dysfunction Syndrome: New Technologies. *Pediatr Crit Care Med*. 2017;18:S24-S31.
36. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296-327.
40. Skinner SC, Iocono JA, Ballard HO, et al. Improved survival in venovenous versus venoarterial extracorporeal membrane oxygenation for pediatric noncardiac sepsis patients: a study of the Extracorporeal Life Support Organization registry. *J Pediatr Surg*. 2012;47:63-67.
41. Doctor A, Zimmerman J, Agus M, et al. Pediatric Multiple Organ Dysfunction Syndrome: Promising Therapies. *Pediatr Crit Care Med*. 2017;18:S67-S82.

A complete reference list can be found online at ExpertConsult.com.

References

1. Varghese HJ, MacKenzie LT, Groom AC, et al. Mapping of the functional microcirculation in vital organs using contrast-enhanced in vivo video microscopy. *Am J Physiol Heart Circ Physiol*. 2005;288(1):H185-H193. [Epub 2004 Sep 23].
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864-874.
3. Ramirez M. Multiple organ dysfunction syndrome. *Curr Probl Pediatr Adolesc Health Care*. 2013;43(10):273-277.
4. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8. Review.
5. Guidet B, Aegerter P, Gauzit R, et al. Incidence and impact of organ dysfunctions associated with sepsis. *Chest*. 2005;127(3): 942-951.
6. Proulx F, Fayon M, Farrell CA, et al. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest*. 1996;109(4):1033-1037.
7. Wilkinson JD, Pollack MM, Ruttimann UE, et al. Outcome of pediatric patients with multiple organ system failure. *Crit Care Med*. 1986;14:271-274.
8. Typpo K, Petersen N, Hallman D, et al. Impact of premorbid conditions on multiple organ dysfunction syndrome in the PICU. *Pediatr Res*. 2007.
9. Dosa NP, Boeing NM, Ms N, et al. Excess risk of severe acute illness in children with chronic health conditions. *Pediatrics*. 2001;107:499-504.
10. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. International Consensus Conference on Pediatric Sepsis. *Pediatr Crit Care Med*. 2005;6(1):2-8. Review.
11. Bestati N, Leteurtre S, Duhamel A, et al. Differences in organ dysfunctions between neonates and older children: a prospective, observational, multicenter study. *Crit Care*. 2010;14(6):R202. doi:10.1186/cc9323. [Epub 2010 Nov 9].
12. Graciano AL, Balko JA, Rahn DS, et al. The Pediatric Multiple Organ Dysfunction Score (P-MODS): development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. *Crit Care Med*. 2005;33(7):1484-1491.
13. Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicenter study. *Lancet*. 2003;362(9379): 192-197.
14. Janota J, Simak J, Stranak Z, et al. Critically ill newborns with multiple organ dysfunction: assessment by NEOMOD score in a tertiary NICU. *Ir J Med Sci*. 2008;177(1):11-17.
15. Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? *JPEN J Parenter Enteral Nutr*. 2007;31:246-258.
16. Alverdy J, Laughlin RS, Wu L. Influence of the critically ill state on host pathogen interactions within the intestine: gut derived sepsis redefined. *Crit Care Med*. 2003;31:598-607.
17. Meakins JL. Etiology of multiple organ failure. *J Trauma*. 1990;30:5165-5166.
18. Wan L, Bagshaw SM, Langenberg C, et al. Pathophysiology of septic acute kidney injury: what do we really know? *Crit Care Med*. 2008;36(suppl):S198-S203.
19. Nguyen TC, Carcillo JA. Bench-to-bedside review: thrombocytopenia-associated multiple organ failure–a newly appreciated syndrome in the critically ill. *Crit Care*. 2006;10(6):235.
20. Karapinar B, Yilmaz D, Balkan C, et al. An unusual cause of multiple organ dysfunction syndrome in the pediatric intensive care unit: hemophagocytic lymphohistiocytosis. *Pediatr Crit Care Med*. 2009;10(3):285-290.
21. Gatterre P, Oualha M, Dupic L, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med*. 2012;38(5):872-878.
22. Rossetti E, Bianchi R, Chiusolo F, et al. Extracorporeal membrane oxygenation in a 10-year-old girl with macrophage activation syndrome. *Paediatr Anaesth*. 2012;22(9):937-938.
23. Rossetti E, Bianchi R, et al. Lung ultrasound assessment of influenza A(H1N1)-associated ARDS in a child with acute lymphoblastic leukemia outbreak undergoing extracorporeal membrane oxygenation. *Paediatr Anaesth*. 2015;25(12):1301-1302.
24. Maclaren G, Butt W, Best D, et al. Extracorporeal membrane oxygenation for refractory septic shock in children: One institution's experience. *Pediatr Crit Care Med*. 2007;8:447-451.
25. Vohra HA, Adamson L, Weeden DF, et al. Use of extracorporeal membrane oxygenation in the management of septic shock with severe cardiac dysfunction after Ravitch procedure. *Ann Thorac Surg*. 2009;87(1):e4-e5.
26. Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009;37:666-688.
27. Mussap M1, Puxeddu E, et al. Soluble CD14 subtype (sCD14-ST) presepsin in premature and full term critically ill newborns with sepsis and SIRS. *Clin Chim Acta*. 2015;451(Pt A):65-70. doi:10.1016/j.cca.2015.07.025. [Epub 2015 Jul 29].
28. Zhang X1, Liu D, et al. The accuracy of presepsin (sCD14-ST) for the diagnosis of sepsis in adults: a meta-analysis. *Crit Care*. 2015;19:323.
29. Pugni L, Pietrasanta C, et al. Presepsin (Soluble CD14 Subtype): Reference Ranges of a New Sepsis Marker in Term and Preterm Neonates. *PLoS ONE*. 2015;10(12).
30. Dholakia S, Inwald D, et al. Endotoxemia in pediatric critical illness–a pilot study. *Crit Care*. 2011;15(3):R141. doi:10.1186/cc10264. [Epub 2011 Jun 8].
31. Ricci Z, Haiberger R, et al. Evaluation of Endotoxemia After Pediatric Cardiac Surgery With the Endotoxin Activity Assay: An Exploratory Prospective Cohort Study. *Pediatr Crit Care Med*. 2016;17(2):e76-e80. doi:10.1097/PCC.0000000000000582.
32. Algorithm to Guide Antibiotic Use in the Pediatric Intensive Care Unit: The Optimizing Antibiotic Strategies in Sepsis (OASIS) Study. *J Pediatric Infect Dis Soc*. 2016 May 4.
33. Pierce R, Bigham MT, Giuliano JS Jr. Use of procalcitonin for the prediction and treatment of acute bacterial infection in children. *Curr Opin Pediatr*. 2014;26(3):292-298.
34. Di Nardo M, Ficarella A, Ricci Z, et al. Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: an observational study. *Blood Purif*. 2013;35(1-3):172-176.
35. Typpo KV, Wong HR, Finley SD, et al. Monitoring Severity of Multiple Organ Dysfunction Syndrome: New Technologies. *Pediatr Crit Care Med*. 2017;18:S24-S31.
36. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296-327.
37. Selewski DT, Cornell TT, Blatt NB, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. *Crit Care Med*. 2012;40:2694-2699.
38. Ruth A, McCracken CE, Fortenberry JD, et al. Extracorporeal therapies in pediatric severe sepsis: findings from the pediatric health-care information system. *Crit Care*. 2015;19:397.
39. Spinale JM, Laskin BL, Sondheimer N, et al. High-dose continuous renal replacement therapy for neonatal hyperammonemia. *Pediatr Nephrol*. 2013;28(6):983-986.
40. Skinner SC, Iocono JA, Ballard HO, et al. Improved survival in venovenous versus venoarterial extracorporeal membrane oxygenation for pediatric noncardiac sepsis patients: a study of the Extracorporeal Life Support Organization registry. *J Pediatr Surg*. 2012;47:63-67.
41. Doctor A, Zimmerman J, Agus M, et al. Pediatric Multiple Organ Dysfunction Syndrome: Promising Therapies. *Pediatr Crit Care Med*. 2017;18:S67-S82.
42. Romagnoli S, Ricci Z, Ronco C. Novel Extracorporeal Therapies for Combined Renal-Pulmonary Dysfunction. *Semin Nephrol*. 2016;36(1):71-77.