


# Improvement of Oxygenation in Severe Acute Respiratory Distress Syndrome With High-Volume Continuous Venovenous Hemofiltration

Global Pediatric Health  
Volume 3: 1–6  
© The Author(s) 2016  
Reprints and permissions:  
sagepub.com/journalsPermissions.nav  
DOI: 10.1177/2333794X16645699  
gph.sagepub.com  


Wenmin Yang, MD<sup>1</sup>, Jie Hong, MD<sup>1</sup>, Qiyi Zeng, PhD<sup>2</sup>,  
Jianping Tao, MD<sup>1</sup>, Feiyan Chen, MD<sup>1</sup>, Run Dang, MD<sup>1</sup>,  
Yufeng Liang, MD<sup>1</sup>, Zhiyuan Wu, PhD<sup>1</sup>, and Yiyu Yang, MD<sup>1</sup>

## Abstract

The efficacy and therapeutic mechanisms of continuous renal replacement therapy (CRRT) for improvement of oxygenation in acute respiratory distress syndrome (ARDS) remain controversial. These questions were addressed by retrospective analysis of severe ARDS patients admitted to the pediatric intensive care unit of our hospital from 2009 to 2015 who received high-volume continuous veno-venous hemofiltration during mechanical ventilation. There was a significant improvement in partial oxygen pressure/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) 24 hours after CRRT onset compared with baseline (median change = 51.5; range = -19 to 450.5;  $P < .001$ ) as well as decreases in  $\text{FiO}_2$ , peak inspiratory pressure, positive end-expiratory pressure, and mean airway pressure ( $P < .05$ ). The majority of patients had a negative fluid balance after 24 hours of CRRT. White blood cell (WBC) count decreased in the subgroup with high baseline WBC count ( $P < .05$ ).  $\text{PaO}_2/\text{FiO}_2$  was higher in ARDS patients with extrapulmonary etiology than in those with pulmonary etiology ( $P < .05$ ). Improvement in oxygenation is likely related to both restoration of fluid balance and clearance of inflammatory mediators.

## Keywords

acute respiratory distress syndrome; hemofiltration; inflammation; pediatrics, oxygenation

Received March 22, 2016. Received revised March 22, 2016. Accepted for publication March 25, 2016

## Introduction

Acute respiratory distress syndrome (ARDS) is an inflammatory lung disorder characterized by increased permeability of the alveolar-capillary barrier, leading to alveolar leukocyte infiltration and protein-rich pulmonary edema. Clinically, it presents as refractory hypoxemia and bilateral pulmonary infiltrates without evidence of left-heart failure or volume overload. ARDS is driven primarily by inflammatory chemokines and cytokines produced endogenously in response to a variety of inciting agents and events. In children, one study reported that the mortality from mild and moderate ARDS was about 10%, whereas that from severe ARDS was as high as 25%.<sup>1</sup> The severity of the oxygenation deficit as measured by the partial oxygen pressure/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) correlates well with mortality.

Hemofiltration has been proposed as one possible therapeutic option for improving oxygenation by promoting

fluid removal, but its efficacy is still contentious. Some studies have concluded that continuous renal replacement therapy (CRRT), which is indicated for acute fluid overload (FO) as well as acute renal failure, improves oxygenation in patients with respiratory failure.<sup>2-4</sup> However, others have found no improvement in oxygenation.<sup>5</sup> Even if CRRT can improve oxygenation in children with ARDS, there is still debate as to whether the beneficial effects on pulmonary gas exchange are mediated by mechanisms

<sup>1</sup>Guangzhou Women and Children's Medical Center, Guangzhou City, China

<sup>2</sup>Zhujiang Hospital of Southern Medical University, Guangzhou City, China

### Corresponding Author:

Yiyu Yang, Pediatric Intensive Care Unit, Guangzhou Women and Children's Medical Center, Guangzhou City 51000, China.

Email: 18198915270@163.com



other than fluid removal, such as through continuous removal of inflammatory mediators.<sup>4,6</sup>

To examine the efficacy of CRRT for improvement of lung function in pediatric ARDS and the contribution of inflammatory mediators, we retrospectively compared gas exchange and inflammatory parameters before and after continuous veno-venous hemofiltration (CVVH) in pediatric patients with severe ARDS. We selected only patients with severe ARDS because patients in this high-mortality group may derive the greatest benefit from CRRT.<sup>7,8</sup>

## Materials and Methods

### Patients

This was a retrospective cohort study in which clinical and laboratory data were gathered for 30 consecutive children with severe ARDS treated at Guangzhou Women and Children's Medical Center. Inclusion criteria were the following: (1) age 1 month to 18 years, (2) admission to the pediatric intensive care unit (PICU) between January 2009 and December 2015, (3) diagnosis of severe ARDS according to the Berlin definition criteria,<sup>9</sup> (4) need for mechanical ventilation, and (5) initiation of CRRT. The Berlin criteria define severe ARDS as the following:  $\text{PaO}_2/\text{FiO}_2 \leq 100$  mm Hg with  $\text{PEEP} \geq 5$  cm  $\text{H}_2\text{O}$  occurring within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules on chest radiography without evidence of cardiac failure or FO; and objective assessment to exclude hydrostatic edema.<sup>9</sup>

The present study was approved by the ethics committee of Guangzhou Women and Children's Medical Center. Written informed consent was obtained from the parents or legal guardians of all participants.

### Treatment

**Routine Treatment.** Respiratory support consisted of mechanical ventilation with relatively small tidal volumes ( $V_T$ s; 6-8 mL/kg) in the prone position with allowable  $\text{PaCO}_2$  within 45 to 70 mm Hg. However, respiratory support was not regulated by protocol.

**Renal Replacement Therapy.** CVVH was performed with a flow-controlled blood roller pump machine to treat FO unresponsive to diuretics. The parameters were replacement solution infusion at 50 to 60 mL/kg/h and blood pump flow rate at 5 to 10 mL/kg/min. An automated system (PRISMA, Gambro AB, Stockholm, Sweden) was used to deliver CVVH continuously for at least 24 hours. The initial replacement solution was composed of 2000 mL normal saline, 500 mL of 5% glucose, 1 mL of 25%

magnesium sulfate, 10 mL of 10% calcium gluconate, 10 mL of 10% potassium chloride, and 250 mL of 5% sodium bicarbonate. The formula was adjusted according to individual blood glucose and electrolyte levels. Conventional heparin was used as the anticoagulant. Fluid removal rate was determined by the PICU physician according to clinical condition and fluid status of the patient.

### Data Collection

Data were extracted from the ICU medical records. Fluid balance/weight was defined as  $[\text{Fluid in}] - [\text{Fluid out}]$  (in mL)/ $[\text{Admission weight}]$  (in kg). The degree of FO from PICU admission to CRRT initiation (%FO) was calculated using the following formula:  $\%FO = \{([\text{Fluid in}] - [\text{Fluid out}] \text{ (in L)})/[\text{Admission weight}] \text{ (in kg)}\} \times 100$ .<sup>10</sup> The rationale for using FO from PICU admission to CRRT initiation was based on many previous pediatric studies.<sup>10-12</sup> The following variables were collected just before CVVH (0 hours) and 24 hours after initiation: arterial blood gas levels; ventilator settings, including  $\text{FiO}_2$ ; peak inspiratory pressure (PIP); positive end-expiratory pressure (PEEP);  $V_T$ ; mean airway pressure (Paw);  $\text{PaO}_2/\text{FiO}_2$ ; and laboratory values for white blood cell (WBC) count and creatinine. The hemodynamic variables heart rate and mean arterial blood pressure (MAP) were also recorded before and after CRRT.  $\text{PaO}_2/\text{FiO}_2$  at 6 hours before CRRT was also collected to assess any spontaneous change prior to intervention. Patients were also classified according to etiology as having ARDS of pulmonary or extrapulmonary origin.

### Statistical Analysis

Changes of each variable were calculated for all patients from baseline (0 hours) to 24 hours after onset of CRRT. The Wilcoxon signed-rank test was applied to test whether the median change was 0.  $\text{PaO}_2/\text{FiO}_2$  at 6 and 0 hours before CRRT were also compared. The Mann-Whitney U test was used for comparison of patients with pulmonary versus extrapulmonary ARDS. Significance was set at  $P < .05$ . All statistical calculations were performed using SPSS 11.5 for Windows.

## Results

### Patient Characteristics

Between 2009 and 2015, 30 patients meet the inclusion criteria. Patient characteristics are summarized in Tables 1 and 2. Before the start of CRRT, all children had positive fluid balance, and most had pre-CRRT %FO <10%. There was no significant difference between  $\text{PaO}_2/\text{FiO}_2$  at 6 and at 0 hours before CRRT.

**Table 1.** Baseline Clinicodemographic Characteristics (n = 30).

	Number	Percentage of Total
Median age (years)	2 (range = 0.25-11)	
Sex (male/female)	19/11	
Etiology of ARDS		
Pneumonia (%)	17	56.7%
Severe sepsis (%)	3	10%
Septic shock	10	33.3%
%FO pre-CRRT > 20%	1	3.3%
%FO pre-CRRT > 10%	6	20%
%FO pre-CRRT < 10%	23	76.7%
Negative fluid balance/weight >30 mL/kg after 24 hours of CRRT	28	93.3%
Oliguria	5	16.7%
ICU survivors	23	76.7%

Abbreviations: ARDS, acute respiratory distress syndrome; FO, fluid overload; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

**Table 2.** Baseline Respiratory, Ventilator, Hemodynamic, and Laboratory Values.

	Median	Range
PaO <sub>2</sub> /FiO <sub>2</sub> before CRRT (0 hours at CRRT)	80 (47-99)	47-99
%FO from PICU admission to CRRT initiation	6.8% (1%-22%)	1%-22%
Fluid balance/weight after 24 hours of CRRT (mL/kg)	-88	-198 to 39
Cr at CRRT initiation (μmol/L)	45	11-646
Mean arterial blood pressure (mm Hg)	70.8	56-111.3
Heart rate (beats/min)	161	117-203
WBC (10 <sup>9</sup> /L)	15.1	1.5-57.2
Baseline ventilator settings		
PIP (cm H <sub>2</sub> O)	30	27-40
PEEP (cm H <sub>2</sub> O)	10	6-20
Paw (cm H <sub>2</sub> O)	20	13-24
V <sub>T</sub> (mL)	110	56-257
FiO <sub>2</sub>	0.7	0.4-1

Abbreviations: PaO<sub>2</sub>/FiO<sub>2</sub>, partial oxygen pressure/fraction of inspired oxygen; CRRT, continuous renal replacement therapy; FO, fluid overload; PICU, pediatric intensive care unit; Cr, creatinine; WBC, white blood cell; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Paw, mean airway pressure; V<sub>T</sub>, tidal volume.

### Effect of CRRT on Oxygenation, Ventilator Settings, Hemodynamics, and WBC Count

Median changes in respiratory, ventilator, hemodynamic, and laboratory parameters from baseline (0 hours) to 24 hours after initiation of CRRT are shown in Table 3. The main gas exchange parameter PaO<sub>2</sub>/FiO<sub>2</sub> improved significantly 24 hours after the start of CRRT compared with the 0-hour baseline value (increase in median = 51.5; range = -19 to 450.5; *P* < .001), whereas the ventilatory parameters, FiO<sub>2</sub>, PIP, PEEP, and Paw, all decreased significantly (*P* < .05). MAP increased and heart rate decreased after CRRT (*P* < .05).

WBC count decreased significantly after 24 hours of CRRT in the 18 patients with elevated baseline WBC count (*P* = .001), whereas no significant change was observed in patients with normal or below normal baseline WBC count. However, of those with baseline WBC count in the high-normal range, there was a trend toward a drop after treatment.

### Effect of CRRT on Fluid Balance

It was found that 28 patients had negative fluid balance >30 mL/kg following 24 hours of CRRT, whereas only one had a zero fluid balance and one a positive fluid balance of +39 mL/kg.

**Table 3.** Median Changes in Respiratory, Ventilator, Hemodynamic, and Laboratory Values.<sup>a</sup>

Measurement	n <sup>b</sup>	Median Change	Range	P <sup>c</sup>
PaCO <sub>2</sub> (kPa)	30	0	-2.9 to +3.2	.691
PaO <sub>2</sub> (kPa)	30	+2.95	-10.2 to +22	.001
PaO <sub>2</sub> /FiO <sub>2</sub>	30	+51.5	-19 to 450.5	<.001
FiO <sub>2</sub>	30	-0.02	-0.55 to +0.15	.003
PIP (cm H <sub>2</sub> O)	30	-1	-12 to +1	.001
PEEP (cm H <sub>2</sub> O)	30	-2	-7 to +4	.004
Paw (cm H <sub>2</sub> O)	30	-1	-6 to +6	.007
V <sub>T</sub> (mL)	30	0	-36 to +35	.861
MAP (mm Hg)	30	10.35	-16.4 to 38	.003
Heart rate (beats/min)	30	-25	-75 to +33	.003
High WBC (10 <sup>9</sup> /L) <sup>d</sup>	18	-6.5	-22.6 to +1.7	.001
Low WBC (10 <sup>9</sup> /L) <sup>e</sup>	7	+0.3	-1.4 to +13.2	.933
Normal WBC (10 <sup>9</sup> /L)	5	-1.4	-3.7 to +0.3	.08

Abbreviations: CRRT, continuous renal replacement therapy; PaCO<sub>2</sub>, carbon dioxide pressure; PaO<sub>2</sub>, partial oxygen pressure; FiO<sub>2</sub>, fraction of inspired oxygen; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Paw, mean airway pressure; V<sub>T</sub>, tidal volume; MAP, mean arterial blood pressure; WBC, white blood cell.

<sup>a</sup>From baseline (0 hours) to 24 hours after CRRT.

<sup>b</sup>Number of patients with available data.

<sup>c</sup>P value from Wilcoxon signed-rank test.

<sup>d</sup>WBC count elevated for age.

<sup>e</sup>WBC count depressed for age.

**Table 4.** Comparison of Respiratory and Ventilatory Variables for ARDS Patients With Pulmonary (n = 17) and Extrapulmonary Etiology (n = 13).

Variable	Time Point	Median (Range)		P <sup>a</sup>
		Pulmonary	Extrapulmonary	
PaCO <sub>2</sub> (kPa)	CRRT 0 hours	5.1 (3.9-7.9)	6.8 (3.7-7.5)	.153
	CRRT 24 hours	5.9 (4-7.9)	6.3 (3.5-7.6)	.706
PO <sub>2</sub> (kPa)	CRRT 0 hours	8 (6.3-12.5)	8 (5.2-19.7)	.691
	CRRT 24 hours	11 (6-24.2)	11.7 (6-28)	.295
PaO <sub>2</sub> /FiO <sub>2</sub>	CRRT 0 hours	83.7 (47-98)	78.75 (47-99)	.834
	CRRT 24 hours	125 (45-240)	162 (69-548)	.024
FiO <sub>2</sub>	CRRT 0 hours	0.7 (0.4-1)	0.69 (0.5-1.0)	.966
	CRRT 24 hours	0.6 (0.3-1)	0.5 (0.35-0.98)	.077
PIP (cm H <sub>2</sub> O)	CRRT 0 hours	30 (28-40)	31 (27-37)	.866
	CRRT 24 hours	29 (23-35)	30 (21-35)	.509
PEEP (cm H <sub>2</sub> O)	CRRT 0 hours	10 (6-14)	10 (7-20)	.282
	CRRT 24 hours	9 (5-14)	10 (5-14)	.555
Paw (cm H <sub>2</sub> O)	CRRT 0 hours	22 (15-24)	20 (13-24)	.212
	CRRT 24 hours	20 (9-30)	18 (9-25)	.303
V <sub>T</sub> (mL)	CRRT 0 hours	110 (59-257)	110 (56-220)	.621
	CRRT 24 hours	105 (55-245)	108 (64-220)	.509

Abbreviations: ARDS, acute respiratory distress syndrome; PaCO<sub>2</sub>, carbon dioxide pressure; PaO<sub>2</sub>, partial oxygen pressure; FiO<sub>2</sub>, fraction of inspired oxygen; CRRT, continuous renal replacement therapy; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; Paw, mean airway pressure; V<sub>T</sub>, tidal volume.

<sup>a</sup>P value from Mann-Whitney U test.

### Comparison of ARDS Patients With Pulmonary Versus Extrapulmonary Etiology

In a second analysis, respiratory and ventilatory changes were evaluated separately (Table 4) in those patients

with pulmonary etiology (n = 17) and those with extrapulmonary etiology (n = 13). PaO<sub>2</sub>/FiO<sub>2</sub> after 24 hours of CRRT was higher in ARDS patients with extrapulmonary etiology than in those with pulmonary etiology (P = .024). FiO<sub>2</sub> did not differ between the 2 groups after

CRRT, but there was a trend for lower post-CRRT  $\text{FiO}_2$  in the extrapulmonary group. There were no group differences in the other respiratory and ventilatory parameters.

## Discussion

Our study demonstrates that CRRT can substantially improve oxygenation (as measured by  $\text{PaO}_2/\text{FiO}_2$ ) and decrease ventilatory parameters ( $\text{FiO}_2$ , PIP, PEEP, and Paw) in pediatric patients with severe ARDS. Moreover, these results also strongly suggest that suppression of inflammation is a major contributor to this therapeutic effect, in addition to restoration of fluid balance.

There was no change in  $\text{PaO}_2/\text{FiO}_2$  from 6 hours before to immediately before CRRT, indicating no spontaneous improvement, whereas a significant increase was observed after 24 hours of CRRT, indicating that improved oxygenation is the result of CRRT. The effect was at least partially a result of reduction of FO. All patients had positive fluid balance prior to CRRT, and the majority had a negative fluid balance 24 hours following CRRT. Many clinical studies have shown that reducing or eliminating positive fluid balance in patients with ARDS can reduce mechanical ventilation times<sup>13</sup> and mortality,<sup>14</sup> presumably by preventing fluid accumulation in the lungs, which aggravates respiratory insufficiency in ARDS.

However, most patients with severe ARDS in our study did not have severe FO before CRRT (23 of 30 or 76.7% had baseline %FO <10% and only one had %FO >20%). Moreover, many studies have shown that <10% FO is advantageous for both  $\text{PaO}_2/\text{FiO}_2$  and survival.<sup>11,13-15</sup> Nonetheless, all patients had very low baseline  $\text{PaO}_2/\text{FiO}_2$ . Considering the lack of severe FO, we suggest that mitigating severe FO was not the only mechanism by which CRRT improved  $\text{PaO}_2/\text{FiO}_2$ . Patients with high baseline WBC counts showed significant WBC count reductions after CRRT, suggesting that suppression of inflammation may be an additional contributing mechanism for improved oxygenation. Indeed, several studies have shown that CRRT can remove serum systemic inflammatory mediators that contribute to ARDS pathogenesis by convection and absorption.<sup>6,16-19</sup>

To further elucidate whether modulation of inflammation is clinically relevant, we compared patients with ARDS having an extrapulmonary cause with those having a pulmonary etiology because these 2 ARDS subgroups have distinct pathogenic characteristics. Edema and alveolar collapse caused by capillary leak and systemic inflammation play a central role in extrapulmonary ARDS, whereas consolidation secondary to pneumonia and lung inflammation is essential for progression of

pulmonary ARDS.<sup>20</sup> In our study,  $\text{PaO}_2/\text{FiO}_2$  after CRRT was higher in ARDS of extrapulmonary origin, again suggesting that suppression of the systemic inflammatory response could be one of the mechanisms for improving oxygenation.

We used high-volume hemofiltration rates of 50 to 60 mL/kg/h to facilitate the removal of inflammatory mediators associated with ARDS. Much experimental and some clinical evidence also suggests that high-volume hemofiltration efficiently removes cytokines by a convective mechanism and can be beneficial for critically ill patients with severe inflammatory states such as septic shock.<sup>21-23</sup> Indications for CRRT in our institution are broader than in many other institutions, where CRRT is indicated primarily for renal failure and FO. In our study, early CRRT was implemented for severe ARDS patients with renal laboratory parameters and urine output within normal limits. CRRT use was based on past successes treating severe inflammatory states, and some of our severe ARDS patients were still deteriorating at the time of treatment, even in the absence of FO.

Limitations of this study include those inherent to the retrospective design and single-center case population, including the potential for selection bias. Thus, large multi-institutional studies are needed to verify if CRRT can improve oxygenation by reducing inflammation.

We demonstrate that 24 hours of CRRT can improve oxygenation in mechanically ventilated pediatric patients with severe ARDS, likely because of clearance of inflammatory mediators as well as mitigation of FO. However, determining the relative contributions of these 2 mechanisms requires further study.

## Author Contributions

WY contributed to the design and drafted the manuscript. JH contributed to the conception. QZ critically revised the manuscript for important intellectual content. JT critically revised the manuscript for important intellectual content. FC drafted the manuscript. RD gave final approval. YL gave final approval. ZW agreed to be accountable for all aspects of the work, in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YY agreed to be accountable for all aspects of the work, in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Authors' Note

Wenmin Yang and Jie Hong made equal contributions to this study.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Guangzhou Science and Technology Project (No. 2014Y2-00181).

## References

- De Luca D, Piastra M, Chidini G, et al. Respiratory Section of the European Society for Pediatric Neonatal Intensive Care (ESPNIC). The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus. *Intensive Care Med.* 2013;39:2083-2091.
- Bagshaw ON, Anaes FR, Hutchinson A. Continuous arteriovenous haemofiltration and respiratory function in multiple organ systems failure. *Intensive Care Med.* 1992;18:334-338.
- Matamis D, Tsagourias M, Koletsos K, et al. Influence of continuous haemofiltration-related hypothermia on haemodynamic variables and gas exchange in septic patients. *Intensive Care Med.* 1994;20:431-436.
- Elbahlawan L, West NK, Avent Y, et al. Impact of continuous renal replacement therapy on oxygenation in children with acute lung injury after allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer.* 2010;55:540-545.
- Hoste EA, Vanholder RC, Lameire NH, et al. No early respiratory benefit with CVVHDF in patients with acute renal failure and acute lung injury. *Nephrol Dial Transplant.* 2002;17:2153-2158.
- Cui HX, Xu JY, Li MQ. Efficacy of continuous renal replacement therapy in the treatment of severe acute pancreatitis associated acute respiratory distress syndrome. *Eur Rev Med Pharmacol Sci.* 2014;18:2523-2526.
- Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med.* 2009;37:2448-2454.
- Flori HR, Glidden DV, Rutherford GW, et al. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. *Am J Respir Crit Care Med.* 2005;171:995-1001.
- ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA.* 2012;307:2526-2533.
- Goldstein SL, Currier H, Graf CD, et al. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics.* 2001;107:1309-1312.
- Flores FX, Brophy PD, Symons JM, et al. Continuous renal replacement therapy (CRRT) after stem cell transplantation: a report from the prospective pediatric CRRT Registry Group. *Pediatr Nephrol.* 2008;23:625-630.
- Goldstein SL, Somers MJ, Baum MA, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int.* 2005;67:653-658.
- National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
- Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest.* 2009;136:102-109.
- Foland JA, Fortenberry JD, Warshaw BL, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Crit Care Med.* 2004;32:1771-1776.
- Koperna T, Vogl SE, Pöschl GP, et al. Cytokine patterns in patients who undergo hemofiltration for treatment of multiple organ failure. *World J Surg.* 1998;22:443-448.
- Yekebas EF, Eisenberger CF, Ohnesorge H, et al. Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. *Crit Care Med.* 2001;29:1423-1430.
- DiCarlo JV, Alexander SR, Agarwal R, et al. Continuous veno-venous hemofiltration may improve survival from acute respiratory distress syndrome after bone marrow transplantation or chemotherapy. *J Pediatr Hematol Oncol.* 2003;25:801-805.
- Bock KR. Renal replacement therapy in pediatric critical care medicine. *Curr Opin Pediatr.* 2005;17:368-371.
- Gattinoni L, Pelosi P, Suter PM, et al. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: different syndromes? *Am J Respir Crit Care Med.* 1998;158:3-11.
- Rogiers P. High-volume hemofiltration in septic shock. *Crit Care.* 2005;9:329-330.
- Cornejo R, Downey P, Castro R, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. *Intensive Care Med.* 2006;32:713-722.
- Rimmelé T, Kellum JA. High-volume hemofiltration in the intensive care unit: a blood purification therapy. *Anesthesiology.* 2012;116:1377-1387.