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Implementation and results of a new ECMO program for lung transplantation and acute respiratory distress

Implementación y resultados de un nuevo programa de ECMO para trasplante de pulmón y distrés respiratorio agudo

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ABSTRACT

Objective: The development of the extracorporeal membrane oxygenation in Latin America represents a challenge in this specialty field. The objective of this article was to describe the results of a new extracorporeal membrane oxygenation program in an intensive care unit.

Methods: This retrospective cohort study included 22 patients who required extracorporeal membrane oxygenation and were treated from January 2011 to June 2014. The baseline characteristics, indications, duration of the condition, days on mechanical ventilation, days in the intensive care unit, complications, and hospital mortality were evaluated.

Results: Fifteen patients required extracorporeal membrane oxygenation after lung transplantation, and seven patients required oxygenation due to acute respiratory distress. All transplanted patients were weaned from extracorporeal membrane oxygenation with a median duration of 3 days (Interquartile range - IQR: 2 - 5), were on mechanical ventilation for a median

of 15.5 days (IQR: 3 - 25), and had an intensive care unit stay of 31.5 days (IQR: 19 - 53) and a median hospital stay of 60 days (IQR: 36 - 89) with 20% mortality. Patients with acute respiratory distress had a median oxygenation membrane duration of 9 days (IQR: 3 - 14), median mechanical ventilation time of 25 days (IQR: 13 - 37), a 31 day stay in therapy (IQR: 11 - 38), a 32 day stay in the hospital (IQR: 11 - 41), and 57% mortality. The main complications were infections (80%), acute kidney failure (43%), bleeding at the surgical site and at the site of cannula placement (22%), plateletopenia (60%), and coagulopathy (30%).

Conclusion: In spite of the steep learning curve, we considered this experience to be satisfactory, with results and complications comparable to those reported in the literature.

Keywords: Extracorporeal membrane oxygenation; Lung transplantation; Acute respiratory distress syndrome; Respiratory insufficiency; Primary graft dysfunction; Intensive care units

Conflicts of interest: None.

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INTRODUCTION

The utility and safety of extracorporeal membrane oxygenation (ECMO) in patients with acute respiratory distress syndrome (ARDS) has been the subject of debate over the past 50 years. Although the mortality and incidence of ARDS have decreased in recent decades,⁽¹⁾ in patients with refractory hypoxemia who are supported by adequate mechanical ventilation (MV), the mortality rate can surpass 50%.⁽²⁾ One objective of ECMO support is to guarantee adequate oxygenation. In addition, this support allows for MV to have very low tidal

volumes and, consequently, lower inspiration end pressures to prevent pulmonary lesions associated with mechanical ventilation.⁽³⁻⁶⁾ The positive experience with ECMO during the 2009 H1N1 pandemic^(7,8) and its increasing use in Great Britain and the U.S.A. could justify the implementation of ECMO as a vital support measure during severe ARDS.^(9,10)

In lung transplantation patients, ECMO is a vital support tool during primary graft failure (PGF) and/or in peritransplant circulatory collapse.^(11,12)

For these reasons, in the year 2011, an ECMO program was launched in the adult intensive care unit (ICU) of the *Hospital Italiano de Buenos Aires* (HIBA). Because the majority of the published experiences with this type of technology have originated from developed countries, we considered the launch of this type of program to be very important for this region. This work analyzes the characteristics, complications, and results of the first patients to receive ECMO in our adult intensive care unit. The main objective of this study is to describe the baseline characteristics of the population that required ECMO in our center (age, sex, comorbidity load using the Charlson score,⁽¹³⁾ indications ECMO), the duration of the intensive care stay, the duration of mechanical ventilation and mortality. As secondary objectives, we seek to describe and compare the ventilation strategy utilized before and during ECMO and the complications that were presented. These complications were classified into clinical complications and ECMO-associated complications and were extracted from patients' compiled electronic medical records.

METHODS

A retrospective observational study of 22 patients requiring ECMO in the UCI from the start of the program in January 2011 until June 2014 was conducted. Data were obtained from patient electronic hospital medical records. This study was approved by the *Hospital Italiano de Buenos Aires* Research Protocol Ethics Committee (Protocol no. 2410). The patients included or their next of kin signed the corresponding consent for their confidential data to be used for investigative purposes.

Our ICU is polyvalent and has 38 beds equipped for highly complex situations. The Italian Hospital has been a lung transplantation center since 1993. The adult intensive care ECMO program was developed based on the recommendations from the ELSO⁽¹⁴⁾ and NICE guidelines.⁽¹⁵⁾ For our program, we utilized the 1994 American-European Consensus definition of ARDS,⁽¹⁶⁾ and after 2012, we utilized the Berlin classification.⁽²⁾

Following our critical care unit's ARDS protocol, the protective ventilation strategy consisted of low tidal volumes (TV = 6 - 7 ml/kg theoretical weight) and plateau pressures (Ppl) < 30 mmHg.⁽¹⁷⁾ After a recruitment maneuver, positive end-expiratory pressure (PEEP) titration occurred in all patients following a PEEP/deflation complacency curve.⁽¹⁸⁾ Sedation was optimized to reach a Richmond agitation-sedation score (RASS) of -4,⁽¹⁹⁾ and in patients with a Pa/FiO₂ < 150 neuromuscular blocking agents (NBA) were used in continuous infusion.⁽²⁰⁾ During the last year, ventilation in a prone position in patients with ARDS and a Pa/FiO₂ < 150 were incorporated into the distress protocol despite adequate MV.⁽²¹⁾ Those patients who continued to exhibit refractory hypoxemia (Pa/FiO₂ < 100, FiO₂ > 0.6), respiratory acidosis with a pH < 7.2, and/or evidence of barotrauma after 12 to 24 hours of these ventilatory strategies⁽²¹⁾ were evaluated for veno-venous (VV) ECMO. Patients who also presented hemodynamic instability secondary to cardiogenic shock were candidates for veno-arterial (VA) ECMO. In our study, this group included lung transplantation patients with acute heart failure in the intraoperative or early postoperative period following severe pulmonary hypertension (due to PGF or during pulmonary artery clamping).

Contraindications for ECMO included the presence of multiple organ failure, recent central nervous system bleeding, active hemorrhaging, or the presence of an anticoagulation contraindication, acute or sub-acute pulmonary fibrosis without the possibility of transplant, and cardiogenic shock secondary to an aortic valve insufficiency.

An ECMO system (Permanent life support system - PLS, Jostra - Quadrox D, Maquet Cardiopulmonary, Hirrlingen, Germany) with a centrifugal pump (Rotaflow, Jostra, Maquet Cardiopulmonary, Hirrlingen, Germany) was used. The PLS utilizes a poly-methylpentene membrane. Medtronic cannulas (17 Fr to 25 Fr) were used. The cardiovascular surgery team placed the vascular access cannulae peripherally using the modified Seldinger technique. For VA ECMO, the afferent cannula was placed through the femoral vein up to the union of the inferior vena cava with the right atrium, and the efferent cannula was placed in the femoral artery. For VV ECMO, the afferent cannula was placed in the right femoral vein, and the efferent cannula was placed in the superior vena cava through the internal jugular vein. Central cannulation of the VA ECMO was performed in only one case. The correct position of the cannulae was controlled with a transesophageal echocardiogram.

All patients were additionally evaluated and monitored by the nutritional support (NS) team following the ASPEN/ESPEN guidelines recommendations^(22,23) and the guidelines of the institution implementing the nutritional treatment.

The patients were cared for by a multidisciplinary team of doctors, respiratory kinesiologists, nurses, and pulmonologist who received continuing training.

The continuous variables were reported as medians and IQRs after normality evaluation with the Kolmogorov-Smirnov test. The categorical variables were presented as absolute values and frequencies. The matched samples were analyzed with the Wilcoxon signed rank test. We utilized IBM SPSS Statistics 21.0 to conduct the statistical analysis. Results with values of $p < 0.05$ were considered statistically significant.

RESULTS

For the analysis, patients were divided into two groups according to baseline disease: Group I (15 perioperative lung transplantation patients) and Group II (7 patients with ARSD that did not undergo a lung transplant). The baseline characteristics and indications of both groups are described in tables 1 and 2.

In Group I, veno-venous ECMO was indicated as a respiratory support in four patients with PGF. In seven patients with severe pulmonary hypertension (PHT) VA ECMO was utilized as a surgical strategy during the pulmonary transplant, and the VV modality was continued in the immediate postoperative period. In four patients, VA ECMO was indicated due to a circulatory collapse secondary to severe PHT and heart failure, of which three patients continued with VV ECMO until recovery. All of these patients were intubated and put on ventilation when the anesthesia for the transplant was initiated. Ventilation with nitric oxide (NO) was conducted during the first 48 hours as part of the pulmonary transplant protocol.⁽²⁴⁾ In 13 patients, cannulation was performed in the operating room, and in two patients, VV and VA ECMO were indicated in the ICU due to PGF and cardiogenic shock, respectively. In all cases, the initiation of ECMO was early (< 48 hour post-transplant).

In Group II, two patients suffered from ARDS secondary to multiple injuries (one patient required ECMO on two occasions; the second occasion was due to MV-associated pneumonia), two patients had postoperative ARDS, two patients had severe community-acquired pneumonias, and one patient was found to have alveolar proteinosis. Due to the presence of contraindications, only three

Table 1 - Group I characteristics

Patient	Age (years)*	Sex	Diagnosis	Charlson Score*	BT	Indication	Type of ECMO	Days of ECMO*	Days on MV*	Days in ICU*	Days of hospital stay*
1	56	F	PGF	2	No	Scheduled for surgery	VA/VV	4	35	41	72
2	57	F	COPD	4	No	PGF	VV	8	18	18	18
3	28	F	CF	1	Yes	Scheduled for surgery	VV	2	51	63	63
4	19	M	CF	1	Yes	PGF	VV	2	4	19	97
5	48	F	PF	1	No	Cardiogenic shock	VA	10	52	79	101
6	67	M	PF	7	No	Cardiogenic shock	VA	1	13	53	100
7	36	M	Bronchiectasis	1	Yes	Cardiogenic shock	VA	2	11	28	43
8	24	F	CF	1	Yes	Scheduled for surgery	VV	1	1	15	45
9	23	F	CF	1	Yes	PGF	VV	4	34	52	63
10	57	F	COPD	2	No	PGF	VV	5	15	35	57
11	35	M	CF	1	Yes	Scheduled for surgery	VA/VV	3	37	37	37
12	52	F	COPD	2	No	Scheduled for surgery	VA/VV	1	2	10	36
13	19	F	CF	1	Yes	Scheduled for surgery	VA/VV	2	3	26	31
14	25	F	CF	1	Yes	Scheduled for surgery	VA/VV	3	6	20	26
15	50	F	COPD	2	No	Cardiogenic shock	VA	5	46	58	89
Me (IQR)	36 (24.5 - 54)			2 (1 - 2)				3 (2 - 4.3)	15.5 (3 - 35)	31.5 (19 - 53)	60 (36 - 89)

BT - bilateral lung transplant; ECMO - extracorporeal oxygenation membrane; MV - mechanical ventilation; ICU - intensive care unit; F - female; M - male; PGF - primary graft failure; COPD - chronic obstructive pulmonary disease; CF - cystic fibrosis; PF - pulmonary fibrosis; VA - veno-arterial; VV - veno-venous. * Results are expressed as the median (25% - 75%).

Table 2 - Group II characteristics

Patient	Age (years)*	Sex	Diagnosis	Charlson Score*	Indication	Type of ECMO	Days of ECMO*	Days on MV*	Days in ICU*	Days of hospital stay*
1	23	M	Multiple trauma	0	2 nd ARDS	VV	2	12	6	6
2	23	M	POP thoracic surgery	6	1 st ARDS	VV	15	17	18	18
3	58	F	CAP	3	1 st ARDS	VV	7	32	38	42
4	45	F	Alveolar proteinosis	1	Hypoxemia	VV	2	15	25	27
5	56	F	CAP	1	1 st ARDS	VV	6	8	8	8
6	21	M	Multiple trauma	0	1 st ARDS	VV	11	37	37	37
7	44	M	POP esophagectomy	2	1 st ARDS	VV	15	56	58	72
Me (IQR)	44 (23 - 50.5)			1 (0.5 - 2.5)			9 (3 - 14)	25 (13 - 37)	31 (11 - 38)	32 (11 - 41)

ECMO - extracorporeal membrane oxygenation; MV - mechanical ventilation; ICU - intensive care unit; F - female; M - male; POP - postoperative; CAP - severe community-acquired pneumonia; ARDS - acute respiratory distress syndrome; VV - veno-venous. * Results are expressed as the median (25% - 75%).

patients were ventilated in the prone position prior to ECMO (hemodynamic instability, anterior thorax tube, and external fixation related to unstable pelvic fracture). Those who were ventilated in the prone position did not show improvement with this strategy. In all of the Group II cases, ECMO was indicated due to refractory hypoxemia, and the VV method was utilized. The median Pa/FiO₂ before the start of ECMO was 82 (IQR: 58 to 109), and the median oxygenation index⁽²⁵⁾ was 22 (IQR: 19 to 30.2).

For patients in Group II, we were able to compare the mechanical ventilation data before and after ECMO, which showed that it was possible to reduce TV from a median of 6.3 ml/k theoretical weight (ktw) to 4.6ml/ktw ($p = 0.01$). In the same manner, the FiO₂ could be reduced from a median of 1 to 0.4 ($p = 0.007$), and the gasometric criteria could also be improved with an increase in the median arterial pH from 7.29 to 7.43 ($p = 0.01$) and a reduction of PaCO₂ from 58mmHg to 38mmHg ($p = 0.01$). Statistical significance was not achieved for the decrease in median plateau pressure from 26cmH₂O to 24.5cmH₂O ($p = 0.07$). This comparison was not possible in lung transplantation patients because in all cases except two, the ECMO placement occurred in the operating room almost simultaneously with the start of invasive mechanical ventilation. In these patients, mechanical ventilation during ECMO also conserved the protective strategy, with a median TV of 5.8ml/kpt (IQR: 4.3 to 7.2ml/kpt), median PEEP of 9.2cmH₂O (IQR: 8 to 10cmH₂O), median FiO₂ of 0.4 (IQR: 0.3 to 0.4), median Ppl of 21.8cmH₂O (IQR: 17.8 to 25.8cmH₂O), and a median static complacency of 26.4ml/cmH₂O (IQR: 17 to 35.8ml/cmH₂O).

Sodium heparin in continuous infusion was used in 21% of patients with no evidence of complications

associated with the absence of anticoagulation. The control condition for anticoagulation was conducted with aPTT.

Weaning from ECMO was initiated when the patients presented signs of improvement in pulmonary complacency, arterial oxygenation, and chest x-rays. The ventilation parameters were adjusted to a protective standard ventilation, and the flow of oxygen was gradually decreased. For anticoagulation, patient blood flow was reduced during a period of 2 - 3 hours. In patients without anticoagulation, the contribution of gases was gradually decreased while maintaining a constant blood flow to avoid thrombotic complications during the process.⁽²⁶⁾

All patients in Group I were successfully weaned from ECMO. Three of the 15 patients died during hospitalization and had been previously removed from ECMO support due to infectious complications and multiple organ failure (MOF). In two of these patients, PGF was the cause of ECMO initiation.

In Group II, only three patients (42%) were successfully weaned from ECMO. Four patients died during ECMO, three due to MOF and one patient due to central nervous system bleeding.

All patients presented with complications during hospitalization. This information is shown in table 3. With regard to hemorrhagic and coagulopathic complications, a high variability in the blood platelet recount was observed, with an overall median of 180,000 platelets/mm³ (IQR: 69,625 - 260,950 platelets/mm³). All patients required transfusion of at least one blood product during the ECMO session; the median number of platelet units (U) transfused per patient was 8 U (IQR: 0 - 21.5 U); the median number of fresh frozen plasma units per patient was 2.5 U (IQR: 0 - 6 U); the median number of red blood cell units transfused per patient was 4 U (IQR: 1.5 - 8 U). In many cases, patients required platelet transfusion in spite of adequate platelet levels

(> 50000U/mm³). Although the presence of bleeding in the cannula insertion site and at the surgical site was relatively frequent, major bleedings occurred in only three patients, one at central nervous system, leading to the patient's death, and two at the surgical site requiring re-intervention in the operating room (one in a lung transplantation patient with central VA cannulation and another in a patient with a history of thoracotomy). One patient presented with complications of femoral artery cannulation and limb ischemia with compartment syndrome and subsequently underwent a suprapatellar leg amputation.

Table 3 - Complications and results

	Group I (N = 15)	Group II (N = 7)
Complications related to ECMO		
Oxygenator failure	0	1 (14)
Bleeding		
Cannula insertion site	3 (20)	2 (28)
Cerebral	0	1 (14)
Surgical site	3 (20)	1 (14)
Lung	2 (13)	1(14)
Epistaxis	1 (6)	1 (14)
Thrombocytopenia	9 (60)	4 (57)
Coagulopathy	5 (33)	1 (14)
Limb ischemia	2 (13)	0
Complications not related to ECMO		
Infections		
VAP	6 (40)	4 (57)
CAI	3 (20)	1 (14)
Soft tissue	2 (13)	1 (14)
ARF + RRT	3 (20)	5 (71)
Pneumothorax	5 (33)	3 (42)
Collapsed lung	1 (6)	2 (28)
Arrhythmia	4 (26)	2 (28)
Mortality	3 (20)	4 (57)

ECMO - extracorporeal oxygenation membrane; VAP - ventilator-associated pneumonia; CAI - catheter-associated infection; ARF - acute renal failure; RRT - renal replacement therapy. Results are expressed as numbers (percentages).

As for NS, an average delay of six days to reach the total calories required and an average delay of nine days to reach protein requirements was observed. This result was related to the fact that 91% of patients presented with abdominal distension, 81.8% presented with constipation, 45.4% presented with gastroparesis, and 27.3% presented with diarrhea. In addition, 53.4% of patients had at least two episodes of hyperglycemia (> 200mg/dL). In 20% of the patients, it was necessary to implement parenteral nutrition.

DISCUSSION

The present ECMO program in a polyvalent adult intensive care unit was developed with the objective of guaranteeing adequate support for patients with hypoxemic respiratory failure after conventional treatment in cases of both ARDS and perioperative pulmonary transplantation.

The execution of ECMO is not free of complications, and although we consider its utilization in carefully selected patients to be safe, we must still consider that within our study, there was a central nervous system bleeding event that led the death of the patient and a lower limb ischemia event that required amputation. The frequency and type of complications did not differ from those published in the literature.^(10,27,28) We identified the most important complications according to their frequency and impact as acute kidney failure requiring renal replacement therapy, infectious complications, and bleeding either at the site of cannula insertion or at the surgical site.

Multiple complications associated with anticoagulation existed during ECMO,⁽²⁹⁾ and there are various factors to consider when choosing anticoagulation, including the possibility of reversal in the case of hemorrhages, the bioavailability in cases of organ failure, the detection of clots in the circuit, and the presence of thrombocytopenia.⁽³⁰⁾ In our case, the population consisted of surgical patients with ARDS and lung transplantations with postoperative complications in which the initiation and maintenance of systemic anticoagulation was difficult due to hemorrhagic complications. Despite the reduced use of anticoagulation agents, we did not witness any thrombotic complications. Another point of controversy is when and how much to transfuse this type of patient. We used the presence of hemorrhages with a > 5 point drop in the hematocrit level or Hb < 7g/dL without the presence of bleeding as a criterion. Although patients generally exhibited increased transfusion requirements during ECMO, these requirements did not differ from those reported in prior studies.⁽³¹⁾

Regarding mechanical ventilation, the presence of ECMO allowed patients with lower pressures and volumes to be ventilated without complications due to acidosis. This is perhaps one of the most important functions of ECMO in patients who have heterogeneous lung lesions where ventilation strategies could potentially be harmful.⁽³²⁾

It is necessary to fully understand the impact of ECMO on the alimentary canal. The evidence suggests that early enteral nutrition can be well tolerated if the possible barriers to its implementation are controlled.^(33,34) In our experience, the appropriate combination of nutrients and

calories was difficult and took some time to achieve. This result is probably related to the high rate of complications associated with enteral nutrition (above all abdominal distension). For that reason, we believe that emphasis should be placed on optimizing NS, possibly by adjusting protocols in this subgroup of patients to assure adequate nutrition in the most critical period of this disease.

Finally, although the use of ECMO in the lung transplantation postoperative period does not yet have well-defined indications, this type of technology is a very useful support tool for the most serious patients during their most critical period. From this experience, we obtained an overall survival of 80% at discharge, with a

survival of 50% in the particular case of PGF. Both of these results are similar to or higher than those reported in the literature.⁽³⁵⁻³⁹⁾

CONCLUSION

Despite the controversy concerning the patients who would most likely benefit from extracorporeal membrane oxygenation, we believe that the current evidence should compel university centers and other institutions with a high volume of critical care patients to develop a program that offers this therapeutic option to a select population. We consider the results to be satisfactory despite the steep learning curve that we experienced.

RESUMEN

Objetivo: El desarrollo de la membrana de oxigenación extracorpórea en América Latina representa un desafío para la especialidad. El objetivo de este artículo fue describir los resultados de un nuevo programa de membrana de oxigenación extracorpórea en una unidad de cuidados intensivos.

Métodos: Estudio de cohorte retrospectivo. Incluye 22 pacientes que requirieron membrana de oxigenación extracorpórea desde Enero de 2011 hasta Junio de 2014. Se evaluaron características basales, indicaciones, duración de la corrida, días de ventilación mecánica, días de unidad de cuidados intensivos, complicaciones y mortalidad hospitalaria.

Resultados: Quince pacientes requirieron membrana de oxigenación extracorpórea post-trasplante pulmonar y 7 pacientes por distrés respiratorio agudo. Todos los pacientes trasplantados fueron destetados de membrana de oxigenación extracorpórea, con una duración mediana de 3 días (Rango intercuantil - IQR: 2 - 5), de ventilación mecánica 15,5 días

(IQR: 3 - 35), de estadía unidad de cuidados intensivos 31,5 días (IQR: 19 - 53) y de estadía hospitalaria 60 días (IQR: 36 - 89), con una mortalidad de 20%. Los pacientes con distrés respiratorio agudo tuvieron una mediana de duración de membrana de oxigenación extracorpórea de 9 días (IQR: 3 - 14), mediana de ventilación mecánica 25 días (IQR: 13 - 37), de estadía en terapia 31 días (IQR: 11 - 38), y hospitalaria 32 días (IQR: 11 - 41), y 57% de mortalidad. Las principales complicaciones fueron infecciones (80%), insuficiencia renal aguda (43%), sangrados en sitio quirúrgico y de inserción de cánulas (22%), plaquetopenia (60%) y coagulopatía (30%).

Conclusión: A pesar de encontrarnos transitando una curva de aprendizaje, consideramos la experiencia satisfactoria, con resultados y complicaciones comparables a las reportadas en la literatura.

Descriptor: Membrana de oxigenación extracorpórea; Trasplante de pulmón; Síndrome de dificultad respiratoria agudo; Insuficiencia respiratoria; Disfunción primaria del injerto; Unidades de cuidados intensivos

REFERENCES

- Blank R, Napolitano LM. Epidemiology of ARDS and ALI. *Crit Care Clin.* 2011;27(3):439-58.
- ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-33.
- Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. *Crit Care Med.* 1993;21(1):131-43. Review.
- Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *Am Rev Respir Dis.* 1987;135(2):312-5.
- Barber RE, Hamilton WK. Oxygen toxicity in man. A A/Barber RE, Lee J, Hamilton WK: Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. *N Engl J Med.* 1970;283(27):1478-84.
- Hernandez LA, Peevy KJ, Moise AA, Parker JC. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *J Appl Physiol* (1985). 1989;66(5):2364-8.

7. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-68.
8. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-63. Erratum in *Lancet*. 2009;374(9698):1330.
9. Terragni P, Faggiano C, Ranieri VM. Extracorporeal membrane oxygenation in adult patients with acute respiratory distress syndrome. *Curr Opin Crit Care*. 2014;20(1):86-91.
10. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. 2011;365(20):1905-14.
11. Nguyen DQ, Kulick DM, Bolman RM 3rd, Dunitz JM, Hertz MI, Park SJ. Temporary ECMO support following lung and heart-lung transplantation. *J Heart Lung Transplant*. 2000;19(3):313-6.
12. Oto T, Rosenfeldt F, Rowland M, Pick A, Rabinov M, Prevolos A, et al. Extracorporeal membrane oxygenation after lung transplantation: evolving technique improves outcomes. *Ann Thorac Surg*. 2004;78(4):1230-5.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83.
14. Extracorporeal Life Support Organization. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support [Internet]. In: Ann Arbor, MI, USA: Extracorporeal Life Support Organization, Version 1.3.; November 2013. [cited 2015 Apr 8]. Available from: <https://www.else.org/Portals/0/IGD/Archive/FileManager/929122ae88cusersshyerddocumentselsoguidelin esgeneralalleclsversion1.3.pdf>
15. National Institute for Health and Clinical Excellence. Extracorporeal membrane oxygenation for severe acute respiratory failure in adults [Internet]. NICE interventional procedure guidance 391; April 2011. cited 2015 Apr 8]. Available from: <https://www.nice.org.uk/guidance/ipg391/resources/guidance-extracorporeal-membrane-oxygenation-for-severe-acute-respiratory-failure-in-adults-pdf>
16. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-24.
17. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-8.
18. Suarez-Sipmann F, Böhm SH, Tusman G, Pesch T, Thamm O, Reissmann H, et al. Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Crit Care Med*. 2007;35(1):214-21.
19. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-91.
20. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-16.
21. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-36. Erratum in *N Engl J Med*. 2014;370(17):1668-9.
22. Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, Lyman B, Metheny NA, Mueller C, Robbins S, Wessel J; A.S.P.E.N. Board of Directors. Enteral nutrition practice recommendations. *JPEN J Parenter Enteral Nutr*. 2009;33(2):122-67.
23. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J; DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr*. 2006;25(2):210-23.
24. Meade MO, Granton JT, Matte-Martyn A, McRae K, Weaver B, Cripps P, Keshavjee SH; TorontoLung Transplant Program. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. *Am J Respir Crit Care Med*. 2003;167(11):1483-9.
25. Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. *Intensive Care Med*. 2012;38(3):395-403.
26. Lappa A, Donfrancesco S, Contento C, Vitalini E, Pisani P, Menichetti A, et al. Weaning from venovenous extracorporeal membrane oxygenation without anticoagulation: is it possible? *Ann Thorac Surg*. 2012;94(1):e1-3.
27. Marasco SF, Lukas G, McDonald M, McMillan J, Ihle B. Review of ECMO (extra corporeal membrane oxygenation) support in critically ill adult patients. *Heart Lung Circ*. 2008;17 Suppl 4:S41-7.
28. Paden ML, Conrad SA, Rycus PT, Thiagarajan RR; ELSO Registry. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J*. 59(3):202-210.
29. Butch SH, Knafel P, Oberman HA, Bartlett RH. Blood utilization in adult patients undergoing extracorporeal membrane oxygenated therapy. *Transfusion*. 1996;36(1):61-3.
30. Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth*. 2009;13(3):154-75.
31. Ang AL, Teo D, Lim CH, Leou KK, Tien SL, Koh MB. Blood transfusion requirements and independent predictors of increased transfusion requirements among adult patients on extracorporeal membrane oxygenation -- a single centre experience. *Vox Sang*. 2009;96(1):34-43.
32. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med*. 2005;172(10):1241-5.
33. Ulerich L. Nutrition implications and challenges of the transplant patient undergoing extracorporeal membrane oxygenation therapy. *Nutr Clin Pract*. 2014;29(2):201-6.
34. Ferrie S, Herkes R, Forrest P. Nutrition support during extracorporeal membrane oxygenation (ECMO) in adults: a retrospective audit of 86 patients. *Intensive Care Med*. 2013;39(11):1989-94.
35. Wigfield CH, Lindsey JD, Steffens TG, Edwards NM, Love RB. Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. *J Heart Lung Transplant*. 2007;26(4):331-8.
36. Marasco SF, Vale M, Prevolos A, Pellegrino V, Lee G, Snell G, et al. Institution of extracorporeal membrane oxygenation late after lung transplantation - a futile exercise? *Clin Transplant*. 2012;26(1):E71-7.
37. George TJ, Beaty CA, Kilic A, Shah PD, Merlo CA, Shah AS. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. *J Heart Lung Transplant*. 2012;31(11):1182-91.
38. Fischer S, Bohn D, Rycus P, Pierre AF, de Perrot M, Waddell TK, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. *J Heart Lung Transplant*. 2007;26(5):472-7.
39. Bittner HB, Lehmann S, Rastan A, Garbade J, Binner C, Mohr FW, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation and graft recovery. *Ann Thorac Surg*. 2012;94(3):942-9; author reply 949-50.