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# Extracorporeal Membrane Oxygenation for Immunocompromised Patients with ARDS

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### Improved Outcomes of Immunocompromised Patients Admitted to the ICU

Immunocompromised patients, who include patients with haematological malignancies (HMs), solid tumours, solid-organ transplants, human immunodeficiency virus (HIV) or long-term corticosteroid use, are increasingly admitted to intensive care units (ICUs). Their survival has improved markedly in recent years. For example, most patients with HMs and acute respiratory failure (62%) and/or shock (42%) require ICU admission. Hospital, and 90-day and 1-year post-ICU–admission survival rates were 61%, 52%, and 43%, respectively (Azoulay et al. 2013). Recently, among 1,004 patients with malignancies from mild (252, 25.1%), moderate (426, 42.4%) or severe (326, 32.5%) acute respiratory distress syndrome (ARDS), their respective mortality rates were 59%, 63% and 68.5% ($p=0.06$) (Azoulay et al. 2014). In addition, mortality of such populations declined from 89% in 1990–1995 to 52% in 2006–2011 ($p < 0.0001$). Similar trends were observed for human immunodeficiency virus (HIV)-infected patients admitted to ICUs in a 1999–2010 multicentre cohort study in France (Barbier et al. 2014). In that cohort, 39.8% of the patients were admitted for acute respiratory failure (ARF) and they increasingly received mechanical ventilation (rising from 42.9% to 54.0%) over the study period. Although ICU management of immunocompromised patients has improved for over a decade, their outcomes remain poorer than those of the general population of ARDS patients. However, the higher numbers of immunocompromised patients admitted to ICUs and their decreased ARDS-attributable mortality raise the question of whether to extend and generalise the use of extracorporeal membrane oxygenation (ECMO) to the immunocompromised (Azoulay et al. 2014). Notably, these patients are likely to develop specific ECMO-related complications more frequently and this possibility needs to be taken into account.

### Impact of Immunocompromised Patients' Premorbid Conditions on ECMO-Related Complications

Immunocompromised patients are at risk for life-threatening acute illness as a result of infection, toxicity of intensive treatment and targeted therapies, and decompensation of comorbid conditions.

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### *Bleeding*

A bleeding complication is the first major risk for these patients on ECMO, especially for those with HMs. Indeed, the ECMO device's non-biological surface, in the context of the patient's underlying severe disease, results in massive inflammatory and clotting system activation. Consequently, anticoagulation exposes the patient to haemorrhagic complications, which are common during ECMO management. In a review of the ECMO-associated complications of 1,763 patients, 33% of them experienced severe bleeding (Zangrillo et al. 2013). Similarly, ECMO use during the A($H_1N_1$) influenza pandemic was associated with 29% bleeding events (Davies et al. 2009). In a recent report on ECMO use in a small cohort of patients with HMs, 11/14 patients were thrombocytopenic, with their median (IQR) platelet count at 35 (26–51) G/L (Wohlfarth et al. 2014). Although biocompatible latestgeneration ECMO devices allow reduction of the anticoagulant dose, outcomes and overall costs are strongly impacted by haemorrhagic complications.

### *Nosocomial Infection*

Nosocomial infection is the second major risk for immunocompromised patients on ECMO. Indeed, that risk on ECMO is already very high for patients without immunodeficiency, and obviously affects outcomes. Among 220 patients who received ECMO support for >48 hours, for a total of 2,942 ECMO-days, 142/220 (65%) developed nosocomial infections (Schmidt et al. 2012), with ventilator associated pneumonia, bloodstream or cannula infections and mediastinitis occurring respectively in 55%, 18%,10% and 11% of them. More critical status at ICU admission, which includes being immunocompromised, was associated with a subsequent risk of developing a hospital–acquired infection.

## Data on Paediatric Populations

ECMO use to counter respiratory or cardiac failure in immunocompromised children has been limited (Di Nardo et al. 2014; Gow et al. 2009; Gow et al. 2006). Some authors have argued that patients with cancer or endstage acquired immunodeficiency syndrome should be denied access to ECMO (Green et al. 1995; Masiakos et al. 1999). However, overall survival rates for this paediatric population have continued to improve over the years (Herrera et al. 2000), and more and more clinicians are facing the challenge to implant ECMO in these patients. According to a survey of 118 paediatric ECMO centres, 78% stated that malignancy was not a contraindication for ECMO, with only 17% and 5%, respectively considering it a relative contraindication or who would not offer ECMO to such patients. From 1997 to 2004 ECMO use in 107 children (73 HMs and 34 with solid tumours) was reported in the Extracorporeal Lung Support Organization (ELSO) registry (Gow et al. 2009); it was primarily required for respiratory support in 86 patients (80%) and lasted a median of 6.1 days. Overall survival to hospital discharge was 35% for those with HMs or solid tumours. Although this relatively low survival rate could be considered acceptable in light of these patients' notable disease severity, children with malignancies represent a wide spectrum of disease states and outcomes. Indeed, for a subpopulation of children undergoing haematopoietic stem-cell transplantation (HSCT), the prognosis seemed worse. Over a 22-year period, 29 HSCT patients were entered in the ELSO Registry: 21 (72%) required ECMO respiratory support and 8 (21%) needed ECMO cardiac support. Twenty-three (79%) patients died on ECMO and only 3 (10%) were discharged from the hospital (Di Nardo et al. 2014). These contrasting results, obtained for a mixed-case population of immunocompromised children, suggest offering ECMO on a case-by-case basis, with malignancy prognosis being an important factor.

## Data on Adult Patients

The frequency of ECMO use for immunocompromised adults is unknown. For example, in the cohort of 2009 A($H_1N_1$)-influenza–associated ARDS patients treated with ECMO, 19% were immunocompromised (Pham et al. 2013), representing 31% of the 140 cohort patients with ARDS of multiple aetiologies reported by Schmidt et al. (2013). In that cohort, the "immunocompromised" group comprised patients with HMs (30%), solid tumours (23%), solid-organ transplant (19%), high-dose or long-term corticosteroid and/or immunosuppressant use (19%), and HIV infection (9%). Only 32% were alive 6 months post-ICU admission. In addition, immunocompromised status was independently associated with death at 6 months post-ICU discharge (odds ratio 4.33 [95% confidence interval 1.55–12.12], $p = 0.005$) (Schmidt et al. 2013). Recently, Wohlfarth et al. reported the outcomes of 14 patients with HMs who received ECMO support for severe ARF in their centre (Wohlfarth et al. 2014). HMs were diagnosed in 4 patients during ECMO support. Five patients received their first chemotherapy dose on ECMO and 4 had undergone HSCT within the previous year. At ICU admission, their median (IQR) sepsis-related organ failure assessment (SOFA) score was 12 (11–13) and all patients received vasopressors; 11/14 were thrombocytopenic, with a median platelet count of 35 (26–51) G/L, and 5 were leukocytopenic, with a median leukocyte count of 2.1 (1.8–2.5) G/L. All HSCT recipients died, although 50% survived their ICU and hospital median (IQR) stays of 22 (21–77) days and 63 (49–110) days, respectively.

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Severe bleeding events were common (5/14, 36%). Thus, clinicians must strive to avoid any increment of risk factors for bleeding in this specific population. To achieve this goal, no or very low anticoagulation is strongly encouraged, especially when massive platelet transfusions are unable to restore safe platelet levels (Wohlfarth et al. 2014).

Because haemorrhage and nosocomial infections are the two main risks for immunocompromised patients treated with ECMO, developing new strategies to limit these risks is definitely the next stage to improve outcomes. To reach this objective, Hoeper et al. conducted a single-centre, uncontrolled pilot trial designed to assess the feasibility of venovenous ECMO in awake, non-intubated, spontaneously breathing ARDS patients, thereby avoiding invasive mechanical ventilation (Hoeper et al. 2013). Six patients with severe ARDS (maximum PaO2/FiO2 ratios of 100 mm Hg on noninvasive ventilation), 4 of whom were immunocompromised, were enrolled. After a mean of 7.5 days on ECMO, 4 patients were discharged from hospital; 3 of them had received ECMO alone without invasive ventilation.

**Conclusion**

Using ECMO in immunocompromised patients remains controversial due to the lack of strong scientific evidence for the benefit that this technique might afford these patients, as they, especially adults, develop more frequent and more severe ECMO-related complications. Pending results of large observational or randomized trials on immunocompromised patients, ECMO should be restricted to selected patients with at least a curative prospect of their immunodeficiency, except those with recent (< 3 months) cardiac transplantation, for whom it is essential. However, the markedly improved ICU survival observed over 2 decades suggests extending ECMO use to this population. Results of the ongoing retrospective international Immuno-Deficiency and ECMO for Acute respiratory failure, the IDEA study (International ECMO Network 2016), should 1) provide a first detailed description of ECMO use in immunocompromised adults with acute respiratory failure; 2) identify the major complications arising in this specific population; and 3) describe the related ICU, hospital and 90-day outcomes for the whole population and specific immunodeficiency subgroups

**Abbreviations**

ARF acute respiratory failure
ECMO extracorporeal membrane oxgygenation
HIV human immunodeficiency virus
HM haematological malignancies
HSCT haematopoietic stem-cell transplantation
SOFA sequential organ failure assessment

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