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ECMO in severe acute respiratory distress syndrome.

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tissue, placenta or other sources, also have notable functional differences. Furthermore, functionality of MSCs can change depending on culture conditions, number of passages, culture surface and stiffness, and various other factors. Different clonal populations of MSCs isolated from the same bone-marrow aspirate can vary substantially in functional attributes.[4] These and related issues, including effects of MSC cryopreservation, continue to complicate the use of MSCs. Thus, despite a wealth of data showing that MSCs have beneficial actions in various preclinical acute lung injury models, much remains to be clarified. What exactly is an MSC and what is important about the potentially therapeutic actions and which population or preparation of MSCs might have best efficacy in any given clinical situation?[5–7]

It is becoming increasingly clear that the concept of immunopermissiveness inherent in the use of allogeneic MSCs is not accurate and that MSCs are stimulated by in-vivo factors after clinical administration to express HLA and other cell-surface molecules recognisable to the host immune system.[6] A newly evolving concept suggests that MSCs rapidly undergo apoptosis, autophagy, or efferocytosis after systemic administration, and potentially also after intratracheal administration.[6,8,9] As such, despite the ability of MSCs to release paracrine mediators, the host immune response to an apoptotic MSC might also greatly shape the actions that ameliorate inflammation or injury.[8,9] In this context, the observation by Matthay and colleagues[1] that low MSC viability was correlated with poor efficacy should be investigated further. This finding supports the argument that incorporating mechanistic and hypothesis-generating studies into any clinical investigation should continue.[10] ARDS, however, remains a viable target for MSC-based cell therapies. We just need to figure out how to make them work.

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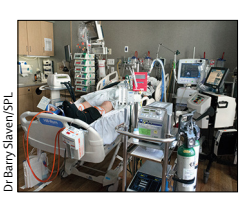
ECMO in severe acute respiratory distress syndrome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As summarised last year in a Comment in *The Lancet Respiratory Medicine*,[1] four randomised trials[2–5] of extracorporeal membrane oxygenation (ECMO) have been done in patients with severe acute respiratory distress syndrome (ARDS) in the past 40 years. The 1979 and 1994 trials[2,3] did not include a lung-protective ventilation strategy for patients in their control groups because they were done before publication of the US National Heart, Lung, and Blood Institute's ARDS Network-sponsored trial,[6] which was published in 2000 and showed a major reduction in mortality with a low tidal volume and plateau pressure limited ventilation strategy. Since then, CESAR, the venovenous ECMO trial[4] that was published in 2009, showed that patients who were transferred to a centre that could institute ECMO had significantly lower mortality and severe disability at 6 months than those who were not transferred to an ECMO centre. However, the result was not definitive because only some of the patients referred to the ECMO centre received ECMO, and there was no evidence that patients in the control group received lung-protective ventilation. In the most recent trial, EOLIA,[5] which was published in 2018, 60-day mortality was numerically lower in the venovenous ECMO group (35%) than in the control group (46%), in which patients received lung-protective ventilation, but

this difference was not significant (p=0·09). For several secondary endpoints, however, ECMO was significantly better than the control group, including more days alive and free of the need for vasopressor therapy, renal replacement therapy, or prone positioning to treat their respiratory failure.[5] The decision to stop the EOLIA trial for futility after enrolment of 249 patients, before the planned enrolment of 331 patients, was based on methods that can decrease power for rejection of the null hypothesis, and might have led to a type 2 error.[7] The trial was powered for a 20% absolute reduction in mortality, which was probably an unrealistic goal.

In this context of uncertainty about interpretation of the results of the EOLIA trial[5] and the increasing use of ECMO, Laveena Munshi and colleagues report the results of a systematic review and meta-analysis[8] of the use of ECMO in adult patients with severe ARDS in this issue of *The Lancet Respiratory Medicine*. The authors included three observational studies and two randomised controlled trials, CESAR and EOLIA. For the three observational studies, matching methods were used to compare ECMO-treated patients with those who did not receive ECMO. Two of the observational trials were done primarily in patients with H1N1 influenza.

The primary analysis, which was restricted to the two randomised controlled trials (429 patients overall), showed that, compared with conventional mechanical ventilation, ECMO was associated with a reduced risk 60-day mortality (risk ratio [RR] 0·73 [95% CI 0·58–0·92]). ECMO was also associated with a reduced risk of treatment failure (0·58 [0·39–0·84]), which was defined as death in the ECMO group and death or crossover to ECMO in the control group. In a meta-analysis of all five studies, which included 773 patients overall, ECMO was associated with a reduced risk of 30-day mortality (RR 0·69 [95% CI 0·50–0·95). However, this meta-analysis was prone to bias because of the inclusion of the observational studies, which did not include randomisation for ECMO treatment. Evidence also suggested that ECMO is associated with a risk of major haemorrhage. Munshi and colleagues concluded that the evidence favouring ECMO is of moderate-to-high quality according to the Grading of Recommendations Assessment, Development and Evaluation criteria. The availability of only two randomised controlled trials for this meta-analysis is an important limitation. It is unusual for a meta-analysis to be based on only two randomised controlled trials, but the authors recognise this limitation and tried to adjust for heterogeneity between the trials. Despite this limitation, this meta-analysis is an important contribution because clinicians need guidance on how to interpret the evidence from CESAR[4] and EOLIA.[5] Although another trial of ECMO versus non-ECMO treatment for severe acute respiratory syndrome has been called for,[1] such a trial is not likely to be organised or funded, and if a trial were done it would not be completed for many years.

In addition to Munshi and colleagues' meta-analysis,[8] Goligher and colleagues have done a Bayesian post-hoc analysis[9] of the EOLIA trial. The Bayesian approach defines the probability of a treatment effect rather than ruling out the absence of a treatment effect as in conventional trial design. Goligher and colleagues used several estimates of posterior probabilities of enthusiasm or scepticism for efficacy of ECMO in patients with severe ARDS. The Bayesian analysis showed that, across a range of assumptions about the probability of benefit from early ECMO, the posterior probability of any mortality benefit with early ECMO in EOLIA was high, ranging from 88% to 99%. A 2018 clinical case analysis[10] also provided a timely example of a patient with severe ARDS. The authors of that analysis addressed the question of whether or not to use ECMO in this clinical setting and provided both pro and con viewpoints.

In view of the results of the EOLIA trial,[5] Munshi and colleagues' meta-analysis,[8] and the Bayesian analysis of EOLIA,[9] what should clinicians conclude about the use of ECMO in patients with severe ARDS? It is important for clinicians to be certain they have instituted other therapies before considering ECMO, including optimal lung-protective ventilation, diuresis, and neuromuscular blockade with deep sedation, prone positioning, and possibly inhaled nitric oxide, recruitment manoeuvres, and renal replacement therapy.[11] If these therapies do not stabilise the patient, and there are no other exclusion criteria (as in the EOLIA trial), I believe that the balance of evidence favours use of ECMO in severe ARDS if available from a medical centre experienced in provision of ECMO.

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ECMO for ARDS: from salvage to standard of care?

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The EOLIA randomised controlled trial,[1] which was published in 2018, did not show a significant difference in its prespecified primary endpoint of 60-day mortality between the extracorporeal membrane oxygenation (ECMO) group and the control group, who received conventional mechanical ventilation. However, the large and clinically important effect size noted in the trial,[2] a post-hoc Bayesian analysis[3] of EOLIA data showing a high likelihood of survival benefit with ECMO even assuming a strongly sceptical prior distribution, and now a meta-analysis[4] published in *The Lancet Respiratory Medicine* by Laveena Munshi and colleagues, all suggest that ECMO is efficacious in some adult patients with severe acute respiratory distress syndrome (ARDS).

Even with these results, some clinicians[5] are calling for another confirmatory randomised controlled trial of ECMO in ARDS. Although theoretically appealing, another similar trial is unlikely. Such a study would require centres that are expert in the use of ECMO. In view of the strong trend toward a decrease in mortality in the ECMO group of EOLIA, many experienced ECMO practitioners would consider withholding of ECMO to be unethical in patients with very severe ARDS. Indeed, even before the results of EOLIA were known, clinical equipoise was problematic: 28% of patients in the control group were crossed over to ECMO. Furthermore, enrolment of 249 patients at 64 centres in EOLIA took 5·5 years. Another study similar to EOLIA is unlikely to be completed to definitively clarify whether ECMO reduces mortality in severe ARDS.

With this information in mind, where should ECMO fit into the treatment algorithm for ARDS? We believe that ECMO is indicated in patients with ARDS when other proven and less invasive strategies have been tried unsuccessfully.[6] In most cases, ECMO—a highly invasive and resource-intensive technique—should not be used without first placing the patient in the prone position. Indeed this approach was used in the EOLIA trial.[1] Unfortunately, non-adherence to evidence-based management of ARDS is common, highlighting the need for the critical care community to improve adoption of proven therapies (mainly prone positioning; a high positive end-expiratory pressure strategy and neuromuscular blockade are also recommended but not as strongly).[7,8] Centres that do not have evidence-based conventional management strategies should work with expert respiratory failure centres to optimise care, with transfer to the expert centres when warranted.

We propose a management algorithm (figure) culminating in early ECMO as used in the intervention group of the EOLIA trial[1]—ie, when EOLIA criteria are met within 7 days of invasive mechanical ventilation, despite management with evidence-based conventional practices. Beyond this use, there are other scenarios when ECMO might be considered. The first we term rescue ECMO, which we define as cases when proven therapies in ARDS cannot be applied—eg, when the patient is too unstable for prone positioning and needs to rapidly undergo ECMO and the algorithm is thus bypassed out of perceived necessity. Separately, rescue ECMO also describes use of ECMO to