CONSENSUS STATEMENT

ISHLT Consensus Statement on the Perioperative use of ECLS in Lung Transplantation: Part I: Preoperative Considerations

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The use of extracorporeal life support (ECLS) throughout the perioperative phase of lung transplantation requires nuanced planning and execution by an integrated team of multidisciplinary experts. To date, no multidisciplinary consensus document has examined the perioperative considerations of how to best manage these patients. To address this challenge, this perioperative utilization of ECLS in lung transplantation consensus statement was approved for development by the International Society for Heart and Lung Transplantation Standards and Guidelines Committee. International experts across multiple disciplines, including cardiothoracic surgery, anesthesiology, critical care, pediatric pulmonology, adult pulmonology, pharmacy, psychology, physical therapy, nursing, and perfusion, were selected based on expertise and divided into subgroups examining

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the preoperative, intraoperative, and postoperative periods. Following a comprehensive literature review, each subgroup developed recommendations to examine via a structured Delphi methodology. Following 2 rounds of Delphi consensus, a total of 50 recommendations regarding preoperative considerations for ECLS in lung transplantation met consensus criteria. These recommendations focus on the criteria for preoperative ECLS as well as select multidisciplinary team management considerations throughout the entire preoperative phase.
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KEYWORDS:
ECLS; ECMO; Lung Transplantation; MDT; End-Stage Lung Disease

1. INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) was first used as a bridge to lung transplant strategy in 1977.[1] Since then, multiple centers have developed extra-corporeal life support (ECLS) strategies for patients with end-stage lung diseases (ESLD), either as a bridge to transplant (BTT), or bridge to decision regarding transplant candidacy (BTD). This patient cohort is distinct from individuals requiring ECLS for severe acute respiratory failure (SARF) without underlying ESLD and as such merit specific consideration. Data regarding ECLS utilization in a pre-lung transplant context are mixed, with most recommendations resulting from single-center retrospective studies. A recent consensus statement from the American Association of Thoracic Surgery (AATS) provided guidance regarding use of ECLS in pre-, intra- and post-operative lung transplant context, however all contributing experts were surgical in discipline.[2] This three-part ISHLT consensus statement utilizes Delphi methodology to capture the views of multiple subspeciality members of the multidisciplinary team (MDT). This approach recognizes the complex and often competing factors requiring consideration prior to embarking on ECLS bridging strategies. It is of paramount importance to balance elements such as severity of underlying lung disease, co-morbidities, frailty, and potential complications of ECLS itself to optimize post lung transplant outcomes both in the short and long term. The terms ECMO and ECLS are used interchangeably throughout this document.

This perioperative utilization of ECLS in lung transplantation consensus statement was approved for development by the International Society for Heart and Lung Transplantation (ISHLT) Standards and Guidelines Committee. Given the breadth and complexity of this subject, agreement for a three-part series was granted. Part 1 will focus on the pre-operative phase of lung transplant care; practical aspects of care regarding decision making and approach in deteriorating patients requiring bridge to transplant or bridge to decision will be discussed. Part 2 focuses on the intra-operative management of patients during the lung transplant procedure itself and ranging from intraoperative planning through to transfer to the intensive care unit (ICU).[3] Part 3 concentrates on the post-operative use of ECLS in the commonest scenarios of primary graft dysfunction (PGD), extended support after transplant for Group 1 pulmonary arterial hypertension (PAH), and organ-system based considerations for ICU management.[4] These three consensus statements are designed with the clinical reader in mind. They are intended to be read either as a series or distinct from one another and dependent on the phase of care of the recipient.

2. METHODOLOGY

International experts across multiple disciplines including cardiothoracic surgery, anesthesiology, critical care, pediatric pulmonology, adult pulmonology, pharmacy, psychology, physical therapy, nursing, and perfusion were selected based on expertise with a balance of geographical, gender, and career grade diversity. After selection, the writing group was separated into preoperative, intraoperative, and postoperative sub-groups. Following a comprehensive literature review, each sub-group developed recommendations to examine via a structured Delphi methodology. Preoperative subgroup members were contacted by email and asked for statements evaluation. These statements were evaluated in 2 rounds of a Delphi consensus survey using a 9-point Likert scale, to rate agreement on the importance of each statement and elicit free-text comments on the wording of each item. Experts were asked not to respond to any statement outside their expertise field. In the Likert scale, a score of 1 to 3 signified limited importance of the item, 4 to 6 important but not critical, and 7 to 9 critical. If > 75% of respondents scored a statement 7 to 9 and < 15% scored it 1 to 3, then that item was

Table 1 Class and Levels of Evidence.

Class I
Evidence and/or general agreement that a given treatment, procedure, or technique is beneficial, useful and effective as applied to patients, clinicians, or researchers
Class II
Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment, procedure, or technique; **Class IIa** Weight of evidence/opinion is in favor of usefulness/efficacy; **Class IIb** Usefulness/efficacy is less well established by evidence/opinion;
Class III
Evidence or general agreement that the treatment, procedure, or technique is not useful or effective and in some cases may be harmful.
Level of Evidence A
Data derived from multiple, high-quality randomized clinical trials, meta-analyses of high-quality RCTs, or one or more RCTs corroborated by high-quality registry studies
Level of Evidence B
Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCTs, or large nonrandomized studies **B1** Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCT **B2** Data derived from one or more high-quality non-randomized, observational, or registry studies
Level of Evidence C
Consensus of expert opinion **C1** Expert opinion supported by small, observational studies, retrospective studies, meta-analyses of such studies, or physiologic/mechanistic studies **C2** Expert opinion alone or with group communications/questionnaires

included in the consensus manuscript. Conversely, consensus that a statement should not be included was defined as > 70% scoring it 1 to 3 and < 15% scoring it 7 to 9. AR, OM, and AM reviewed the responses and modified the checklist drafts based on the participants scoring and feedback, editing phrasing and wording of checklist items, and merging redundant items, but ensuring meaning was not significantly changed. Round 2 of the Delphi survey presented the results of round one to participants, addressed clarifications, and served to refine the statements where consensus was not yet reached. Participants were again asked to score the Round 2 statements on a 1 to 9 Likert Scale. Following two rounds of Delphi consensus, a total of 50 recommendations regarding preoperative considerations for ECLS in lung transplantation met consensus criteria. The class and levels of evidence standards (Table 1) were utilized to grade the respective recommendations (Appendix 1), although many recommendations are based solely on expert opinion due to lack of available data. Where statements did not reach consensus, the points raised are discussed in the associated text for completeness. Recommendations resulting from the Delphi process are not intended to be exhaustive. As such, the absence of a particular recommendation does not necessarily imply disagreement or lack of importance, but rather that consensus was not reached on that specific point.

While there have been recent guidelines discussing mechanical circulatory support within cardiothoracic transplantation,[5] the purpose of this consensus is to provide a practical "how to" guide for multidisciplinary teams as they provide perioperative care for lung transplantation recipients. Part 1 focuses on recommendations for patient selection, planning for bridging initiation and supportive strategies, management during the bridging period, prevention and management of complications, and considerations for future research and technological development for ECLS as bridge to lung transplantation.

3. SECTION I. MULTIDISCIPLINARY TEAM STRUCTURE

Patients requiring a BTT on ECLS are critically ill with complex physiologic and psychosocial care needs. The MDT will need to be suitably experienced and appropriately trained to manage the ongoing needs of the patient. An ICU physician with expertise in ECMO should lead the MDT, working in collaboration with the primary respiratory referring

team and liaising directly with the multi-disciplinary transplant team. Decision making with regards to the suitability for ECMO either as BTT or BTD requires input from all three clinical groups. This capitalizes on the expertise of multiple clinicians and ensures a complex discussion regarding potential for recovery, transplant, and all aspects of patient management in the critical care context are fully explored. The ECMO MDT includes perfusionists, anesthetists, intensivists, surgeons, transplant pulmonologists and cardiologists, intensive care nurses, physical therapists, and other allied health staff to support the patient and ensure they maintain optimal physical and psychological health[6] throughout the course of the pretransplant critical care period.

Round-the clock availability of this MDT team, specifically qualified in the management of the ECLS patient and the ECLS circuits, is necessary to deal with emergencies and for prevention of complications in this highly complex group. Frequent assessment and discussion by members of the team are essential for troubleshooting and prevention of complications before they occur and to ensure ongoing candidacy for transplant. The bedside nurse is central to BTT patient management, providing at a ratio no greater than 1:2 round the clock holistic care, monitoring ventilation and hemodynamic parameters and the ECLS circuitry and patient for complications once ECLS is commenced.[7,8] Perfusion teams are highly qualified in the management of extracorporeal devices and their troubleshooting with extensive knowledge of cardiopulmonary physiology and pathophysiology,[9] and should be called alongside the ICU physician whenever an emergency during an ECMO treatment occurs.[10] Given the vital role of the perfusion team in maintenance of ECMO therapy and response in an emergency, a trained perfusionist should be available 24/7 to respond to ECMO emergencies and give technical support.[9]

An MDT member, ideally an ECLS coordinator, should help to facilitate the organization and implementation of ECLS training, recording of competencies, optimize staffing, develop operational guidelines and quality improvement processes.[11] Communication between all ECLS care providers is crucial when bridging a patient to transplant, to ensure early recognition and potential treatment of any modifiable factors and prevent further deterioration that may result in the patient being deemed no longer suitable for transplant.[6,11,12] All clinical members of the ECLS MDT should have the relevant sub-speciality competencies set by their relevant professional and regulatory organizations.[11] It is recommended that every MDT staff member involved in providing ECLS care must not only receive specific ECLS training, they should continue to demonstrate the relevant competencies on an ongoing basis to ensure provision of safe and optimal patient care.[11] One study showed that 73% of ECMO mechanical emergencies are associated with human error.[13] As such the expertise, development and makeup of the multidisciplinary ECMO team is important for the success of ECMO BTT on both an individual patient and program level. Well established protocols and well trained, harmonious teams are essential and have been shown to contribute to transplant outcomes comparable to patients who do not require mechanical ventilation (MV) or ECMO support.[14]

Recommendations.

- A multi-disciplinary ECLS team managing a bridge to transplantation patient should consist of staff that assess ongoing medical, nursing, rehabilitation, and psycho-social needs of the patient. (CoR: I LoE: C1)
- Daily assessments by the multi-disciplinary team should be conducted to ensure both suitability of ongoing bridging support and avoidance of futile transplantation. (CoR: I LoE: C1)
- The multi-disciplinary team engaged in ECLS bridge to transplantation patient daily care should receive specific ECLS training and meet the ongoing requirements of their training per their national regulatory organizations. (CoR: I LoE: C1)
- Specialized intensive care unit nurses should be available 24 h a day to primarily manage ECLS bridge to transplantation patients in no more than a 1:2 ratio. (CoR: I LoE: C1)
- Perfusion service support should be available 24 h a day to assist with any technical and circuit related ECLS concerns during ECLS bridging to transplantation. (CoR: I LoE: C1)

4. SECTION II. APPROACH TO PATIENT SELECTION

Appropriate patient selection is key to optimizing outcomes from any medical intervention. This is particularly true in the context of ECMO BTT where the support strategy itself may promote complications that render a patient unfit for lung transplant. It is essential that the MDT prioritize individuals with a reasonable chance of being matched with an organ in a suitable time frame with a high likelihood of being able to be maintained in good physical,

physiological and emotional condition whilst awaiting transplant in order that optimal outcomes from lung transplant remain achievable. This section will focus both on generalized considerations and on considerations specific to ECMO during BTT/BTD.

4.1. General considerations

While early referral is paramount in successfully bridging a patient to lung transplant, acute disease progression still poses a significant barrier to transplantation with some patients deteriorating acutely before receiving a life-saving transplant. This may represent progression of underlying end-stage lung disease (ESLD) or an intercurrent infectious/inflammatory insult to the lung. Recent advances in ECMO technology and technique render ECMO an invaluable tool for bridging acutely decompensating lung transplant candidates. Both in United Network for Organ Sharing (UNOS) as well as in the ISHLT registries, the number of ECMO BTT has significantly increased.[15,16] In fact, in some high-volume centers, approximately 10–14% of waitlisted patients are transplanted with pre-transplant ECMO support.[17–19] The overall success rate varies between 60% to 90% depending on patient demographics with higher rate of successful bridging noted in the younger patients and those with non-interstitial end-stage lung disease.[17–20] Older age (> 65 years), development of multisystem organ failure, worsening right or biventricular failure, coagulopathy (thrombosis or hemorrhage), stroke, obesity and malnutrition are risk factors for failed BTT.[18,21,22] Despite optimal ECLS management for patients being bridged to transplantation, the increased disease burden and prolonged period of bed rest will likely worsen frailty status and ICU-acquired muscle weakness, therefore it is essential to consider the rehabilitation capacity of an individual in the context of their physical baseline when considering ECMO BTT.

Recommendations.

– Patients with single organ failure combined with good rehabilitation potential are good candidates for consideration of ECLS bridge to lung only transplant. (CoR: I LoE: B2)

4.2. Indications for bridge-to-transplant (BTT) or bridge-to-decision (BTD)

Any patient with refractory hypoxemia, hypercapnia or cardiogenic shock despite maximal medical support may be considered for ECMO support. In patients already listed for lung transplant, respiratory deterioration warrants discussion with the local ECMO and lung transplant center. These patients are well known to the transplanting teams and by virtue of their waiting list status have already undergone extensive clinical evaluation for lung transplant candidacy. In the absence of new co-morbidities such as multi-organ failure or sepsis that may preclude the patient from ongoing candidacy for lung transplant, semi-elective decision-making and initiation is desirable over emergency cannulation.

In the scenario that a rapidly deteriorating patient is not known to the transplant team, an ECMO BTD strategy may be employed. This allows for diagnosis and treatment of potentially reversible underlying pathologies as well as evaluation for transplant candidacy. It should be noted that the only alternative is almost certain death and as such, candidacy for BTD warrants thoughtful consideration in appropriate cases.

ECMO programs are expensive and carry additional significant resource utilization implications in terms of manpower, emotional resilience, and bed occupancy; it is therefore important to balance the reality that, despite best clinical efforts, there exists the potential for a poor outcome in individual patients. In this context, it is incumbent on clinicians to be vigilant in managing specific clinical challenges germane to this patient population. The consensus panel focused on factors that contribute to increased risk on ECMO support for patients with chronic lung disease. Although local practices vary between institutions and across geographical boarders, there are several specific issues highlighted by the consensus panel that warrant special consideration in the context of ECMO BTT/BTD.

Infection: Within the Burkholderia cepacia complex (Bcc), the species cenocepacia (Bcc, genomovar III) is associated with high pathogenicity and antibiotic resistance. Consequently, patients colonized with *B. cenocepacia* have been shown to have a worse prognosis and higher mortality after lung transplantation, which led some lung transplant centers to decide not to accept patients (usually cystic fibrosis patients) for lung transplantation if colonized with these specific bacteria.[23,24] Positive case reports of such patients with long-term survival are documented in the literature.[25] It is clearly recognized that worse outcomes are solely linked to the *B.*

cenocepacia (genomovar III), necessitating a highly specific microbiological diagnosis and individualized decisions on a case-by-case basis.[25–28] The impact of colonization with Bcc or *B. cenocepacia* in patients who need ECLS as a BTT has not been studied specifically, but it remains sensible that in this situation risks may be even higher for those patients colonized with *B. cenocepacia*. Consequently, the decision for or against ECMO as a BTT needs to be made in consideration of all circumstances, with *B. cenocepacia* being a specific and significant additional risk factor. A similar situation exists for patients colonized with the emerging pathogen *Mycobacterium abscessus.* The subspecies *M. abscessus abscessus* is more pathogenic after lung transplant than *M. abscessus bolletii* or *M. abscessus massiliense* [29] and as such cautious consideration of subspecies evaluation is warranted in the BTT scenario. If this is not possible, teams may consider this a barrier to BTT. There is no literature to support decision making with regards the impact of *M. abscessus* colonization on outcomes during/after BTT. For other infectious pathogens that are common in ESLD, recommendations depend on local practice as guided by local microbiology and transplant infectious diseases physicians where available.

Pulmonary hypertension: Patients with severe WHO Group I pulmonary arterial hypertension (PAH) are usually on maximal medical therapy including intravenous prostacyclin analogs at time of transplant listing.[30] Patients who are treatment naïve may present *in extremis* with cardiogenic shock because of severe untreated PAH. In this scenario, veno-arterial (VA) ECMO may be used as bridge to recovery whilst pulmonary vasodilator therapy is established. Patients on maximal medical therapy for Group I disease may experience disease progression and develop cardiopulmonary failure, cardiac decompensation and/or treatment failure. In this scenario pulmonary vasodilator therapy is usually stopped once VA ECMO is established. Patients may also present with severe secondary pulmonary hypertension, which is more common in some ESLD than others. If medically refractory cardiopulmonary failure and/or multi-organ failure ensues in these patients, VA ECMO may be used as a tool for recovery, BTD or BTT.[30–33] Since VA ECMO support can offer the chance of recovery even in advanced disease and in the context of multi-organ failure, this should be considered in individual patients even when the patient is unknown to the transplant team as BTD. A preemptive decision for transplant candidacy is clearly preferable, however may not be pragmatic.[32] Bilateral lung transplantation is the standard for PAH patients, however in selected cases heart and lung transplantation may still be considered.[34]

Advanced age and frailty: Advancing age is a major risk factor for pre- and post-transplant mortality.[35] This increased risk cannot be explained by numeric age alone but is closely linked to physical and physiological deficits, which are generally referred to as frailty. In the context of ECMO BTT, age and the associated factors of frailty are especially important.[15,36] In the context of re-do-transplant for chronic lung allograft dysfunction (CLAD), the impact of age as a significant risk factor is further heightened when considering the use of ECMO BTT.[37] Additionally, frailty, an indicator of debility regardless of age or sex, is independently associated with increased waitlist and post-transplant mortality across solid organ transplantation, including lung in patients routinely listed and not on ECMO support.[38–42] Singer et al reported that every 1-point increase in frailty, as measured on Fried Frailty Phenotype (FFP) and Short Physical Performance Battery (SPPB), was associated with a 20% mortality increase (aHR: 1.20; 95%CI: 1.08–1.33) after lung transplant. [41] Similarly, 1-year post-transplant survival is significantly reduced in frail subjects with an absolute increased risk of death within the first year after transplantation of 12.2% (95%CI: 3.1%–21%).[41] Not surprisingly, in the critically ill ECMO BTT candidate, debility is common and a significant predictor of failed bridging.[18] Therefore, careful multidisciplinary discussion should guide decisions for support. In the absence of direct evidence examining the impact of frailty in the ECMO BTT scenario, these recommendations have been extrapolated from literature focused on outpatients listed for lung transplant. Given the accelerated functional decline in strength associated with critical illness and ECMO induced immobility, it is highly likely that frailty in the context of ECMO BTT represents a more significant risk factor for poor outcome. This warrants further study.

Acute respiratory distress syndrome (ARDS) and COVID-19: Since the SARS-CoV-2 pandemic, the utility of lung transplant as an exit strategy for patients on ECMO for ARDS has increased exponentially.[43,44] Optimization of ECMO protocols and increasing experience with management of patients on awake ECMO mean that consideration of lung transplant treatment for ARDS is increasingly adopted by large volume centers worldwide. In carefully selected cases, awake ECMO strategies are employed for physical optimization and assessment for lung transplant candidacy even in patients not previously known to the transplant center. Increasingly evidence suggests similar outcomes with this approach compared with patients who were previously known to their transplant center who are bridged during deterioration of their underlying ESLD.[43,45–48] At the time of writing, the ISHLT Consensus Statement for the selection of lung transplant candidates specifically lists patients requiring ECLS or mechanical ventilation as a relative contraindication to lung transplant albeit requiring discussion on a

case-by-case basis. We suggest that this be addressed in the next update of the ISHLT guidelines for selection of lung transplant candidates.

Recommendations.

- Patients colonized with Burkholderia cenocepacia may be considered higher risk candidates for ECLS as a bridge to transplantation, but this requires case by case discussion in the context of local policies. (CoR: IIa LoE: C2)
- Patients with PAH on maximal medical therapy deteriorating with refractory cardiopulmonary failure and/or multi-organ system dysfunction should be considered for ECLS as bridge to decision regarding candidacy for bilateral lung transplantation. (CoR: I LoE: C1)
- Age should be considered as a factor in consideration of a patient for suitability for ECLS as a bridge to lung transplantation. (CoR: I LoE: C1)
- Frailty is a relative contraindication for ECLS bridge to transplantation and should be assessed with formal methodology prior to listing for lung transplantation. (CoR: I LoE: B2)

4.3. Pediatric considerations

The number of pediatric lung transplants being performed worldwide has decreased over the last five years secondary to the improved outcomes in children with cystic fibrosis and the advent of highly successful cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies. While the total number of transplants has decreased, the proportion of children undergoing transplantation from ECLS has increased.[49] There are many case reports and series that describe successful bridging with ECLS in pediatric patients.[50,51] The reported outcomes show similar survival among children who were bridged to transplant versus children who did not require ECLS or mechanical ventilation at the time of transplantation.[49,52] The indication for ECMO BTT in pediatric patients under the age of 12 years is most commonly interstitial lung disease or WHO Group I PAH. Pediatric patients under the age of twelve requiring ECMO BTT are more likely to be significantly more medically complex, need intraoperative cardiopulmonary bypass support and require longer ventilation after transplant, however rates of primary graft dysfunction or longer term chronic lung allograft dysfunction are no different to older children requiring ECMO BTT.[53] As with adults, poor functional status at the time of transplant is associated with worse pre- and post-transplant outcomes.[54] Ambulatory ECMO in children has been successfully implemented at many centers. However, in younger children and infants the cannulation strategy may impact the ability for rehabilitation in these age groups. Several transplant programs have successfully utilized a central cannulation strategy with extracorporeal lung assist devices to improve participation in physical and occupational therapy sessions.[55,56]

Recommendation.

- In infants and children, central cannulation strategies are an appropriate alternative to peripheral cannulation strategies as bridge to lung transplantation. (CoR: IIa LoE: C1)

5. SECTION III. INITIATION OF ECLS & MANAGEMENT CONSIDERATIONS

This section will cover practical issues such as cannulation methods and consideration of an awake versus sedated approach to cannulation and maintenance of ECLS pre-transplant; as well as technical factors requiring optimization to achieve best outcomes such as flow management, anti-coagulation, use of anti-infectives, need for physical therapy and good psychological care whilst supported on ECLS. Optimal management of these factors is essential for prevention of complications associated with prolonged ECLS therapy.

5.1. Cannulation approaches

Venovenous (VV) ECMO is the preferred initial strategy for purely hypoxic and/or hypercapnic respiratory failure. Dual lumen cannulation of the internal jugular vein or left subclavian vein, bifemoral cannulation, or femoral vein to internal jugular vein cannulation can be utilized for VV ECMO whilst allowing the patient to ambulate. The priority in

the ECMO BTT scenario is to facilitate active mobilization and rehabilitation prior to transplant. Serial assessment of the systemic and right-sided hemodynamics as well as echocardiography to assess right (RV) or biventricular function is essential to determine whether VA ECMO support is warranted to support the RV prior to development of end-organ dysfunction. In the event of hemodynamic instability with elevated pulmonary arterial pressure and RV failure with or without hypoxia, VA ECMO is the strategy of choice to support patients in cardio-pulmonary failure. The most widely used approach is the peripheral VA ECMO via either the femoral vessels or the "SPORT model", with an internal jugular vein cannula and a cut down to subclavian or axillary artery approach.[57] Alternatively, in advanced cases of RV failure, conversion to central ECMO via a mini sternotomy or a limited thoracotomy, and cannulation of right atrium to pulmonary artery or right atrium to pulmonary vein or aorta have been described as successful bridge to transplant.[58–60] Each approach has its pros and cons. The femoral VA ECMO approach can be expeditiously deployed in the intensive care unit in an awake acutely deteriorating patient with either a cut-down or percutaneous approach. Limb ischemia can occur, and placement of a distal limb perfusion catheter should be considered to mitigate this. Protocols for regular assessment of distal limb perfusion are mandatory for early assessment of distal ischemia. Programs may be reluctant to ambulate these patients due to concerns regarding risk for cannula dislodgement, however the benefits of mobilization with maintenance of muscle mass and prevention of frailty for maintenance of candidacy are apparent in this cohort.[61] There are limited data to support one cannulation approach over another and strategy should be dictated by patient physiology and anatomy, local MDT expertise, surgeon preference as well as program resources and institutional philosophy regarding rehabilitation.

Recommendations.

- ECLS cannulation strategy should be driven by the recipient end-stage lung disease type, anatomical considerations, and cardiopulmonary comorbidities. (CoR: I LoE: C1)
- Bridging to transplantation ECLS cannulation strategy should prioritize a balance of cardiopulmonary support and post cannulation rehabilitation potential. (CoR: I LoE: C1)

5.2. Awake versus sedated

The first successful use of ECMO in an awake patient was reported in 2012 in an individual with severe respiratory failure and ESLD listed for lung transplant.[62] This represented a paradigm shift in the management of critically ill patients requiring ECLS support and this approach is subsequently recognized as key in lung transplantation BTT patients to avoid complications relating to mechanical ventilation,[63] immobilization, and sedation.[64] This section will focus on considerations relating to initial cannulation and subsequent maintenance prior to transplant.

Cannulation: There is understandable anxiety with regards cannulating a patient with severe respiratory failure without general anesthesia and intubation. Early reports focused on patients with severe PAH and cardiopulmonary compromise. These patients are at high risk of cardiac arrest on induction of anesthesia and awake cannulation was considered as a last-ditch attempt to support an actively deteriorating patient to life-saving transplant.[65] An optimal approach to awake cannulation should prioritize avoidance of ECMO as rescue therapy and requires a multi-disciplinary plan and highly experienced team for safe initiation without physical or psychological harm to the patient. Early ECMO consideration in deteriorating patients limits risk of complications and allows the appropriate team to be assembled in suitable environment with all necessary resources available. Initiation of support often provides instantaneous relief from severe breathlessness without the concomitant disadvantages of intubation, sedation nor requirement for tracheostomy to aid weaning from the ventilator. Patients are immediately able to eat, mobilize and engage fully with all aspects of supportive care, thus avoiding unnecessary acceleration to a position of ineligibility for transplant.

Maintenance: Several retrospective studies have demonstrated the benefit of maintaining a wait-listed patient on awake ECMO as BTT as compared to sedation on ECMO.[66–69] Awake ECMO BTT achieves better early outcomes than sedated ECMO or mechanical ventilation (MV),[67] and as such, efforts to maintain freedom from sedation or MV should be prioritized for as long as is possible. Schechter et al. reviewed all cases of bridged lung transplantation from UNOS database between 2005 and 2013 and found that, regardless of underlying lung disease diagnosis, patients supported by ECMO alone (n=65) had better survival than those supported with MV alone (n=612) or ECMO with MV and sedation (n=119).[67] Awake ECMO was not an independent risk-factor for post-transplant mortality as opposed to ECMO with MV and sedation. Awake ECMO also impacts early outcomes

resulting in shorter ICU stays, better lung function at six months and one year, and lower early mortality.[36] Of interest, the Vienna team reported their 20-year experience in BTT showing, over time, the rate of awake ECMO had increased as well as clinical results improved.[20] Better survival could be achieved with successful awake ECMO bridging when compared to MV.[31] Rates of successful awake ECMO bridging with opportunities to participate to physical therapy while on ECMO have been reported as 69% of patients in a retrospective study, leading to a 2-year survival of 70%.[70] Whilst awake ECMO has been demonstrated effective in bridging patients to transplantation when compared with MV, little is known about the duration of these bridging strategies. One retrospective study[71] comparing 35 awake bridged patients to 53 sedated bridged patients to lung transplantation confirmed the faster recovery in the awake group. The authors concluded that the longer the bridge, the better the post-transplant recovery. Hence, awake ECMO may allow both recovery of respiratory failure and facilitate improvement in physical fitness before transplantation.

Recommendations.

- Patients requiring ECLS bridge to transplant should be considered for awake cannulation, if deemed medically safe and with patient consent, to avoid need for sedation and mechanical ventilation wherever possible. (CoR: I LoE: B2)
- Patients requiring ECLS bridge to lung transplant prior to lung transplant should be maintained on awake ECLS minimizing need for sedation and mechanical ventilation for as long as possible. (CoR: I LoE: B2)

5.3. Flow management

In the initial phase of ECMO therapy, blood entering the circuit contacts non-biological surfaces, resulting in a systemic inflammatory response. This can result in capillary leak, fluid loss into the extravascular space and vasoplegia.[72,73] Furthermore, hemorrhage can occur as a complication during cannulation. To maintain proper blood flow and to deliver an appropriate oxygen supply to the patient, large-volume resuscitation is often needed during the initiation phase of ECMO, resulting in positive fluid balance (PFB).[72] Excessive fluid may lead to pulmonary edema, further diminishing gas exchange.[74] A retrospective, observational single-center study found that PFB at day 7 following ECMO initiation was associated with elevated in-hospital mortality. They observed that poor fluid output rather than fluid input was responsible for in–hospital mortality.[73] One group observed that a 3-day period of PFB following ECMO initiation was independently associated with 90-day hospital mortality in patients with severe ARDS.[75] The primary goal of fluid management during ECMO is maintenance of sufficient intravascular volume for preservation of adequate blood flow and oxygen delivery.[72] Organ function usually improves after ECMO initiation and conservative fluid management can be followed. The guidelines from Extracorporeal Life Support Organization (ELSO) suggest that negative fluid balance should be targeted until a patient reaches their dry weight and is hemodynamically stable.[72] Awake ECMO BTT comes with challenges: intrathoracic pressure variability during respiration, coughing and patient ambulation can influence venous drainage with venous collapse on the venous cannula. This may manifest as a phenomenon known as “chattering” which describes rhythmic pulsations of the ECMO tubing due to erratic nonlaminar blood flow. This may negatively impact blood flow and gas exchange. Under these circumstances, the ECMO pump flow should be reduced, with cautious administration of fluid volume resuscitation to avoid pulmonary edema and a further decrease gas exchange.[74] In the event of cannula displacement or excessive negative fluid balance, “chattering” can also compromise pump flow resulting in hemolysis and cavitation with air embolization. Lowering pump flow temporarily will enable the appropriate remedial action to be taken.[72] Given the importance of optimal fluid management, detailed data collection regarding fluid and output should be recorded. Defined optimal strategies for volume resuscitation during initiation of ECMO, and timing for conversion to a more conservative fluid administration approach are not currently known.

Recommendation.

- Fluid management in patients on ECLS as BTT should be carefully titrated to balance both ECMO flow and the risk of cardiopulmonary overload. (CoR: I LoE: C1)

5.4. Anti-coagulation management

Systemic anticoagulation is typically necessary to avoid complications of oxygenator or pump failure, hemolysis, venous thromboembolism, embolic stroke, and circuit or systemic thrombosis.[76] This need must be weighed

against the possibility of other causes of bleeding such as acquired coagulopathy or recent trauma/surgical intervention. Due to its cost, reversibility (protamine), short half-life, and ease of use, unfractionated heparin (UFH) is the most frequently used anticoagulant in both adult and pediatric ECMO.[77] UFH is administered initially intravenously as a bolus, followed by a continuous infusion adjusted based on tests such as APTT and anti-Xa. The development of heparin-coated tubes with low propensity for thrombosis enables low dose/intensity or anticoagulation-free strategies to be considered in patients with severe bleeding and coagulopathy. While several publications demonstrate comparable thrombosis rates and reduced incidence of bleeding and transfusion requirements with a low/no anticoagulation strategy, important considerations include maintenance of a sufficient flow rate to prevent intracardiac thrombosis and prior clinical history of thrombotic complications.[78–85]

Heparin inhibits thrombin by binding to antithrombin and factors Xa, XIIa, and IXa; however, it has several drawbacks, including the potential to produce heparin-induced thrombocytopenia (HIT) and heparin resistance.[76,86–88] In these scenarios, the patient requires a switch to an alternate anticoagulant such as a direct thrombin inhibitor (DTI). The two commonly used DTIs are argatroban and bivalirudin. These function independently of antithrombin resulting in more predictable dosing regimens and anticoagulant effect. Their disadvantages include limited availability of specific laboratory monitoring, lack of a reversal agent and higher cost. Several retrospective studies have compared the use of DTIs compared with UFH, with bivalirudin frequently used off-label in ECMO with or without HIT.[89]

Anticoagulation monitoring is necessary to ensure adequate dosing and prevention of bleeding and thrombotic complications.[90] Activated clotting time (ACT) is mainly used for UFH dosing but has a poor correlation with heparin plasma level [91] and is influenced by hypothermia and platelet dysfunction.[92] Anti-Xa assay can be used to monitor UFH dosing with one study concluding that anti-Xa was more accurate in monitoring UFH.[92] DTI dosing is monitored with an aPTT test. When elevated doses are administered, aPTT is not valid because of non-linear responses.[93] Viscoelastic testing, such as thromboelastography (TEG) and thromboelastometry (ROTEM), provides information on clot initiation, strength, and lysis. Data have shown the perioperative use of point of care monitoring to direct management of ECLS anticoagulation in lung transplantation results in decreased rates of transfusion, lower anticoagulation doses, and improved outcomes.[94–96] Less aggressive anticoagulation can be considered in VV ECMO, with some centers having postponed systemic anticoagulation altogether.[97] Biocompatible molecules bound to ECMO components may reduce circuit thrombosis, the need for anticoagulation, and thus bleeding complications.[74] There is currently no gold standard anticoagulation strategy for ECMO therapy,[92] and prospective randomized studies are needed.[76,98,99] A personalized anticoagulation approach should be based on patient characteristics, underlying pathology, the phase of care, and the trade-off between clotting and bleeding risks. Reducing or holding anticoagulation during acute bleeding or recent surgery is appropriate when necessary.

Recommendations.

- Low-dose or anticoagulation-free VV-ECMO should be considered in patients with an increased risk of bleeding. (CoR: IIa LoE: B2)
- Low-dose or anticoagulation-free VA-ECMO should be carefully considered in the context of risk assessment for pump thrombosis and systemic embolization in patients with an increased risk of bleeding. (CoR: IIa LoE: C1)
- Direct Thrombin Inhibitors should be utilized for both pediatric and adult ECMO BTT patients with HIT and heparin resistance. (CoR: IIa LoE: C1)

5.5. Anti-infective management

ECLS is associated with a high risk of infection related to the large bore cannulae inserted into the central vessels and the circulation of the blood through the extracorporeal centrifugal pump and oxygenator. Other invasive procedures required over the course of ECLS including bronchoscopy, repeated line insertions, other percutaneous mechanical support devices and surgical manipulations also place ECLS recipients at high-risk of infection.[100] The major types of infections that occur are ventilator-associated pneumonia (VAP) and bloodstream infections (BSI). The 2024 ISHLT Infection Definitions for Durable and Acute Mechanical Circulatory Support Devices recently outlined definitions for ECLS-related infections,[101] but a lack of prior standardization of definitions means there is a wide variation in the reported infection rates between studies. The main source of data

on infections is the ELSO Registry.[102] This registry reports a culture positivity rate of 64.9% when ECLS is used in respiratory failure, and the respiratory tract is the most common site of microbe isolation.[102] However, this registry does not differentiate between true infection and colonization. In other single-center studies, VAP, and BSI rates of 55.4 and 44.26 per 1000 ECMO days are reported in those requiring VA ECMO support.[103–105] Infections in patients on ECLS are impactful as they are associated with higher mortality rates (RR 1.63, $p < 0.001$) and longer durations of ECLS support and hospital lengths of stay (16 ± 17 vs. 8 ± 5 days $p < 0.0001$; 36 ± 30 vs. 26 ± 29 days $p < 0.01$).[106–109] Standard surgical prophylaxis is recommended at the time of cannulation for ECLS, whether this is performed surgically or percutaneously, but should not be continued for longer than 24 h post cannulation without evidence of active infection.[110] Antifungal prophylaxis is recommended in those at high-risk (e.g., prolonged open chest on multiple antibiotics or the significantly immunocompromised).[110] If infection becomes established and progresses to septic/distributive shock with significant pressor requirements, consideration of whether continuation of an ECMO BTT strategy is now futile is strongly warranted.

ECLS therapies alongside critical illness are known to affect the pharmacokinetics (PK) of many drugs.[111] Studies have shown that there is significant inter-patient variability in antimicrobial concentrations which can result in drug accumulation and toxicity, or under-dosing and therapeutic failure.[112–114] ECMO circuits may alter PK by drug sequestration onto the device itself.[115,116] Whilst the use of diuretics, sedatives, inotropes, and vasopressor drugs can be directly titrated to a measurable clinical endpoint, anti-infectives often cannot. Literature guiding antimicrobial dosing in ECMO patients is limited, and *ex vivo* experiments have suggested that drugs that are lipophilic or highly protein bound are likely to be sequestered within the ECMO circuit.[116–119] Dosing strategies derived from critically ill patients not on ECMO are acceptable for empiric dosing with subsequent dose optimization using therapeutic drug monitoring (TDM). Antimicrobial TDM is a crucial practice in healthcare, involving the measurement of plasma drug concentrations to ensure optimal dosing and efficacy while minimizing potential side effects.[120,121] Interpreting plasma antimicrobial drug concentrations in critically ill patients on ECMO presents several challenges due to the complex physiological changes that occur.[122] While not unique to ECMO, a meta-analysis showed that having a pharmacist on the ICU MDT was associated with lower rates of patient mortality, avoidable and nonpreventable adverse drug events, and decreased length of stay.[123]

Recommendations.

- All patients requiring ECLS BTT should be initiated on antibiotics to cover initial ECMO cannulation if not already on appropriate antibiotic therapy. (CoR: I LoE: C1)
- Antimicrobial therapy in patients on ECLS BTT should be dose-adjusted to account for the pharmacokinetic/pharmacodynamic effects of the ECLS device. (CoR: I LoE: C1)
- Specialized pharmacists should be involved in the dosing and the therapeutic drug monitoring of antimicrobials used in the management of patients on ECLS BTT. (CoR: I LoE: C1)
- An algorithm for antimicrobials should be developed by a multidisciplinary group and updated as evidence accumulates. (CoR: I LoE: C2)

5.6. Physical therapy

Physical therapy has been shown to prevent and reduce ICU-acquired muscle weakness and improve functional capacity in critically ill patients.[124] As such, physical therapy is an essential therapeutic intervention for all ECMO BTT patients.[6,125] However this requires a very careful, multi-disciplinary approach from a highly specialized team to balance the benefits of rehabilitation against potential risks including the complexity of the ECLS system and the risk of cannula dislocation.[61,70,125–127] The risks may outweigh the benefits of physical therapy and or exercise rehabilitation in some patients.[125] However, developing appropriate strategies of physical therapy and or exercise rehabilitation in patients requiring ECMO BTT may be an important component of maintaining a patient's transplant candidacy.[128]

After a thorough risk benefit assessment, the feasibility and appropriateness of different physical therapy and or exercise rehabilitation modalities should be assessed. Physical therapy and or exercise rehabilitation interventions may include strengthening and reconditioning exercises in supine, sitting and or standing, progress to mobilization, and active/active-assisted in-bed cycling as medical stability and the ECLS system allows.[61,70,125,127,129] Other interventions may include functional electrical stimulation of lower limb muscles to preserve muscle mass and strength.[130] These exercise rehabilitation interventions are individually tailored for

each patient requiring ECLS due to its complexity. The optimal physical therapy and or exercise rehabilitation interventions including the relative importance of muscle strength training compared to mobilization and or active/active-assisted in-bed cycling with the goal of maintaining a patient's transplant candidacy remains unclear. Further prospective trials are needed. Patients can optimally benefit from ECMO therapy as BTT when they wean from mechanical ventilation and participate in physical therapy, thereby avoiding deconditioning seen in critical illness myopathy with potential for improved intra and postoperative outcomes.[14,74]

Recommendation.

– Physical therapy and/or exercise rehabilitation programs should be implemented and are essential needs for BTT ECLS patients. (CoR: I LoE: C1)

5.7. Organ specific considerations

ECLS is an intensive form of support with significant impact on multiple organ systems. Individual patients are critically ill and are at high risk of sepsis and multi-organ failure. This section will focus on cardiovascular, pulmonary, immunological, and neurological/psychological factors that warrant careful consideration in the ECMO BTT patient, along with consideration of appropriateness of continuation when therapy becomes futile. This will be discussed alongside palliative care and ethical issues relating to withdrawal of care.

5.8. Cardiovascular management

Limb ischemia: VA ECMO is the preferred form of ECLS to provide cardiovascular and respiratory support for patients before lung transplantation when there is associated significant cardiac compromise. Most publications on limb ischemia and VA ECMO are in the context of cardiogenic shock with underlying cardiac etiologies. This is sparsely reported for ECMO BTT, but the concepts are similar. Whenever VA ECMO is instituted peripherally, limb ischemia is one of the significant risks for morbidity and mortality. While bleeding and thromboembolism are among the most frequent complications, limb ischemia is reported to occur between 10% and 50% in the literature.[131,132] A meta-analysis showed that 17% of patients had limb ischemia with 10% progressing to compartment syndrome and 5% needing amputation.[133] In a large registry report from ELSO, 4% were identified to have severe limb ischemia requiring fasciotomy or amputation.[134] Using peripheral VA ECMO after lung transplantation is associated with similar incidences of around 10% of limb ischemia.[135]

Limb ischemia can be mitigated by different strategies such as preventing it by using different cannula sizes and cannulation site selection, but also by monitoring for early detection of ischemia. One of these strategies is to use continuous near-infrared reflectance spectroscopy (NIRS). One study showed a difference in tissue saturation between legs of greater than 15% in all patients with cannula-related obstruction of flow to the distal portion of the leg.[136] In another single center analysis, NIRS together with a small arterial cannula was shown to be effective to prevent limb ischemia.[137] The combination of NIRS and a small arterial cannula was associated with a threefold reduction in limb ischemia, however given their simultaneous implementation, it's difficult to differentiate the impact of NIRS from the impact of the small arterial cannula effect from each other. A subsequent reduction of limb ischemia surgery was observed; however, mortality remained the same before and after initiation of NIRS. The incidence of limb ischemia among patients without a distal leg perfusion cannula was approximately 25% in large sample size meta-analysis, indicating higher incidence when not using a distal leg perfusion cannula.[138]

North-South (Harlequin syndrome): This describes a syndrome of "differential hypoxemia", often discrete, causing clinical problems in peripheral femoro-femoral venoarterial extracorporeal membrane oxygenation, when the upper body is perfused with low saturated blood from the heart and the lower body with well-oxygenated extracorporeal membrane oxygenation blood. This occurs when cardiac function is adequate to overcome retrograde flow of oxygenated blood from the femoral return cannula and deoxygenated blood from the failing lung is delivered to the brain and upper extremities.[139] The incidence of Harlequin Syndrome has not been properly described, but it has been reported to be 8.8%.[140] The risk may very well be higher in bridge-to-lung transplantation patients since most of them have near normal cardiac function. Given poor oxygenation negatively impacts cardiac function, consideration of a VV ECMO strategy to restore oxygenation may be sufficient to rescue cardiac function and avoid the increased risk associated with VA ECMO strategies in patients with primary lung failure. During VA ECMO, early identification and detection of Harlequin Syndrome is important and has been

shown to not only be detectable with invasive blood gas saturation but also with NIRS.[141,142] Monitoring with cranial NIRS in VA ECMO patients has shown that an absolute regional saturation of 15% or less results in dismal neurological and overall outcomes.[143] Furthermore, a metanalysis investigating cardiac arrest patients, a low saturation peripherally by cranial NIRS was associated with reduced survival and worse neurologic status in survivors.[144]

When Harlequin syndrome occurs, brain and cardiac function are under imminent threat. Optimization should be promptly addressed focusing on cardiac output (increasing ECMO output), ventilatory strategy (protective low-pressure ventilation) and optimization of oxygenation (increase FiO_2 in circuit). Unfortunately, these measures often are not enough.[140] If Harlequin Syndrome remains despite these efforts, an urgent change of strategy should be considered. The most common and established way to manage Harlequin Syndrome is by changing cannulation strategy. Addition of an internal jugular venous return cannula, or veno-arterial venous ECMO (VAV ECMO), facilitates an additional return arm from the ECMO circuit directly into the right atrium. This approach enables perfusion of the failing lungs with oxygen-rich blood that passes physiologically in an anterograde direction through the heart and across the aortic arch.[145] The use of a secondary centrifugal pump to manage the blood flow directed to the internal jugular vein in the VAV ECMO setup is thought to reduce the risk of blood clot formation, clotting factor consumption, and pulmonary embolism.[146] Other cannulation strategies in Harlequin Syndrome may be to use a central arterial cannulation approach which definitively delivers physiological anterograde blood.[147] Notably, it has been shown that in ECMO BTT, those needing central cannulation have a more dismal outcome than those who are peripherally cannulated.[18] This is in direct contrast to those who only require intraoperative ECMO support. Analysis of use of intraoperative VA ECMO support shows no difference in outcome between peripheral and central cannulation. This may indicate that duration of central VA ECMO support is essential to consider.[135] Finally, consideration of alternative flow routes may be beneficial.[148] Case studies suggest that drainage from the superior caval vein improves upper body arterial oxygen saturation and oxygen transfer as compared to inferior caval vein drainage in VA ECMO in patients with moderate to severe right ventricular dysfunction. In this situation, a VAV ECMO configuration may worsen the situation by overloading an already compromised RV. RV volume and pressure overload cause displacement of the interventricular septum, impacting LV function. Central venous pressure increases, and the systemic pressure is compromised. Ongoing RV failure causes worsening of lung oxygenation due reduction in blood flow through the lung. In this situation, a veno-venous-arterial ECMO (VVA ECMO) configuration with internal jugular cannula acting as additional venous drainage serves to offload the RV, with improvement in RV function and overall resolution of signs of differential oxygenation associated with Harlequin Syndrome.[149] ECMO support strategies are a rapidly evolving field with novel configurations necessary to address unique case specific factors.

East-West (Riddler syndrome): This novel syndrome of "differential hypocapnia" is very recently described [150] and represents a new diagnostic dilemma for the management of a patient on awake VA ECMO. In this syndrome, a spontaneously ventilating patient develops a mild tachypnoea as an appropriate response to pain, anxiety, or exertion. Increased respiratory rate increases minute volume and CO2 clearance by the lung. If cardiac output is sufficient, decarboxylated blood from the lung passes anterograde from the heart to reach the brachiocephalic artery. Measured pCO2 in the right radial blood gas drops and the patient may appear to have a respiratory alkalosis. However, when the watershed mixing area of anterograde and retrograde blood (from the femoral arterial return cannula) sits between the brachiocephalic artery and the left carotid artery, radial blood gas measurements will show a low CO2 and high pH, despite delivery of hypercapnic blood to the cerebral circulation and respiratory drive centers. In response to the right radial arterial blood gas measurements, providers may be inclined to decrease CO2 clearance by the ECMO circuit by reduction in the device' gas sweep. This results in increasingly hypercapnic retrograde blood flow entering the cerebral circulation; and a further inappropriate centrally driven increase in respiratory rate, thereby exacerbating this deleterious cycle further. An attempt to account for the reduction in measured (right radial) pCO2 by additional reduction in ECMO sweep gas will result in worsening cerebral hypercapnia with worsening paradoxical tachypnea. Early recognition of this syndrome avoids progression to respiratory exhaustion, cerebral edema, and neurological injury. If Riddler Syndrome is suspected, careful examination of central, mixed venous and post-oxygenator pCO2 will be helpful in confirming the diagnosis. Identification of triggers for tachypnea will allow treatment of initiating cause. Titration of sweep gas to both right radial and post-oxygenator pCO2, and confirmation of the watershed zone of blood flow mixing by echocardiography will disrupt the cycle.

Echocardiography: Evaluation of the anatomy of the interatrial septum (IAS) and its integrity for the presence of an interatrial shunt is a necessary step in the preoperative evaluation of lung transplant recipients. Under

normal physiological conditions, elevated left atrial pressure gently pushes the thin septum primum against the septum secundum and seals the potential opening of the patent foramen ovale (PFO).[151] However, commonly in patients with ESLD, elevated or worsening pulmonary vascular resistance with subsequent elevation of right atrial pressure (RAP) increases the likelihood of a right to left intracardiac shunt across a PFO or previously undiagnosed small atrial septal defect (ASD). Cardiac MRI is the gold standard, noninvasive method of choice to study the details of intracardiac shunts and anatomical structures,[152] however this is logistically complex to deliver in ECLS supported patients. Contrast-enhanced echocardiographic evaluation (transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE)) represents a real-time bedside tool to optimize patients for BTT or screen for the presence of such defects.[153,154] The presence of contrast in the left atrium within 3–6 cardiac beats after opacification of the right atrium is considered positive for the detection of an interatrial shunt.[155] The traditional recommendation of using an agitated solution of 1 ml of blood, 1 ml air and 8 ml of saline while asking for cough, performing Valsalva, or applying abdominal compression may result in a false negative result in the presence of VA ECMO and create a systemic air embolization, therefore its practice is contraindicated in VA ECMO supported patients.[156] Instead, the use of IV contrast agents is recommended. The potential for "false negative" findings in ECLS patient populations should be considered and can be minimized by temporarily adjusting the flow rate if tolerated by the patient. False negative results may occur due to: inadequate opacification of right atrium secondary to venous cannula drainage; an inability to perform Valsalva in spontaneously breathing and tachypneic ESLD patients; mechanical obstruction of PFO/ASD by large venous cannula preventing the contrast agent or microbubbles entering from right to the left; a venous-pulmonary artery (VPA) ECMO cannulation strategy with significant unloading of the right atrium, makes pressurizing the RA difficult if not impossible, and poor image quality as a result of cannula induced artifacts.

Discovery of a PFO or ASD may help the team to consider surgical closure at the time of transplantation or percutaneous closure after lung transplantation which may reduce postoperative stroke risk.[156] Consideration of PFO repair at the time of transplant is not studied extensively. Hybrid ECMO / Cardiopulmonary Bypass (CPB) circuit may provide the opportunity to perform the lung transplantation on VA ECMO with conversion to CPB for a concomitant PFO closure or other cardiac procedure.[157] Future studies looking at the risk benefits of PFO closure (ECMO versus CBP), postoperative atriotomy complications, postoperative stroke risk of unrepaired PFO and postoperative hypoxia in a newly transplanted lung will help the team formalize a management strategy.

Vascular thrombosis: No coagulation test is predictive of thrombotic risk in patients supported with ECMO. Venous thrombosis has been reported up to half of patients supported by VV ECMO,[158] while circuit thrombosis rate is about 21%.[99,159–161] Low flow, inadequate anticoagulation and prolonged ECMO run has been associated with the potential clot formation.[158] Several studies (small, single center retrospective) tried to identify markers for predicting thrombotic complications of circuits. One study proposed daily measurement of D-dimers in plasma as a marker for early diagnosis of thrombus formation and dysfunction of heparin-coated membrane oxygenators.[161] Another identified soluble fibrin but not D-dimers as an independent factor for the need of circuit exchange.[159] In patients supported with ECMO, detection of venous cannula thrombosis should not always act as an immediate trigger for cannula exchange.

Clinical assessment of circuit flow, hemolysis markers, RV function, potential impact of embolization of thrombus and progression of thrombus size are an initial step. If a number of conditions are met including relatively stable circuit flow, stable or only mildly elevated hemolysis level, non-elevated patient risk for consumptive coagulopathy (and therefore blood products transfusion), lack of pulmonary embolus induced RV dysfunction and the size of the thrombus is stable and embolization of venous/cannula thrombosis would not impose a potentially life-threatening pulmonary embolism, then keeping the current ECMO cannula in place and optimizing the dose of anticoagulation to higher target levels is recommended.[99] If necessary, the use of anticoagulation strategies such as direct thrombin inhibitors have been shown to have a more favorable hemocompatibility profile by minimizing the incidence of circuit thrombosis and complications.[162,163] If despite conservative management strategies described above, the risk of leaving the venous cannula associated thrombus in situ is high, then the cannula should be exchanged.

Recommendations.

- Limb ischemia monitoring should be utilized following institution of peripheral lower extremity VA-ECMO. (CoR: I LoE: B2)
- Insertion of a distal leg perfusion cannula should be considered following the institution of peripheral lower extremity VA-ECMO depending on patient risk and vascular anatomy. (CoR: I LoE: B2)

- When peripheral VA-ECMO is instituted as a bridge to lung transplantation, multi-organ system clinical monitoring for North-South/Harlequin Syndrome should be utilized. (CoR: I LoE: C1)
- When North-South/Harlequin Syndrome occurs on VA-ECMO, optimization of cardiac output, ventilatory strategy and optimization of oxygenation should be the first clinical priorities before reconsideration of cannulation approach. (CoR: I LoE: C2)
- On initiation of ECMO as a BTT, echocardiography should be used to evaluate presence of inter-atrial shunt. (CoR: I LoE: C1)
- During ECMO as BTT, thrombus removal from venous cannulae should not necessarily be the first step as adjustment of anti-coagulation may be the only requirement. (CoR: IIa LoE: C2)

5.9. Pulmonary management

Tracheostomy: Percutaneous and surgical tracheostomy can be safely performed with equivalent outcomes as in non ECLS supported patients.[164,165] Early tracheostomy, within 10 days from initiation of ventilation, is associated with overall better critical care endpoints such as a reduction in sedation, liberation from mechanical ventilation, mobilization and length of ICU stay.[166–170] However, a recent retrospective multicenter review of severe ARDS patients receiving early tracheostomy on VV ECMO, surprisingly failed to see the benefit of expected lower sedation.[170] There is a lack of evidence investigating whether the benefits of early tracheostomy extend to the ECMO BTT lung transplant candidate. Pragmatically, benefits include a decrease in the need for sedation, decreased work of breathing and more effective airway secretion suctioning and oral hygiene. It also improves patient mobilization, enhances participation in physical therapy and provides comfort and ability to speak.[170–172] These are all essential elements to maximize preoperative optimization, whilst waiting for transplant.

Bleeding risk during tracheostomy: ECMO induced coagulopathy and bleeding are significant tracheostomy peri-procedural risk factors. The incidence of bleeding has been reported as high as 40%,[172] therefore the best technical approach to avoid bleeding is an important consideration for the proceduralist. Two studies demonstrate the safety of a percutaneous approach in patients on ECMO.[173,174] In one of the few published studies comparing outcome of a percutaneous versus open surgical approach, a similar safety outcome was seen, although bleeding rate was 44% in percutaneous group compared to 27% in surgical group.[175] Percutaneous tracheostomy has been favored due fewer associated logistical challenges including operating room time, staff, transport,[170] while surgical tracheostomy is often chosen when there is an anatomic constraint, such as a very short neck, an inability to extend the neck, previous tracheostomy, or the presence of scar tissue.[175] In the absence of clear outcome studies, a balance of institutional preference and local experience of the clinical team governs decision making for best approach in individual patients.

Mechanical ventilation: Goals of ECLS during BTT extend beyond simple enhancement of oxygenation and ventilation. The priority should be to adjust ECMO flow or cannulation strategy to optimize physiological gas exchange, alleviate distressing symptoms of air hunger and minimize sedation, however some patients may require additional mechanical ventilation, even temporarily, to achieve adequate gas exchange or for symptom management. The primary role of mechanical ventilation in patients receiving ECLS outside a BTT scenario, is to maintain adequate ventilation and oxygenation while minimizing the risk of lung injury. Organ injury induced by MV (barotrauma, volutrauma, atelectrauma, ergotrauma, myotrauma, and biotrauma) is directly deleterious to the lung and impacts optimal lung recovery.[176–179] In the context of lung transplant for ESLD however, the primary goal of MV is not lung protection, but ventilatory strategy tailored to the ESLD as well as the protection of multiple organ systems outside of the lungs. Unfortunately, there is a paucity of high-quality studies specifically addressing optimal mechanical ventilation practices in patients supported by ECMO as BTT. Most available data and studies focus on lung recovery strategies, and consequently ventilator settings, therefore are often geared towards that specific objective. The irreversible nature of ESLD in transplant candidates, alongside the distinct needs of these patients in the preoperative period, poses unique challenges. Issues around obtaining informed consent during emergent intubation, facilitating rehabilitation, and addressing critical illness-related muscle atrophy, including diaphragmatic dysfunction exist with MV. ECLS offers a valuable opportunity to address these issues and stability to make clinical improvements.

In the absence of randomized controlled trials specifically investigating the optimal ventilator settings for this patient population, expert consensus-based guidelines have been established. These guidelines are largely informed by major outcome trials, such as EOLIA and CESAR, which have been implemented and adapted, for

clinical practice.[180,181] Classic lung protective strategy endorsed by major guidelines has typically left the tidal volume unspecified, concentrating instead on parameters such as plateau pressure, positive end-expiratory pressure (PEEP),driving pressure, and minimizing fraction of inspired oxygen (FiO2). In contrast, an "ultra-lung-protective" ventilation strategy has been proposed to further reduce the mechanical energy delivered to the lungs. This approach involves lowering tidal volume to ≤ 4 ml/kg, maintaining a respiratory rate of < 20 breaths/min, and ensuring airway pressures remain within specific limits, namely, plateau pressure below 25 cmH_2O and driving pressure at or below 15 cmH2O. Adopting an ultra-protective ventilation strategy has been shown to significantly reduce mechanical power; however, it has not demonstrated a clear clinical benefit in patients supported by ECMO.[182,183] Permissive hypercapnia and hypoxia are considered acceptable practices to facilitate ventilator weaning and adjustment of settings. ECMO sweep gas should be used liberally to support these lung-protective strategies and to address air hunger.[184] The use of ECMO allowed for greater tidal volume reduction (< 4 ml/kg) in patients randomized to the ECMO group in the EOLIA trial[180] and in the LIFEGUARD cohort.[183] Current guidelines from ELSO recommend targeting a tidal volume of less than 4 ml/kg in such patients.[72] Drawing from both past and recent pandemic experiences, a plateau pressure of less than 25 cmH2O is now recommended.[72,185] Driving pressure has been identified as a strong independent predictor of mortality in patients with ARDS supported by VV ECMO.[186,187] Consequently, it is recommended to target a driving pressure of less than 14 cmH2O to improve mortality, supporting the concept of reducing tidal stretch and mechanical energy.[72,188] Mechanical power, a concept quantifying the energy delivered by the ventilator to the respiratory system, incorporates respiratory rate in addition to other established factors such as driving pressure.[189]

While large trials have demonstrated significant reductions in mechanical power,[180,183] the full clinical implications of its application remain to be further investigated. Most current guidelines recommend a PEEP level greater than 10 mmHg to enhance lung recruitment and improve compliance. However, the hemodynamic effects of high PEEP on elevated pulmonary vascular resistance (PVR) and right ventricular function, as well as the necessity for sedation weaning and mobilization with the goal of potential liberation from mechanical ventilation, should be carefully and continuously evaluated.[190] Alternatively, nocturnal non-invasive positive pressure ventilation (NIPPV) or intermittent positive pressure ventilation (IPPV) with tracheostomy can partially achieve these goals by utilizing high PEEP while minimally affecting daily patient activities or ventilator settings.

Extubation: The purpose of awake ECLS is primarily centered on minimizing the use of sedative and analgesic administration and promoting early rehabilitation with the goal of achieving ambulation up to the day of surgery. Despite the clear advantages, there is limited evidence regarding the standardized approach for transitioning patients from invasive mechanical ventilation to spontaneous breathing while on ECMO BTT. We advocate a tailored approach combining institutional protocols with individualized patient management strategies. Prolonged mechanical ventilation is an independent risk factor for diaphragmatic atrophy and has been identified as a leading cause of weaning failure in critically ill patients. This is particularly concerning in pre-transplant candidates with comorbidities, who are at heightened risk for mechanical ventilation failure postoperatively.[191,192] The transition from controlled to spontaneous ventilation offers numerous benefits, including the preservation of muscle function, reduced sedation requirements, and enhanced hemodynamic stability and mobility. Gradual weaning of sedation and avoidance of paralytic agents are expected to reduce the incidence of critical illness-induced myopathy.[193] That said, spontaneous breathing in patients with high respiratory drive and reduced pulmonary compliance can result in excessive respiratory effort and elevated transpulmonary pressures, potentially leading to patient self-inflicted lung injury (P-SILI).[194] The goal is to minimize the risk of P-SILI while maintaining a degree of diaphragm activity, ensuring a successful transition to spontaneous ventilation.

During this period, the focus is on weaning sedation and minimizing respiratory drive through adjustments in sweep gas flow and rehabilitation efforts. As patients become more alert and stronger, the next phase involves transitioning from controlled or assisted ventilation to spontaneous breathing if feasible.[195] Ellouze et al.[196] were among the first to propose a structured approach for safe extubation in patients on ECLS highlighting the importance of stable hemodynamics, effective hemostasis, intact limb perfusion, and the avoidance of immediate invasive procedures. They implemented intermittent non-invasive positive pressure ventilation (NIPPV) immediately post-extubation, demonstrating a reduction in the incidence of VAP. Data from high-volume transplant centers indicate that approximately 35% of patients are successfully extubated after the initiation of ECLS, while 19% require tracheostomy to facilitate partial liberation from mechanical ventilation.[19] Clinicians should tailor their decision-making to each patient's specific clinical context and underlying etiology of ESLD. Careful consideration is required when comparing different management approaches, especially concerning

sedation weaning and transitioning the patient to spontaneous breathing, to optimize liberation from invasive positive pressure ventilation.

Oxygen goals: Preoperative ECMO BTT may be used for either primary pulmonary or cardiopulmonary failure. For either indication, one of the primary goals of the circuit is to improve overall systemic oxygenation. Due to the deleterious effects, avoidance of hyperoxia has been recommended in the literature, but the definition varies, and studies focus on cardiogenic shock.[197–199] An ELSO Registry study, examining patients undergoing VA ECMO for cardiogenic shock, delineated three groups of patients: Those who maintained normoxia (PaO2 60–150 mmHg), mild hyperoxia (PaO2 151–300 mmHg), and severe hyperoxia (PAO2 > 300 mmHg) while being maintained on VA ECMO. In-hospital mortality increased in cohorts with increasing PaO2, even when adjusting for confounders. PaO2 was noted to be one of the most powerful predictors of in-hospital mortality.[197] A separate retrospective multicenter study examined the mortality rate of patients in a similar clinical setting, finding that overall mean PaO2 was an independent predictor for 28-day mortality (Odds Ratio [OR] 2.85). [198] Finally, a meta-analysis of patients undergoing VA ECMO for cardiogenic shock also showed a nearly two fold increase in both mortality (OR: 1.80) and worsened neurological outcome (OR: 1.97) when exposed to elevated severe hyperoxemia.[199] Although this is a different patient population, these data inform our statement that normoxia should be targeted in patients receiving ECMO BTT.

Approach to hypoxia: In patients with a natural airway but persistent hypoxia, all efforts should be made to avoid re-initiation of mechanical ventilation. As already described, maintaining awake ECMO in BTT patients has several key advantages, including ongoing physiotherapy, avoidance of sedating medications, and maintenance of physiological pulmonary mechanics.[200] A single-center retrospective study examined the benefits of awake ECMO and found significant mortality and morbidity advantages including decreased ICU length of stay, improved postoperative physiotherapy, and better lung function as compared to the non-awake ECMO cohort.[36] The integration of a systems-based approach for managing ECLS BTT takes into consideration the relationship of co-management variables, and it is for this reason we recommended avoidance of invasive mechanical ventilation in the setting of persistent hypoxia at all possible, with a focus on ECLS circuit optimization prior to its initiation.

Recommendations.

- Tracheostomy should be prioritized to wake and mobilize patients, with either percutaneous tracheostomy or open surgical tracheostomy in patients on ECLS as bridge to transplant. Choice of approach should be agreed based on individual patient risk factors for bleeding as well as available expertise. (CoR: I LoE: C2)
- Patients requiring mechanical ventilation during ECLS BTT should receive lung protective ventilation that achieves optimal ventilatory / perfusion balance with the minimal possible cardiopulmonary insult. (CoR: I LoE: C1)
- Patients requiring mechanical ventilation during ECLS BTT should ideally be weaned to extubation utilizing a standardized institutional protocol as quickly as possible to either non-invasive ventilation or oxygen support. (CoR: I LoE: C1)
- Normoxia (PaO2 60-100 mm Hg) should be targeted in patients with ECLS bridge to transplantation. (CoR: I LoE: B2)
- In the setting of persistent hypoxia refractory to medical management during ECLS bridge to transplantation, ECLS circuit optimization including cannulation strategy, ECLS type, or cannulation size should be pursued prior to reinitiation of invasive mechanical ventilatory support. (CoR: I LoE: C1)

5.10. Immunological management

HLA sensitization: Testing for presence of HLA antibodies before lung transplantation is of fundamental importance for successful transplantation.[201] In most centers, calculated panel-reactive antibodies (cPRA) are used for risk stratification. Besides the presence of antibodies, mean fluorescence intensity (MFI) and complement-fixing properties are of additional relevance to assess the potential clinical impact of an antibody.[202] Antibody MFI and complement-fixation properties may contribute to wide variations reported in outcome following transplant of HLA antibody positive or “pre-sensitized” (according to cPRA) recipients.[203,204] Commonly, a cPRA above 50% is associated with a prolonged time on lung transplant waiting lists and lower probability of receiving a transplant.[205,206] To avoid reduced access to transplantation for HLA pre-sensitized candidates, many centers have successfully implemented desensitization protocols for patients with high (> 80–95%) cPRA to improve the

chances of matching with a donor organ.[207] Desensitization protocols consist of a combination of therapies including immunoglobulins, plasma exchange, rituximab and bortezomib.[208] Whilst pre-emptive and peri-operative desensitization are of proven efficacy in renal transplantation, benefit in lung transplant remains limited to single center studies.[207,209–211] This is of relevance when considering ECMO BTT strategies in a highly sensitized candidate given the likelihood of further prolongation of waiting time in a critically unwell patient. In centers where desensitization protocols are offered, this may occur in parallel with ECMO therapy or intraoperatively as required. The requirement for multiple blood transfusions whilst on ECMO may exacerbate sensitization further with generation of additional HLA antibodies. If a desensitization protocol is not locally available, transfer of the patient to another center with this option in place may be considered. If not possible, a high cPRA may become a significant barrier to matching with an organ, rendering transplant unfeasible and ECMO BTT unlikely to succeed. Single center data with regards to mid-to-long-term outcome after desensitization therapy suggest similar outcomes to unsensitized patients, however no randomized control trial data exists with regards optimal approach or timing. Whilst specific guidance does not exist with regards definitions of "highly sensitized", a general rule of thumb is that antibodies with an MFI of less than 1000 may be considered unlikely to be harmful and are infrequently treated. Conversely antibodies with an MFI of greater than 5000 are considered a high immunological risk even with desensitization therapy.[211] Further discussion regarding this important issue is beyond the scope of this paper and the reader is directed to this excellent review by Roux and Hachem.[208]

Recommendation.

– In centers where desensitization therapy is unavailable, high panel reactivity (e.g., PRA > 95%) should be considered for likely impact when approaching ECLS as bridge to transplantation and requires clinical expertise and knowledge of local organ availability. (CoR: IIa LoE: C2)

5.11. Neurological Management

Neurocognitive testing and Imaging: Neurological complications are common amongst patients receiving ECMO.[212,213] The initial psychosocial evaluation of lung transplant candidates encompasses assessment of psychological function, neuro-psychiatric function, social support as well as behavioral adherence.[214] Pre-transplant cognitive impairment may impact patients' ability to consent to invasive procedures or requirements for physical therapy whilst supported on ECMO and therefore impact the potential longer-term success of transplantation.[215] Teams evaluating patients for ECMO BTT should ensure they pay attention to avoid implicit bias against subsets of the population. This could include those with a history of substance abuse, those with developmental delays in cognition, and patients with limited formal education who may require more time and support to make informed decisions, however, there is evidence that carefully selected individuals from any of these groups can achieve similar outcomes with the correct support.[214]

Neurocognitive tests should be undertaken to assess the patient's baseline cognitive function, ideally at initial transplant assessment, prior to bridging with ECLS, given the associated risk of inducing neurological impairment, especially if there is pre-existing impairment. This may not always be possible, especially given the rise in the use of ECLS in SARF and ARDS. Tests should be standardized pre- and post-ECLS to avoid selection bias whilst ensuring certain patient groups are not unfairly discriminated against. This means considering educational and developmental attainment, language and cultural barriers,[216] and any organic medical confounders, such as an active infection or the use of opioids. Where previous neurocognitive assessment reports are available, consideration should be given to a patient's ability to cope emotionally and behaviorally with ECLS and the critical care environment. Ensuring the correct support is available, from both expert healthcare professionals and family is essential.[217] Despite this, neurocognitive assessment remains part of the standard psychosocial assessment of patients to assess suitability for transplant. Where the usual standardized tests cannot be undertaken, a full and careful MDT assessment by expert healthcare professionals may be needed to ensure the patient is not unfairly discriminated against nor listed for transplantation inappropriately.

Neurologic complications are associated with significantly increased morbidity and mortality in ECLS; however, the reported incidence of neurologic complications is highly variable.[218] Neuroimaging findings in neonates on ECMO, and their short- and long-term outcomes has been extensively discussed in the published literature and longer-term these children score less well than their peers in neurodevelopmental tests.[219–221] Standardized awake assessment of cognition remains the gold standard,[214] however, this is not always possible.

An example would be where there is a language barrier, and decisions need to be made rapidly in a critically unwell patient. Neurological imaging tests should be used where there is a suspicion of an acute neurological change as part of the assessment of the central nervous system.

Substance abuse: Active substance use, or dependence is considered an absolute contraindication when assessing patients' candidacy for lung transplantation, according to the consensus guidance produced by ISHLT. This includes, but is not limited to, smoking, vaping, marijuana, and intravenous drug use.[222–224] At initial assessment, an appropriate healthcare professional should undertake a comprehensive assessment of any history of illicit substance abuse, including type of substance, mode of substance abuse, duration of substance abuse and evidence of engagement with drug rehabilitation services. Length of recovery from substance abuse should be noted. There will be discrepancies in the definition of substance abuse, for example recreational versus daily use, more regular use as a younger person versus current abstinence. The multidisciplinary team should take into consideration the assessment of the psychosocial healthcare provider within the team and be more concerned about chronic daily use than a patient who engaged in substance abuse in their adolescent years recreationally. The context for the substance misuse should be explored by an appropriate psychosocial healthcare professional and consideration should be given to the patient's developmental stage when engaging in substance misuse and steps taken to shift away from that behavior.

Assessment of adherence: Non-adherence to the medical and drug regimens post-lung transplantation has been associated with poorer long-term outcomes.[225] Evidence should be sought from patients regarding previous ability and willingness to adhere to medical treatment and advice. The assessment of adherence is nuanced and multifactorial. The primary facets of good adherence are engagement with healthcare providers and adherence to prescribed medications as indicated. Adherence assessment should be undertaken by healthcare professionals with a good understanding of the multifactorial domains to be considered and where poor or suboptimal adherence is identified, consideration should be given to the barriers to good adherence and whether systems can be implemented to optimize adherence. Given the pressing clinical situation when considering ECLS as a bridging tool, there may not be time to optimize adherence. Consideration should be given to the available psychosocial support, within the patient's family and peer network and the transplant center, to support the patient's improved adherence postoperatively. The multidisciplinary team may consider any evidence of poor or suboptimal adherence in the context of developmental stages, cognitive impairment, and relevant psychosocial stressors. A decision to decline bridging with ECLS to lung transplantation, based on evidence of non-adherence, should be a multidisciplinary decision within the clinical team at the transplant center.

Recommendations.

- Standardized awake neurocognitive tests should be performed to assess recipient suitability for transplant listing in patients bridged with ECLS. (CoR: I LoE: C2)
- Neurological imaging tests may be used in the context of acute neurological change as part of the assessment for suitability for transplantation listing but should not be used in lieu of or in isolation of awake bedside assessment with the patient to ensure appropriate baseline cognitive functioning. (CoR: I LoE: C2)
- Patients considered for ECLS bridge to decision should be assessed for any significant history of illicit substance abuse, as defined by national laws, as well as undergo an assessment by an appropriate psychosocial health care professional. (CoR: I LoE: C2)
- Patients being considered for ECLS as a bridge to lung transplantation should have demonstrated an ability and/or willingness to adhere to the medical treatment regimen. (CoR: I LoE: C1)

5.12. Palliative Care Considerations

Suitability, futility, and ethics for ECMO BTT: ECMO BTT has become an increasingly viable and utilized pathway with the advent of improved BTT devices and technology, however not all lung transplant candidates are medically or psychologically suitable to have initiation or continuation of BTT therapy. Decisions regarding suitability for ECMO BTT are ideally made at the time of waitlisting and should be reassessed during the patient clinical journey with the input of the multidisciplinary team.[21,224] This is not always feasible, but efforts to garner opinion from multiple team members will facilitate optimal decision making even during emergency or crisis initiation of ECMO support. The concept of ECMO as bridge to decision is useful here, however withdrawal of ECMO support in an awake patient without the option of transplant can be harrowing for patients, their families, and staff alike. Therefore, it is advantageous to consider suitability for ECMO as early as possible.

Palliative care utilization in patients requiring ECLS for BTT has the potential to improve patient experience, care, and quality of life. The multidisciplinary team should incorporate palliative care clinicians to assist with symptom control, help facilitate decision-making, discuss patient orientated goals of care, and alleviate suffering for patients and their families.[21,226] Communication to the clinical team of patient wishes with regards their perspectives around acceptable morbidity and potential for long-term disability is of paramount importance as patients with ESLD have the potential to deteriorate rapidly and timely assessment and decision making is vital.[21] With rapid clinical deterioration, there is the potential for patients to become unable to participate in discussion and decision making about their care, including whether admission to ICU or suitability for ECMO BTT is clinically appropriate. If patients clearly do not meet criteria for ICU admission or ECLS implementation as determined by the multidisciplinary team consensus decision, then discussion about goals of care and end of life should be undertaken.

The term "futility" is used to denote the absence of benefit from interventions.[227] The purpose of ECLS is to help patients survive until recovery, either of their own accord or by receiving a lung transplant. When there is no prospect for either, ECLS becomes futile. Futility needs to be carefully assessed to allow appropriate withdrawal from ECLS. This assessment can vary among clinicians and transplant centers based on previous experience, and resource allocation, provoking extensive ethical debate.[228] To support decision making, it is necessary that specific institutions develop their own criteria to define futility to guide decision making for ECLS withdrawal, thereby allowing this challenging decision to be supported by standardized practice.

The development of non-recoverable extra-thoracic organ dysfunction and/or uncontrolled sepsis renders a patient ineligible for transplant in most centers; however other specific institutional factors may need to be considered.[6,224,226] Patients should be monitored closely for the development of ECLS related problems, the risk of which increase over time.[6] When lung transplant is no longer appropriate or likely to result in a successful outcome, it is important that the decision to withdraw ECLS is made by the clinical team with multidisciplinary input and with careful and clear communication and engagement with patients and their families. Patients may be so acutely unwell that they are unable to contribute to decisions about their medical care, and families will often lean towards more aggressive treatments in the hope of recovery or successful bridge to life-saving transplant.[229] The most common disagreements in healthcare staff regarding to patients on ECLS center around the ethics of continuation of ECLS support.[230] Given there are no clear definitions or guidelines describing when patients are in a state of futility on ECLS, involving the wider MDT from an early stage allows for relationships to be built and nurtured with family members. Clearly defined goals and time parameters are helpful for family members to see for themselves if patients are improving or not, as well as maximize patients' comfort and avoid prolonged patient suffering. The MDT are key to helping families understand and accept goals and limitations. To achieve this, early clarification of expectations, exit strategy plans, and acceptable outcomes following ECLS (which may or may not include transplantation) are necessary. The health care team must respect and sustain autonomy while being prepared to recognize futility of support. A consensus between staff, patient, and family should be the aim, and second opinions sought if conflict or disagreements arise. Ideally, end of life, ICU and ECLS discussions should endeavor to include the patient themselves, however this is not always possible and, in such cases, efforts should be made to understand an individual patients pre-morbid wishes through discussion with close family members. The use of ECLS has become more prevalent worldwide as has its utilization as a BTT strategy.[14] Many large transplant centers with high volumes of ECLS experience have developed an increasingly liberal approach to their acceptance criteria for candidate suitability for ECMO BTT.[6] Nevertheless the ongoing limited supply of donor lungs means that the ethical principles of utility and justice need to be at the forefront of decision-making when it comes to allocating lungs to recipients.[231]

Recommendations.

- The decision to put someone on ECLS as bridge to transplant should be an MDT decision in conjunction with the patient or their representative as well as the palliative care team. (CoR: I LoE: C2)
- Discussions around end of life, ICU, and ECLS should be conducted when patients are clinically stable or in a position to make decisions for themselves, preferably with key family members also present. (CoR: I LoE: C2)
- A specific institutional framework outlining key criteria of futility and subsequent withdrawal from ECLS should be developed to support decision making. (CoR: I LoE: C2)
- When patients bridged to transplant with ECLS achieve futility, withdrawal of ECLS should be primarily a clinical MDT decision with patient and family engagement. (CoR: I LoE: C2)

6. SECTION IV. PREOPERATIVE ECLS OUTCOMES AND PERSPECTIVES FOR FURTHER RESEARCH

6.1. Multicenter research and future technological focus

This section will discuss areas for development as agreed by the ISHLT Consensus Panel involved in development of this document. Specific areas include the creation of international registries for patients undergoing ECMO as bridge to lung transplant or to facilitate decision making around candidacy for transplant; guidelines for optimal cannulation approach to facilitate mobilization; research to identify optimal anti-coagulation strategies; use of point of care ultrasound; development of miniaturized ECLS circuits and novel perspectives on examination of ECMO-induced immune system dysregulation that may provoke altered susceptibility to infection and/or rejection after transplant.

ECLS as a contraindication to transplant listing: The role of ECMO strategies in the management of lung transplant recipients has evolved significantly over the last decade with developments and optimization in ECMO care. This is especially true in the context of ECLS before lung transplant. At the time of publication, current ISHLT guidelines consider ECLS before lung transplant as a relative contraindication. In the context of emerging data showing comparable outcomes for carefully selected patients, both in groups already known by their transplant center and listed for transplant, and those with ARDS who may not have been previously known to a transplant center, we strongly recommend this be reconsidered in the next iteration of ISHLT Consensus for selection of lung transplant candidates. Given the direct conflict with current ISHLT Guidelines, we have not put this through a Delphi voting process at this stage.

Registry data: Despite the increasing adoption of ECLS BTT as a rescue therapy, several critical questions regarding patient selection and associated risk factors remain unanswered. Much of the existing literature is derived from small, single-center studies, which exhibit significant heterogeneity. In contrast, large lung transplant registries such as United Network for Organ Sharing (UNOS), often lack the granularity needed for a comprehensive analysis. Their primary focus is on the outcomes of patients who were successfully bridged to transplant with ECLS,[232] while overlooking those who did not survive while waiting for a transplant. This omission excludes a key portion (20–40%) of the patient population, the denominator, which is critical for accurately assessing patient selection and optimizing the use of this resource-intensive intervention. Well-designed comprehensive international registry-based studies have the potential to address critical clinical questions and guide patient selection by including all patients with the intention of bridging them to transplant, offering insights that inform and shape clinical practice, particularly in areas where randomized trials are not feasible or practical.

Optimal cannulation approach: Ambulation and rehabilitation prior to lung transplantation are shown in independent case series as independent predictors of successful BTT.[124,128] As experience with ECLS has grown, a plethora of ambulation protocols in multiple clinical scenarios have developed.[57,233] Although rehabilitation of ECLS BTT patients is ideal for optimizing outcomes, the ability to mobilize is often constrained by the severity of critical illness alongside cannulation strategy. Even with the availability of hybrid ECLS configurations tailored to physiological needs, achieving meaningful rehabilitation can be challenging. High-volume centers that employ comprehensive protocols and innovative strategies, such as bilateral pneumonectomies, central VA ECMO and PA-LA Novalung approaches, have effectively bridged patients despite these obstacles, achieving long-term outcomes comparable to non-bridged patients.[234,235] However, whether these approaches are generalizable to lower-volume programs is not known. The development of guidelines to support decision-making around cannulation approach to optimize mobilization before transplant is highly desirable to facilitate optimal outcomes for ECMO BTT patients.

Anti-coagulation strategies: Anticoagulation is recommended with ECMO to prevent thrombotic events. The non-endothelialized circuit triggers proinflammatory and hemostatic responses causing thrombus formation, which may necessitate ECMO circuit exchange and cause ischemic complications.[76,236] The aim is to prevent thrombosis of the ECMO circuit while limiting bleeding risks for the patients. The 2021 ELSO Adult and Pediatric Anticoagulation Guidelines have associated both hemorrhage and thrombosis with increased morbidity and mortality in ECMO patients.[93] We recommend that future studies are needed to define and further characterize significant bleeding during ECMO therapy, to identify thrombotic events which necessitate ECMO circuit change and identify downstream impact on longer-term patient outcomes. Identification of novel cellular damage biomarkers and biomarkers associated with thrombosis and bleeding complications would improve early diagnostics and therefore impact care. Additional research to develop specific heparin infusion, monitoring

protocols, and anticoagulation algorithms, as well as studies to identify new anticoagulant drugs that are easily reversible, easily monitored and do not activate an unfavorable immune response are required.

POCUS: The utilization of point of care ultrasound (POCUS) in the placement and management of ECMO patients has been discussed extensively in the literature.[237] A single-center retrospective study examined the impact of a structured POCUS-guided management of ECMO, that while more focused on the cannulation stage, showed that a standardized approach may prove to have some benefit in the management of ECMO patients.[238] All phases of ECMO management, from pre-cannulation cardiopulmonary and vascular screening, cannulation guidance, or post-placement monitoring have been described for both VA and VV ECMO.[237] A potentially serious complication carrying a morbidity burden during prolonged BTT support is the increased risk of the development of thrombosis in the cannulae, which may impact overall ECMO flows and function. While there have been reports of TEE utilized in identifying thrombosis impacting ECMO flows,[239] the invasive nature of this monitoring procedure combined with need for sedation and user expertise decrease its practical utility in preoperative BTT patients. As such, POCUS is an important non-invasive adjunct for the ongoing monitoring of ECMO cannulae position, as malposition of the cannulae has been shown to increase the risk of cannula tip thrombosis in both VA and VV ECMO.[240,241] It is recommended that POCUS be incorporated into routine practice by the multidisciplinary team, with structured exams focused on surveillance of cannulae position and thrombosis. POCUS may be utilized by physicians and non-physicians alike during their ongoing management of these patients.

Miniaturized ECLS systems: Pre-transplant support by ECMO showed similar or better outcomes than mechanical ventilation (MV).[31,242] However, long-term ECMO is challenging and ECMO devices are cumbersome and complex. Patients are commonly bedridden, thereby resulting in muscular atrophy leading to negative impact on long term outcomes.[243] The recent development of dual lumen canula (Avalon-Elite, Getinge AB, Goteborg, Sweden & Crescent, Medtronic, Minneapolis, USA) allow single site cannulation and therefore patient ambulation.[244,245] Patient mobilization and physical rehabilitation with ECMO shows improved posttransplant results.[70,246] Although ECMO devices are not miniaturized and non-portable, ambulation during ECMO is used in only 22 to 34% of centers.[247,248] Miniaturized oxygenator devices are currently in evaluation and showed promising results in term of mobility and long-term use.[249–251] Research focusing on miniaturized ECLS devices allowing patient ambulation and in-hospital rehabilitation need to be pursued.

Immunological impact of ECMO: Pro-inflammatory responses and SIRS are common in the setting of ECMO.[107,252] VA ECMO in non-transplant patients is associated with a significant increase in circulating immature neutrophils, a decrease in C5a receptor expression, lymphocyte dysfunction and expansion of myeloid-derived suppressor cells alongside increases in proinflammatory cytokines such as interleukin (IL)–6, IL-8, tumor necrosis factor (TNF)-α and IL-10.[253] ECMO patients are very prone to infections.[107] ECMO in transplant patients has been associated with primary graft dysfunction (PGD), donor specific antibodies, HLA-sensitization, and antibody-mediated rejection.[254–256] However, the immune mechanisms underlying these clinical phenomena have not been identified. Much research is required in the transplant setting to determine the immune and cellular perturbations underlying the immune dysfunction that occurs in transplant patients on ECMO.

Recommendations.

- An ISHLT registry examining BTT ECLS variables to define optimal patient selection criteria and factors that influence transplant outcomes should be developed. (CoR: I LoE: C2)
- Guidelines for novel cannulation strategies to optimize mobilization and engagement in physical rehabilitation should be established. (CoR: I LoE: C2)
- Research examining minimal anti-coagulation strategies and the monitoring of thrombus formation within the ECLS circuit should be pursued. (CoR: I LoE: C2)
- Future research should focus on the development of point of care ultrasound (POCUS) standards for ongoing ECMO assessment during BTT, including routine screening of cannulae thrombosis by echocardiography. (CoR: I LoE: C2)
- Research examining the future development of miniaturized ECLS systems that would facilitate mobilization of patients and promote rehabilitation potential should be pursued. (CoR: I LoE: C2)
- Research examining ECMO induced changes in the immune system to increase the risk of infection should be pursued. (CoR: I LoE: C2)

7. SECTION V. CONCLUSION

The preoperative ECLS management of lung transplantation patients has significantly changed since the first lung transplantation BTT with ECMO in 1977. Over time the evolution of management has been progressed through the efforts of multiple medical disciplines, often driven more by expert opinion than rigorous data. The multidisciplinary nature of this consensus statement adds significant weight to the expert opinion achieved, but it is our hope that these statements form the foundation of future scientific investigations of these diverse topics within the preoperative utilization of ECLS in lung transplantation.

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APPENDIX A. SUPPORTING INFORMATION

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