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International consensus recommendations for anesthetic and intensive care management of lung transplantation. An EACTAIC, SCA, ISHLT, ESOT, ESTS, and AST approved document

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Abbreviations: 6MWD, 6-minute walking distance; AKI, acute kidney injury; ANA, anti−nuclear antibody; ANCA, anti−neutrophil cytoplasmic antibody; AST, American society of transplantation; BMI, body mass index; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; BOS, bronchiolitis obliterans syndrome; CAD, coronary artery disease; cf, cystic fibrosis; CKD, chronic kidney disease; CMV, CytoMegalo virus; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CPET, cardiopulmonary exercise test; DAS, duke activity status; DLCO, diffusion capacity of the lung for carbon monoxide; DM, diabetes mellitus; EACTAIC, European association of cardio-thoracic anesthesiologists and intensive care; EBV, Epstein barr virus; ECMO, extra-corporeal membrane oxygenation; eGFR, estimated Glomerular filtration rate; ENA, extra nuclear antigen; ESOT, European society for organ transplantation; ESTS, European society of thoracic surgeons; FFP, fried frailty phenotype; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HRQL, health-related quality of life; IPF, Idiopathic Pulmonary Fibrosis; ISHLT, International society for heart & lung transplantation; JHLT, journal of heart and lung transplantation; KPS, Karnofsky performance scale; LAS, lung allocation Score; LTx, lung transplantation; LV, left Ventricular; MDT, multi-disciplinary team; MET, metabolic equivalent task; MRI, magnetic resonance imaging; NTM, non−tuberculous mycobacteria; PAH, pulmonary arterial hypertension; PGD, primary graft dysfunction; PVR, pulmonary vascular resistance; RCRI, revised cardiac risk index; RFT, respiratory function test; RV, right ventricular; SCA, society of cardiovascular anesthesiologists; SF-36, short-form health survey; SPPB, short physical performance battery; V/Q, ventilation/perfusion.

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Lung transplantation (LTx) is an established therapy with major current limitations

For patients with end-stage lung disease, LTx remains the only therapeutic option toward better chance of survival as well as improved quality of life. According to the International Society for Heart and Lung Transplantation (ISHLT) Transplant Registry, the number of LTx procedures has been rising despite limitations in available and suitable donor lungs and in the face of persistent donor shortages.[1] The modern era of LTx is characterized by increasing complexity of recipient candidates including those receiving bridging extracorporeal support, a trend toward acceptance of suboptimal or extended criteria donors, and increasingly complicated surgical strategies.[2] Despite these adverse conditions, contemporary survival figures for LTx continues to improve, especially considering the early period after LTx.[1,2]

While these achievements are remarkable and only possible by pushing the limits of what is conceivable, the procedure remains associated with high perioperative morbidity and mortality and the lowest long-term survival of all solid organ transplants. The leading cause of perioperative mortality, remains primary graft dysfunction (PGD).[3-8] Registry data and recent randomized clinical trials conducted with the involvement of the leading transplant centers identify nearly 30% prevalence of severe allograft dysfunction with important influence on patient recovery, allograft quality, long term survival and quality of life.[9] Beyond PGD, surgical complications account for approximately 10% of the perioperative mortality and infections are responsible for another 20%. Moreover, there is increasing evidence that in-hospital, extra-pulmonary complications comprising mainly of renal, cardiac, hepatic, and vascular adverse events are nearly ubiquitous and impact negatively on long-term outcomes.[10,11] As only a fraction of

these complications can be explained by recipient and donor risk factors, there is increasing focus on adverse events and procedural influences during the perioperative period. This endeavor has identified potentially modifiable perioperative risks that provides novel opportunities for improved anesthesia and intensive care management strategies.[12]

Justification for a paradigm change

Such analysis of the state of art highlights the need for anesthesia and intensive care specialties to foster an enhanced role in the entire process of LTx and to take clearer ownership of the total morbidity burden and failure to strive following LTx. It also calls for ongoing critical appraisal of our management goals and for constant quality improvement to understand and exploit new strategies to reduce complications, to enhance patient's perioperative journey and to improve both short- and long-term survival of lung transplant recipients.[13-18] This redefined role has major implications for our specialties in pushing the boundaries of super specialization in transplant anesthesia and intensive care and also with regard to closer team working with the surgical and respiratory teams from the time of patient listing through the transplant operation and postoperative ICU stay.[19,20]

Building a consensus framework

These worldwide trends have been considered by the Transplant Subcommittee of the European Association of Cardiothoracic Anesthetists (EACTA), which represents a distinctive international subspecialty group of cardiothoracic anesthetists and critical care physicians delivering perioperative care for lung transplants recipients. By developing a European (and increasingly worldwide) network that recently conducted one of the first practice surveys in perioperative management of lung transplantation, we have realized that there were significant variations in anesthetic and intensive care practice of LTx and a lack of international guidelines to benchmark such practice.

For instance, the International Guidelines for the Selection of Lung Transplant Candidates in 1998 and subsequent updates in 2006 and 2014 by International Society for Heart and Lung Transplant (ISHLT) focus exclusively on the medical selection criteria for transplantation.[21-23] While these guidelines consider patients with various respiratory diseases, physical status, and comorbidities they do not include any major anesthetic considerations. Although the ISHLT Primary Lung Dysfunction Working Group reports from 2005 (and the 2017 updates) are helpful in terms of definition, risk factors and outcomes and relevant in terms of postoperative treatment of PGD, it is specific for this complication, and does not address other important perioperative management issues.[5-7,24,25] Finally, The Cystic fibrosis guideline by the ECORN-CF Study Group is a comprehensive review of preoperative and late postoperative issues with some discussion on surgical approaches but lacks any anesthetic, early postoperative, and intensive care content.[26] Furthermore, it is specific to the unique condition of cystic fibrosis.

Significant variations in practice of lung transplantation worldwide,[27,28] diverse concepts from scattered opinion papers[13,16-18,20,29-35] and the lack of comprehensive society backed recommendations prompted the leadership of the EACTA Transplant Subcommittee to initiate the first expert consensus process specifically dedicated to the anesthetic and intensive care management of lung transplantation. The overall goal was to mobilize the worldwide transplant network toward a consensus on the entire spectrum of clinical issues associated with perioperative management of lung transplantation. This has focused on the patient journey from preoperative evaluation to intensive care discharge to highlight significant clinical dilemmas in anesthesia and critical care practice at every stage. A related but independent goal was to discuss and develop a scientific academic agenda to tackle the current limitations and new controversies in perioperative management of LTx.

To ensure a wide consensus base, we invited the leadership of nearly all subspecialty committees of EACTA, from thoracic anesthesia to hemostasis to amalgamate their expertise in predefined areas of lung transplantation and ultimately achieve the first EACTA subcommittee cooperation on clinical aspects of LTx. We also built a multi-society collaboration with the Society of Cardiovascular Anesthesiologists (SCA), ISHLT and other international societies with an interest in lung transplantation and identified international leads to chair the consensus recommendation process. Consequently, the consensus process and the resulting documents were developed through the collaborative efforts of EACTA, SCA, ISHLT, the European Association of Cardiothoracic Surgeons, the European Society of Thoracic Surgeons, the European Society of Organ Transplantation and the American Society of Transplantation. The project was designed to deliver consensus statements rather than formally graded clinical guidelines from the outset as available literature is overwhelmingly comprised of observational studies, case series and individual opinion statements, thereby representing low-quality evidence.

Under the auspices of and recommendations by the collaborating societies, a multidisciplinary, multi-institutional expert panel was convened (>80 delegates), incorporating expertise from anesthesia, intensive care medicine, lung transplant surgery, pulmonary medicine, pharmacology and nursing representing approximately 50 leading international lung transplant centers with an accumulated senior clinical experience of over 1,000 years and several thousand lung transplant procedures. Members of the management committee of the Transplant Subcommittee of EACTA, and named delegates from each collaborating society comprised the ultimate leadership (Consensus Developing and Coordinating Group, CDCG) of the consensus process. The overall framework, consensus strategy and initial scope of the individual Task Forces were discussed at our first face to face meeting at the Gothenburg EACTA meeting in 2015. Members of the consensus project were divided into 11 task force subgroups, each specifically focusing on one of the following general or more specific areas: preoperative evaluation, monitoring, intraoperative management, pulmonary hypertension and inotropic support, role of transesophageal

echocardiography, primary graft dysfunction, perioperative bleeding, mechanical support, general intensive care management, postoperative pain and specific aspects of pediatric lung transplantation. Task Forces were asked to identify any relevant clinical dilemmas in their domains and to provide specific recommendations for these issues. They were asked to perform a thorough review of the literature, consider relevant published evidence, institutional policies, national and international surveys to reach a consensus within the group. The organization of the consensus project and membership of the Task Forces are detailed in Appendix 2. Summary of the Conflict-of-Interest statements of members is listed under the disclosure statement.

This was followed by rigorous subgroup discussions, Task Force teleconferences and review of on-line submissions by members on subtopics. Progress and publication strategy were further reviewed at a specially convened meeting at the 2016 EACTA conference in Basel to collate the recommendations and provide feedback to the Task Forces. After further deliberations, an open symposium was organized at the Berlin EACTA meeting in 2017, where the most significant preliminary recommendations were presented to the wider EACTA and congress membership to seek further consensus and feedback. The Task Force recommendations were then finalized and approved by the CDCG for anonymous online voting by the entire membership of the consensus project. This was completed by 76 members from the consensus delegate body representing more than 50 institutions involved in lung transplantation in all 5 continents. Members expressed their agreement on all the Task Force recommendations anonymously using Survey Monkey on a graded 0 to 100-point scale (0%-20%, 21%-40%;41%-60%;61%-80%; 81%-95% and above 95% agreement). After averaging, a total score above 70 points was considered an agreed consensus, above 80 points a strong consensus and above 95 points was considered a full consensus. We asked members to justify their opinion in writing if they expressed disagreement (0%-20%) regarding a particular recommendation. Recommendations achieving majority consensus were incorporated into this executive summary toward publication in Journal of Heart and Lung Transplantation (JHLT), while all recommendations together with their full justification and with the anonymous comments of voting members were assembled into individual Task Force reports as manuscripts to be submitted to Journal of Cardiothoracic and Vascular Anesthesia (JCVA) as the official EACTA society journal. These draft documents were then subjected to predetermined peer review by a committee of external experts representing independent delegates of the collaborating societies. In addition, they were open for public review and comments by the relevant membership of these societies. The final manuscripts were then reviewed by the appropriate Standards and Guidelines Committees of the collaborating societies and approved by their Board of Directors.

These recommendations thus represent the first global, multidisciplinary and multi-society approved consensus on anesthetic, and intensive care clinical management of lung transplantation. While we hope these recommendations provide significant guidance for the practicing clinicians in nearly every domain of transplant, there has been 2 significant departures from the stated initial goals. Firstly, despite various leadership changes in the Pediatric Lung Transplant Task Force, the group has not been able to deliver a comprehensive set of recommendations. Thus, ultimately our scope is restricted to ADULT lung transplantation. Secondly, parallel to these activities, the ISHLT also reconvened the 2005 PGD Task Force, which has recently delivered their comprehensive revision into the definition, mechanisms, prevention and principal management of PGD.[5-7,36] In the light of these developments and to avoid repetition, our review of this important topic was concentrated primarily on the impact of anesthesia and intensive care with a focus on potentially modifiable perioperative factors. Moreover, taking advantage of strong surgical representation among the consensus delegates, we have established a Task Force for reviewing, and developing a comprehensive description of surgical complications.

Redefining the perioperative management goals for lung transplantation

While the consensus documents crystallize many established concepts and express expert opinion on various emerging models of care, perhaps the most germane outcome is the paradigm shift in the philosophy and scope of anesthetic and intensive care management which has parallels with recent trends in general anesthetic profession toward broader perioperative medicine and enhanced recovery.[37]

With such intention, the consensus group recommends an extended, holistic and comprehensive role for anesthesia/intensive care for the entire perioperative period commencing with more active involvement in recipient evaluation, listing and preoperative assessment. By recognizing that PGD is a primarily a medical rather than surgical complication, and the ripple effects of postoperative morbidity burden on outcomes,[10,11] the consensus group has also redefined the perioperative goals of management by recognizing a trend away from purely technical aspects of anesthetic care and embracing a broader concept of allograft and multiorgan protection. These now focus explicitly on preservation of allograft quality, maintenance of cardiovascular stability and prevention of extrapulmonary complications. The same applies for intensive care and anesthesia management of the lung donor, but these concepts are being considered in updated donor management guidelines.

It is hoped that the new mission statement will mobilize the anesthetic and critical care community to discover and exploit new opportunities to improve upon PGD, perioperative systemic organ dysfunction, postoperative morbidity and thereby positively influence long-term survival. On the more holistic aspects, we also aim to ensure patient comfort and enhance the patient journey from the time of listing through to transplant and intensive care stay toward an expedited and full recovery.

Table 1 highlights these broader management goals and lists examples of extended tasks and means to achieve these goals. These are detailed in subsequent sections by the various individual Task Force recommendations.

Table 1

1. To facilitate enhanced patient journey and to ensure patient wellbeing for the entire duration of the transplant period
   - Taking more active part in MDT discussions by focusing on patient evaluation during listing of referred patients
   - Extended anesthetic preassessment with specific emphasis on perioperative implications, highlighting risks for the development of PGD and extrapulmonary complications.
   - Reducing waiting list anxiety by thorough discussions of the predicted perioperative patient journey.
   - Leading intensive care management (ICU) of patients bridged to lung transplantation
   - Reducing preoperative patient anxiety and facilitating family support/comfort before transfer to the operating room
   - Improving team efforts in conducting the transplant operation and leading multidisciplinary teams toward enhanced recovery
   - Ensuring adequate depth of anesthesia and by eliminating awareness.
   - Providing adequate postoperative analgesia for patient wellbeing, to facilitate physiotherapy, early extubation, mobilization and expedited transfer from ICU to transplant wards.
   - Reducing hospital stay, improving short and long-term survival, allograft function and quality of life of the recipient.
2. To take ownership of perioperative medical complications and to optimize perioperative management toward improving the quality of the allograft and reducing total burden of postoperative complications.
   - Safe induction and maintenance of anesthesia by ensuring adequate gas exchange, hemodynamic stability, Oxygen delivery for end organ protection.
   - Facilitating surgical performance by accurate lung isolation, promoting minimally invasive strategies, responding promptly to surgical manipulations, bleeding, and technical problems.
   - Protecting graft function by promoting off pump implantation and optimizing mechanical support when necessary.
   - Attenuating pulmonary and systemic inflammatory response and optimizing metabolism.
   - Employing protective ventilation and reperfusion strategies.
   - Instituting all efforts for conservative management of PGD and implementing early mechanical support if appropriate.
   - Preventing extrapulmonary postoperative complications by ensuring hemodynamic stability and end organ Oxygen delivery throughout.
   - Reducing infection by employing strict asepsis throughout, adequate antibiotic cover and aggressive bronchial toilet before and during pneumonectomy and following implantation of the allograft
   - Actively participating in ex vivo lung perfusion, evaluation and reconditioning of marginal lung allografts and by facilitating transplantation and preservation of recovered lungs

Limitations

This consensus paper has important limitations in its intention, the format of the publication, and regarding bias. In particular, it contains no new original research in the field of lung transplantation. Instead it presents as a consensus project resulting in the current executive summary and ten reviews by the established Task Force subgroups on main aspects of LTx. Although we surveyed worldwide practices as a pelude to the current consensus statement, we decided not to commission new systematic reviews or original research. Our experience is that metaanalysis of low-quality observational studies and small clinical trials usually generates a low-quality conclusion with important imitations. Instead we have recruited a large, diverse and leading membership and developed a consensus on most important aspects of perioperative management. A degree of bias in selecting the consensus membership is unavoidable and also identifying the main practice dilemmas and their solutions. This was balanced by the unique consensus group uniting multiple specialties and the unusually large number of experts and the direct involvement of nearly all relevant societies. We have also balanced the special interest Task Force groups by the review process of the whole membership and practiced full transparaency in publishing the individual anonymous views and comments beyond group recommendations in the detailed Task Force manuscripts.

Our recommendations fall short of legally binding clinical guidelines. In setting up the consensus project, we have considered if there was sufficient high quality evidence for clinical practice guidelines with definite RCT and systematic reviews of clinical trials on practical aspects. Our assessment suggested that this was not the case and most areas remain controversial. Hence our approach intentionally focused on consensus development from the outset. We hope that our consensus correctly presents a snapshot, where perioperative management of LTx currently stands as a useful guidance to clinicians at every level of their expertise. We strongly believe that these recommendations provide some important practical guide to juniors, the novice and infrequently involved lung transplant anesthesiologist and critical care physician and to programs who just start LTx. It also provides some alternative approaches to centere with strong history and large volumes. Beyond the practical recommendations our ambitious new mission has a huge chance to change attitudes, responsibilities, and to some degree accountabilities for postoperative outcomes.

Another limitation is the long development phase of the consensus and the duration of external review and approvals by the various societies involved. While our consensus documents were under review, there has been some important developments in relevant areas by other societies. For instance, EACTS/EACTAIC has published their project on Patient Blood Management in Cardiac Surgery and the Blood Conservation in Cardiac Surgery Working Group of the SCA developed a best practice advisory summary and algorithms.[38,39] However, these practice guidelines are based on more general cardiovascular surgery and specialist fields such as LTx received less attention. Similarly, The

AST has recently updated their Transplant Infectious Diseases Guidelines (Fourth Edition).[40] This reinforces the benefit of strong communication within the transplant team, including input from transplant infectious disease and transplant pharmacy team members to enhance the care of these complex patients. These recommendations resonate with our conclusions and new mission statements. As practice in these areas continues to evolve, we offer these practice guidelines as a resource to the transplant community.

Future implications

This consensus project has important future implications for monitoring the impact of the proposed changes and adherence to our extensive recommendations both in terms of clinical uptake and possibly considering regulatory options. We believe the current consensus provides an excellent framework for further international dialogue. Organisations, academic networks and special interest groups can take our current recommendations and decide to validate these in prospective studies or challenge our conclusions and design appropriate high-quality clinical trials. On this basis we anticipate generation of strong new evidence in the next few years. To serve these developments, the consensus group has also mandate to define research priorities as a second goal beyond the clinical recommendations. Thus, we intend to shape the research agenda in the future and to review new scientific and clinical evidence and perhaps revisit and upgrade the current consensus to clinical practice guidelines in 5 years time.

1. Preoperative assessment and planning the perioperative patient journey

1. Recommendations for preoperative anesthesia and intensive care mission.

Anesthesiologists and intensivists are integral members of the multidisciplinary team assessing a patient's suitability for transplantation with specific emphasis on perioperative implications and risks for the development of primary graft dysfunction (PGD) and extra-pulmonary complications.

Strength: strong consensus

Score: 93%

Anesthetic preassessment should include an evaluation of fitness for transplant surgery/anesthesia, appraisal of existing comorbidities, and identifying opportunities to improve perioperative care.

Strength: strong consensus

Score: 93%

2. Recommendations for patient selection

Based on preoperative multidisciplinary evaluation, lung transplantation should not be considered in a patient with advanced, uncontrolled or non−reversible medical conditions, continued addictive behavior, or lack of reliable social support.

Strength: strong consensus

Score: 91%

Relative contraindications to lung transplantation should take into consideration individual center volume and multidisciplinary expertise including anesthesia and intensive care in managing higher risk patients with advanced age and increased comorbidities.

Strength: strong consensus

Score: 90%

As part of the multidisciplinary team, anesthesiologists and intensivists should assist in the identification and selection of potential urgent lung transplantation candidates.

Strength: strong consensus

Score: 87%

Anesthesiologists and intensivists should help conditioning hospitalized patients especially those receiving mechanical ventilation by optimizing cardiopulmonary status, and by promoting pulmonary rehabilitation and physical exercise programs.

Strength: strong consensus

Score: 91%

Lung transplantation may be associated with severe postoperative early and late pulmonary and extra-pulmonary complications and persistently and unacceptably high morbidity and mortality. Anesthesiologists and intensivists should help identify potentially modifiable pre- and perioperative risk factors for these complications and implementing strategies to minimize postoperative mortality and morbidity.

Strength: strong consensus

Score: 91%

3. Recommendations regarding disability, frailty and rehabilitation

Beyond chronological age and established co-morbidities, patient disability and frailty are considered independent risk factors for increased complications on the waiting list and for poor outcomes after transplantation.

Strength: strong consensus

Score: 93%

Disability, functional status and exercise capacity of the lung transplantation candidate should be estimated and assessed preoperatively using a combination of appropriate questionnaires (e.g., KPS, SPPB, FFP, MET) and the 6MDW, quadriceps strength, hand grip and short battery tests. Interventions to improve upon the frailty status should be considered in frail patients before lung transplantation listing.

Strength: strong consensus

Score: 90%

Pulmonary rehabilitation should be continued or started in patients being assessed for lung transplantation, particularly those with impaired functional status.

Strength: strong consensus

Score: 94%

4. Recommendations for perioperative planning according to recipient pathology

Beyond pulmonary issues of airflow limitations and static hyperinflation (residual volume to total lung capacity) and recent infections, anesthetic assessment of COPD patients should focus on functional limitations. Most transplants can be completed without mechanical circulatory support and intraoperative ventilation should be tailored to avoid dynamic hyperinflation while optimizing venous return, pulmonary hemodynamics, and right ventricular dysfunction.

Strength: strong consensus

Score: 90%

Patients with end stage restrictive lung disease pose many challenges both for waiting list management and the perioperative period. Their restrictive physiology pattern requires unique ventilation strategies with higher risk of planned or emergency extracorporeal respiratory and circulatory support. Surgery could be more complicated and prolonged with compromised postoperative graft function.

Strength: strong consensus

Score: 89%

Patients with idiopathic pulmonary hypertension represent some of the most challenging population for perioperative management. Right ventricular failure at any phase of surgery is possible and requires implementation of extensive hemodynamic monitoring, aggressive vasoactive management, and timely planned mechanical support. Planned prophylactic ECMO is increasingly employed as a management strategy to minimize cardiopulmonary decompensation during anesthesia and to attenuate the risk of primary graft dysfunction in high-risk pulmonary hypertension patients.

Strength: strong consensus

Score: 88%

Pulmonary infection with multi-resistant and unique organisms represents the most important perioperative limitations of lung transplantation in cystic fibrosis patients with important implications to the technical conduct of airway management and ventilation requirements. Nutritional supportive and rehabilitative interventions should be planned and monitored. The full spectrum of anti−infection strategies should be planned preoperatively, including the most effective antibiotic cover, asepsis, and aggressive bronchial toilet. Measures to avoid cardiopulmonary bypass need to be implemented to control/prevent sepsis, vasoplegia and hemodynamic instability. Previous thoracic surgery, especially pleurodesis represents additional surgical risks for increased bleeding, blood transfusion, increased incidence of PGD, and renal complications.

Strength: strong consensus

Score: 87%

5. Recommendations for cardiovascular assessment

Pretransplant cardiovascular assessment should include clinical risk stratification according to the ACC/AHA and ESC/ESA guidelines.

Strength: strong consensus

Score: 88%

A coronary angiogram and carotid Doppler ultrasound are recommended in patients older than 50 years and in younger patients with increased cardiovascular risk factors, those with poor aerobic capacity and/or a positive stress test.

Strength: strong consensus

Score: 88%

Right heart catheterization and/or cardiac MRI is recommended in patients with known pulmonary hypertension and impaired right or left ventricular function.

Strength: strong consensus

Score: 93%

Interventional myocardial revascularization is preferentially scheduled before lung transplantation in suitable patients with significant coronary artery disease. Alternatively, concomitant coronary revascularization, and lung transplantation can be performed with acceptable perioperative outcome.

Strength: agreed consensus

Score: 76%

6. Recommendations regarding renal evaluation and renal protection

Pretransplant assessment should include clinical risk stratification for the development of postoperative acute kidney injury.

Strength: strong consensus

Score: 90%

Preoperative renal assessment should include measurement of serum creatinine concentration to estimate basal glomerular filtration rate (based on MRD equation) and a reference value to document changes induced by lung transplantation and immunosuppressive treatments.

Strength: strong consensus

Score: 89%

Modifiable risk factors (obesity, diabetes, hypertension, physical activity, nephrotoxic drugs) should be identified and whenever possible optimized before listing or/and while on the waiting list. The major impact of renal dysfunction on lung transplantation outcomes warrants close collaboration with a nephrologist in the evaluation of patients with reduced eGFR to optimize all the reversible causes. This may include special diagnostic measures such as renal US and hemodynamic optimization to increase GFR.

Strength: strong consensus

Score: 89%

A perioperative renal protection plan should be developed aiming to reduce the likelihood or attenuate the severity of postoperative acute kidney injury. These include minimization of renal insults such as prolonged hypotension, renal hypoperfusion, and hypoxemia. The timing of and exposure to potential nephrotoxic drugs including immunosuppression and antibiotics should be carefully considered and planned.

Strength: strong consensus

Score: 92%

Lung transplantation of patients with high risk for the development of acute kidney injury should preferentially be performed in high volume centers since chronic impairment in renal function influences long term survival.

Strength: strong consensus

Score: 81%

7. Recommendations for preoperative anesthetic visit/consent and premedication

Following anesthetic evaluation, consent for anesthesia should be documented either as part of the general lung transplantation listing consent or as a standalone anesthetic consent. The consent should include general anesthesia, central venous access including pulmonary artery catheters, transesophageal echocardiography, thoracic epidural in the setting of deranged coagulation, urinary catheterization and

potentially prolonged mechanical ventilation, and intensive care stay.

Strength: strong consensus

Score: 90%

A preoperative visit on the day of the transplant is mandatory by the actual anesthetic team performing the transplant. This visit is vital in integrating all of the information gathered during listing, identifying physiologic and clinical changes while on the waiting list, as well as alleviating patient anxiety and discussion of operative, and postoperative plans. Additional consent issues should be documented to cover those areas not specified in the transplant consent pending institutional practices and the preferences of the senior anesthetist attending the transplant.

Strength: strong consensus

Score: 91%

As premedication is largely contraindicated, alleviating patient anxiety preoperatively through reassurance and building rapport by all multidisciplinary team members is essential particularly utilizing the help of a trusted coordinator and supporting family members.

Strength: strong consensus

Score: 91%

2. Monitoring

1. Recommendations for hemodynamic monitoring

Basic cardio-respiratory and metabolic monitoring (ECG, NIBP, SpO_2, $etCO_2$, temperature) should be used for all patients undergoing lung transplantation. In the setting of peripheral VA-ECMO the right upper limb, ear or nose is the preferred site for continuous SpO2 monitoring.

Strength: strong consensus

Score: 89%

Perioperative invasive arterial blood pressure monitoring should be used in all patients undergoing lung transplantation with the right upper limb representing the preferred option to limit the risk of unrecognized differential hypoxia in the setting of peripheral VA-ECMO.

Strength: strong consensus

Score: 92%

Perioperative pulmonary artery catheterization should be used in patients undergoing lung transplantation to facilitate measurement of central venous pressure and pulmonary artery pressures and to provide central venous access.

Strength: strong consensus

Score: 88%

Perioperative monitoring of cardiac output may be useful in patients undergoing lung transplantation.

Strength: strong consensus

Score: 87%

Dynamic markers of preload are not recommended to guide perioperative fluid administration in patients undergoing lung transplantation.

Strength: agreed consensus

Score: 78%

Perioperative monitoring of $ScvO_2$ and/or $SmvO_2$ may be useful in patients undergoing lung transplantation.

Strength: strong consensus

Score: 85%

Recommendations for imaging and hemodynamic monitoring using transesophageal echocardiography (TEE) is listed at various stages of perioperative management.

2. Recommendations for respiratory and gas exchange monitoring

Measurement of airway resistance and compliance is reasonable for patients undergoing lung transplantation.

Strength: strong consensus

Score: 85%

Frequent perioperative monitoring of arterial blood gases and other point-of-care biochemical parameters including sodium, potassium, hemoglobin, glucose, and ionized calcium is recommended for patients undergoing lung transplantation.

Strength: strong consensus

Score: 94%

3. Recommendations for monitoring anesthetic agents and depth of anesthesia

Where a volatile agent is used, intraoperative end-tidal agent monitoring (ETAg) may be useful in patients undergoing lung transplantation. However, the relationship between measured ETAg and volatile anesthetic agent concentration in the brain may be abnormal in this setting, potentially providing misleading quantitative information.

Strength: strong consensus

Score: 85%

Intraoperative depth of anesthesia monitoring should be used in patients undergoing lung transplantation.

Strength: strong consensus

Score: 82%

4. Recommendations for organ function assessment

Urine output monitoring may be useful in patients undergoing lung transplantation.

Strength: strong consensus

Score: 91%

Intraoperative cerebral oximetry monitoring may be useful in patients undergoing lung transplantation.

Strength: agreed consensus

Score: 79%

3. Limited recommendations for donor aspects and ex vivo perfusion

An acceptable donor predicted total lung capacity ratio should be decided upon by a multidisciplinary transplant meeting before listing after consideration of the planned procedure and native lung disease.

Strength: strong consensus

Score: 85%

Anesthetists and/or intensivists should take special interest and be an integral part of the ex-vivo lung perfusion team to maximize expertise regarding optimal ventilation and perfusion strategies along with assessment of specific and global lung functions and to facilitate decision making regarding transplantation.

Strength: strong consensus

Score: 88%

Mechanical ventilation (MV) with high tidal volume (>8 mL/kg) and high inspiratory pressures (>25 cmH_2O) should be avoided at any phase of lung transplantation including

donor management, ex vivo lung perfusion, intraoperative and postoperative MV.

Strength: strong consensus

Score: 94%

For the donor, a low tidal volume strategy together with strict supportive measures to avoid atelectasis and lung collapse should be implemented including higher PEEP in the range of 8 to 10 H_2O, regular recruitment maneuvers, CPAP during apnea test and close circuit suctioning.

Strength: strong consensus

Score: 90%

4. Extracorporeal support for bridging the lung transplant candidate

ECMO support should be considered for patients who present with a rapid deterioration of their end stage lung disease with therapy-refractory hypoxemia and hypercapnia with respiratory acidosis despite maximum non−invasive mechanical ventilatory support.

Strength: strong consensus

Score: 91%

Mechanical ventilation should be avoided, and awake and extubated patients should be preferred during ECMO support.

Strength: strong consensus

Score: 87%

Extracorporeal bridging therapy should be restricted to patients who have been successfully listed before ECMO initiation

Strength: agreed consensus

Score: 79%

ECMO support should be avoided in patients who present with complications such as renal and liver failure, severe neurologic complications, and sepsis

Strength: strong consensus

Score: 86%

5. Intraoperative management

1. Recommendation for paradigm change in anesthetic management

By embracing the trend away from purely technical aspects of anesthesia toward the broader concepts of perioperative medicine and enhanced recovery, and by taking better ownership of postoperative complications, the goals of intraoperative management should focus on preservation of allograft quality, maintenance of cardiovascular stability, and prevention of extrapulmonary complications.

Strength: strong consensus

Score: 94%

2. Recommendations for surgical aspects

The surgical strategy including the type of incision and sequence of pneumonectomy and implantation (in the case of bilateral transplantation) needs to be clearly discussed between the surgeon and anesthetists before transplantation. This discussion needs to take preoperative assessment, physiologic findings, and the ability to tolerate single-lung ventilation into consideration.

Strength: strong consensus

Score: 93%

"Minimally invasive" lung transplantation using bilateral anterior thoracotomies requires special knowledge, skills, and experience for both surgeon and anesthetist. Such a program should only be implemented after successful training and sign off.

Strength: Strong consensus

Score: 91%

3. Recommendations regarding preparation for anesthesia

Sedative premedication outside of the operating room is best avoided in lung transplant recipients especially those who require supplemental oxygen therapy or have significant pulmonary hypertension. Sedative premedication should only be given with extreme caution and under strict supervision even in the operating room.

Strength: strong consensus

Score: 93%

Planning and coordination of commencing an aesthesia should take into consideration center and surgeon specific practices and in general, should aim to minimize ischemia time, especially in the setting of unfavorable recipient/donor characteristics.

Strength: strong consensus

Score: 93%

Appropriate time should be allocated for potentially difficult peripheral venous access, challenging airways, and surgical complexities.

Strength: full consensus

Score: 96%

Airway anatomy should be fully examined, including CT images, if necessary, to evaluate for difficult ventilation/intubation. If difficulty is anticipated, one should be totally prepared to avoid delays in securing the airway which may lead to detrimental hemodynamic consequences.

Strength: strong consensus

Score: 93%

Anesthesia for lung transplantation requires intense monitoring and immediate availability of therapeutic interventions including vasoactive agents, inhaled vasodilators, and a repertoire of medications affecting the immune system. A checklist should be performed that all equipment and drugs are available and ready to use according to local protocols.

Strength: strong consensus

Score: 94%

Critical periods of intraoperative management may require rapid volume replacement and blood product administration. Transfusion strategy has to be agreed before induction, especially in recipients on anticoagulation therapy. The availability of blood products and anticipated transfusion requirement should be confirmed and communicated to the blood bank.

Strength: full consensus

Score: 95%

Maintaining intraoperative normothermia could be difficult, especially in off pump implantation; therefore, warming devices should be prepared and up and running.

Strength: full consensus

Score: 95%

Reviewing the preoperative echocardiogram is important as it guides the anesthetic management during induction and predicts earlier utilization of mechanical support.

Strength: strong consensus

Score: 89%

4. Recommendations for induction of anesthesia

Induction of anesthesia in lung transplant recipients should be performed with the goal of maintaining hemodynamic stability, given the greater risk of cardiovascular collapse in these subjects.

Strength: strong consensus

Score: 96%

Surgeon and perfusionist should be immediately available during induction and prepared to urgently perform sternotomy, cannulation, and cardio-circulatory assistance.

Strength: strong consensus

Score: 94%

Safe induction can be achieved by multiple means, but requires clinical vigilance including slow and incremental administration of the agent of choice with constant multimodal evaluation of physiologic trends and timely and aggressive implementation of corrective measures.

Strength: strong consensus

Score: 95%

When selecting the agent for anesthesia maintenance one should consider the recipient's underlying disease and the particularities of the surgical procedure. Total intravenous anesthesia is to be preferred when adequate minute ventilation (difficult ventilation in case of suppurative or severe restrictive disease) and/or blood flow through the lung (cardiopulmonary bypass, extracorporeal membrane oxygenation) may not be guaranteed.

Strength: strong consensus

Score: 86%

From a bio-molecular, preconditioning, and allograft protection perspective, there is a lack of clinically relevant outcome data to prove the superiority of inhalation anesthesia over total intravenous anesthesia during lung transplantation.

Strength: strong consensus

Score: 87%

5. Recommendations for airway management, native lung ventilation, management of 1 lung ventilation

There are multiple benefits of using double lumen tubes as the primary choice of lung separation and an isolation device, but lung transplantation anesthetists should be familiar with bronchial blockers as an alternative method especially in difficult intubation scenarios.

Strength: strong consensus

Score: 94%

From the moment of mask ventilation, dynamic hyperinflation should be considered in COPD patients. Specific protective ventilation strategies should be employed to minimize this adverse event. First line of treatment should include disconnecting from the ventilator, positioning, fluid load, and vasopressor support to restore hemodynamic stability.

Strength: strong consensus

Score: 92%

Careful attention should be paid to signs of pneumothorax during initial ventilator settings after induction and/or lines positioning.

Strength: strong consensus

Score: 93%

Ventilation of patients with restrictive lung disease generally require higher airway pressures, increased PEEP, and relatively higher I:E ratios with potentially significant systemic effects.

Strength: strong consensus

Score: 88%

Cystic fibrosis patients should be hyperventilated often with high airway pressures and larger tidal volumes to maintain adequate gas exchange. Considering these patients' adaptation to chronic hypercapnia, one should focus primarily on arterial pH rather than arterial carbon dioxide tension.

Strength: strong consensus

Score: 83%

To perform adequate pulmonary toilet of secretions in patients with cystic fibrosis or bronchiectasis, placement of a single lumen tube is advised initially to be changed to a double lumen tube.

Strength: agreed consensus

Score: 72%

Aggressive management of secretions is advised at all the times during pneumonectomy.

Strength: strong consensus

Score: 83%

Before 1 lung ventilation, position of the double lumen tube (or bronchus blocker) has to be confirmed by fiberoptic bronchoscopy, and extra care should be made to secure the tube in place to prevent tube movement during extensive hilar surgical manipulations.

Strength: strong consensus

Score: 93%

All efforts should be directed toward success of 1 lung ventilation including optimization of all components of ventilation and managing shunt circulation. Long-acting inhaled pulmonary vasodilators should be targeted to the ventilated lung.

Strength: strong consensus

Score: 87%

If optimization of 1 lung ventilation does not achieve sufficient gas exchange and severe respiratory acidosis and/or hypoxia and low SvO_2 persist, early mechanical extracorporeal life support should be initiated as suggested by the Mechanical Support Task Force.

Strength: strong consensus

Score: 94%

6. Recommendations for general TEE imaging

A complete initial intraoperative transesophageal echocardiography examination is useful in evaluating deteriorating preoperative conditions and detecting new ones that may change the course of the procedure. Cardiac surgery may be required concomitantly with the lung transplantation.

Strength: strong consensus

Score: 87%

Visual qualitative estimation of the global right ventricular function and/or dilation remains the expert's choice to evaluate the right ventricle, assess changes, and decide if pharmacologic or mechanical support is required. Although

many objective and/or quantitative methods are available, they may be technically challenging, unreliable and time-consuming during arrhythmias, fluid fluctuations, and rapid hemodynamic changes.

Strength: strong consensus

Score: 91%

The right ventricular function and size and its response to required inotropes, should be assessed after the pulmonary artery clamping, unclamping and reperfusion of the lungs. The acquired information in combination with the concurrent hemodynamics is crucial in making the decision to initiate ECMO and/or CPB (extracorporeal membrane oxygenation and/or cardiopulmonary bypass).

Strength: strong consensus

Score: 91%

Evaluation of the tricuspid valve is essential as worsening tricuspid regurgitation may indicate a dilated right ventricle from right ventricular failure, pulmonary hypertension or fluid overload.

Strength: strong consensus

Score: 89%

In the presence of tricuspid regurgitation, Doppler echocardiography can be used to estimate the peak pulmonary artery systolic pressure. Pulmonary valve regurgitation is used to calculate mean and end diastolic pulmonary pressures. Significant tricuspid regurgitation and pulmonary valve regurgitation may indicate high pulmonary pressure. Since most of the patients undergoing lung transplantation have pulmonary artery catheters in place, pressure calculation by echocardiogram may be a secondary method.

Strength: strong consensus

Score: 88%

Other echocardiographic methods (than that described in the previous recommendation) exist for evaluating pulmonary pressures and pulmonary vascular resistance, but their practicality, and reliability during lung transplant is not confirmed.

Strength: strong consensus

Score: 89%

Evaluation for persistent foramen ovale (PFO) is essential as changes in the right heart pressures may cause right to left shunt and hypoxemia. Paradoxical embolism and stroke may occur in the presence of a PFO.

Strength: strong consensus

Score: 91%

Intraoperative TEE evaluation of left ventricular function, regional wall motion abnormalities and size is essential as these may change during the procedure and cause hemodynamic instability. This serves as a guide in managing fluid support and vasoactive medication administration.

Strength: strong consensus

Score: 91%

Evaluation of the mitral and aortic valves, aorta, and pericardium is important to rule out incidental findings that may contribute to hemodynamic instability and need to be addressed concurrently during the lung transplantation.

Strength: strong consensus

Score: 89%

7. Recommendations for pulmonary artery clamping

As clamping of the pulmonary artery is one of the most significant aspects of transplantation, all efforts should be directed toward preoptimization of hemodynamics by non −specific means and by judicious application of pulmonary vasodilators and systemic vasoconstrictors.

Strength: strong consensus

Score: 91%

Hypoxia, hypercapnia, acidosis, and hypothermia must be strictly avoided in patients with pulmonary hypertension. Hypocapnia has beneficial effects on pulmonary vascular resistance and moderate hyperventilation (pCO_2 30-35 mm Hg) is a valuable therapeutic goal to reduce pulmonary vascular resistance, but only in patients without respiratory disease impairing CO_2-elimination.

Strength: strong consensus

Score: 88%

Concerning the ventilator settings, the lowest possible inspiratory pressures, and tidal volumes should be used that allow the maintenance of normocapnia.

Strength: strong consensus

Score: 89%

In patients with pulmonary hypertension and right ventricular dysfunction and/or failure, arterial hypotension has to be strictly avoided.

Strength: strong consensus

Score: 94%

Noradrenaline and vasopressin appear to be the vasopressors of choice for the treatment of hypotension in the management of perioperative pulmonary hypertension and right ventricular dysfunction.

Strength: strong consensus

Score: 91%

Inotropes should not be used in a prophylactic approach, but only in patients with cardiac failure and evidence of organ hypoperfusion. Other reasons for cardiovascular deterioration (e.g., hypovolemia, vasoplegia) should be excluded and/or treated first before starting inotropic therapy.

Strength: strong consensus

Score: 84%

When starting an inotrope, doses should be titrated. Efficacy and adverse effects have to be carefully monitored. Typical side effects (e.g., arterial hypotension after administration of an inodilator) should be anticipated and immediately treated.

Strength: strong consensus

Score: 93%

Dopamine should no longer be used in the perioperative setting.

Strength: strong consensus

Score: 81%

In patients with (impending) right ventricular failure in the presence of pulmonary hypertension, every effort should be undertaken to maintain and/or restore sinus rhythm.

Strength: strong consensus

Score: 93%

Vasodilators should be preferentially administered via inhalation (“selective pulmonary vasodilation”).

Strength: strong consensus

Score: 87%

When administering vasodilators intravenously, worsening of right ventricular dysfunction, and deterioration of pulmonary right-left shunting can occur. This can lead to a vicious cycle of hypotension, further deterioration of right ventricular function, low cardiac output, and ultimately cardiogenic shock.

Strength: strong consensus

Score: 86%

Sufficient time to determine the hemodynamic impact of pulmonary artery clamping is mandatory. Information from complimentary sources including direct visualization of the heart, functional imaging by TEE, arrhythmia analysis and hemodynamic monitoring should be integrated and satisfactory to proceed without extracorporeal life support.

Strength: strong consensus

Score: 85%

Inhaled nitric oxide (20ppm) is the pulmonary vasodilator of choice in the rescue therapy of right ventricular failure. Alternatively, inhaled prostacyclins can be used. While many clinicians use pulmonary vasodilators in a prophylactic approach, this has not been associated with an outcome benefit so far.

Strength: strong consensus

Score: 88%

Volume resuscitation in patients with pulmonary hypertension and/or right ventricular dysfunction and/or failure should be guided by close monitoring of the combination of central venous pressure, stroke volumes, and echocardiography.

Strength: strong consensus

Score: 89%

8. Recommendations for intraoperative mechanical support

Intraoperative extracorporeal support should not be used routinely but for selected patients only.

Strength: strong consensus

Score: 88%

Intraoperative VA-ECMO might be preferred over CPB.

Strength: strong consensus

Score: 85%

Intraoperative ECMO should be considered in case of: (1) Intraoperative hypoxemia (Horowitz < 80 mm Hg), under FIO_2 1,0 and PIP > 35 cm H_2O; (2) Suprasystemic PA pressures (3) impossible lung-protective ventilation strategy.

Strength: strong consensus

Score: 87%

TEE is instrumental in identifying the indications for mechanical support and should be utilized in making this decision.

Strength: strong consensus

Score: 88%

During femoral and/or peripheral ECMO cannulation the position of the venous guide wire and/or cannula is confirmed by TEE in the right atrium, the junction of the right atrium-inferior vena cava or the superior vena cava, depending on the surgical technique. The tip of the venous cannula should move freely within the lumen. Color Doppler may be helpful in detecting free blood flow. The placement of the femoral arterial wire may be confirmed in the descending aorta. The tip of the arterial cannula usually cannot be visualized by TEE as it is positioned in the iliac artery or abdominal aorta.

Strength: strong consensus

Score: 93%

TEE is essential in assessing ECMO dysfunction and/or complications due to malposition of the cannula, thrombosis, tamponade or inadequate ventricular decompression.

Strength: strong consensus

Score: 92%

TEE should be used for guidance and confirmation of the correct placement of the dual-lumen cannula (Avalon). The tip of the cannula should be visualized freely in the inferior vena cava and the return flow should be directed across the tricuspid valve.

Strength: strong consensus

Score: 92%

9. Recommendations for implantation and reperfusion,

Airway tasks during implantation include reconfirmation of double lumen tube positioning, irrigation of the airways with antiseptic solution in suppurative disease, checking of bronchial anastomosis upon completion, and essential bronchial toilet.

Strength: strong consensus

Score: 88%

Apart from "minimally invasive" lung transplantation using bilateral anterior thoracotomies, reperfusion, and deairing should be performed after gentle inflation of the lungs. Lung protection strategies including gentle inflation with low FiO2, low respiratory pressures, low cycling rate, and gradual and progressive increments in tidal volumes and PEEP should be utilized.

Strength: strong consensus

Score: 90%

Moderate hypoxia maybe tolerated in minimally invasive transplantation until all vascular anastomoses secured.

Strength: strong consensus

Score: 87%

TEE should be used to image and interrogate the pulmonary artery, as it offers quick, real-time information about the patency of the anastomoses.

Strength: strong consensus

Score: 85%

TEE examination of the pulmonary veins is essential to rule out stenosis which may present as primary graft failure, acute rejection or pulmonary edema.

Strength: strong consensus

Score: 89%

Combination of TEE and contact ultrasound may be useful in clinical situations where pulmonary artery or vein anomaly is suspected but not clearly visualized by TEE.

Strength: strong consensus

Score: 84%

10. Recommendations for minimizing development of PGD

Anesthesia should take strong ownership of early primary graft dysfunction, and all efforts should be undertaken

to effectively control modifiable intraoperative risk factors of primary graft dysfunction development.

Strength: strong consensus

Score: 88%

Reduction of pulmonary hypertension and pulmonary vascular resistance is a principal goal of intraoperative management at every stage of the operation.

Strength: strong consensus

Score: 89%

Safe avoidance of cardiopulmonary bypass during lung transplantation may represent the single most influential aspect to reduce postoperative morbidity in lung transplant recipients. However, institution of CPB or VA-ECMO should not be delayed in case of severe and ongoing cardiorespiratory instability.

Strength: strong consensus

Score: 86%

Controlled reperfusion by surgical and anesthetic means should be encouraged. Permissive systemic hypotension and utilization of vasoactive agents should be employed to maintain low pulmonary artery pressure and pulmonary blood flow to reduce microvascular stresses for the first 10 minutes of reperfusion.

Strength: strong consensus

Score: 89%

On the basis of strong theoretical considerations, results of experimental studies and emerging clinical biomarker knowledge, the panel believes that antioxidant treatment would be desirable to attenuate the consequences of reperfusion, particularly in high-risk recipients and smoking donors. However, there is insufficient evidence regarding the antioxidant of choice (mannitol, N-acetylcysteine, Vitamin C, Statins, Cyclosporine) and the effective doses.

Strength: agreed consensus

Score: 78%

The exclusive use of iNO as a biologic agent for reperfusion therapy cannot be recommended. However, it could be part of the hemodynamic strategy to control pulmonary artery pressure during reperfusion and to manage shunt circulation.

Strength: strong consensus

Score: 83%

11. Recommendations for protective ventilation of lung allograft

Intraoperative ventilation practice should avoid injurious large tidal volumes, high inspiratory pressures, and low PEEP strategies and should employ lung protective and open concept ventilation strategies. These include low tidal volumes below 6 mL/kg PBW, recruitment maneuvers, and appropriate PEEP. Lung protective strategies should also consider driving pressures and stress index. However, the influence of high PEEP on pulmonary vascular resistance and right ventricular function should also be taken into consideration.

Strength: strong consensus

Score: 89%

Both volume controlled and pressure-controlled ventilation modes are acceptable, although the panel believes that pressure-controlled ventilation has potential clinical benefits as it may result in lower peak airway pressures, more homogenous gas exchange, and reduced regional over-distension.

Strength: agreed consensus

Score: 80%

Beyond recipient characteristics, donor body weight and allograft size should also be taken into consideration, especially in undersized grafts where normal ventilation may cause ventilator-induced lung injury.

Strength: strong consensus

Score: 89%

Ventilation of the allograft should avoid high FiO_2 for prolonged periods, and FiO_2 should be kept as low as possible to achieve $SpO_2 > 90$ and $PaO_2 > 60$ mm Hg to reduce the potential of hyperoxia, and oxidative stress. This should be balanced by the goal of maintaining adequate O_2 delivery, $SmvO_2$ particularly in the setting of perioperative end-organ dysfunction.

Strength: strong consensus

Score: 90%

12. Recommendations for fluid management

Intravenous fluid therapy remains the cornerstone of intraoperative management of lung transplantation and is required for hemodynamic stability and organ perfusion. This should be primarily in the form of crystalloid administration and to a lesser degree, utilization of higher molecular weight colloids.

Strength: agreed consensus

Score: 79%

Excessive fluid administration, infusion of low molecular weight colloids such as gelatins and allogenic blood transfusion may augment lung injury and predispose to primary graft dysfunction by causing fluid overload, increased hydrostatic forces in the pulmonary microcirculation, and by transfusion-related acute lung injury.

Strength: strong consensus

Score: 85%

The fluid and transfusion restriction, however, should be balanced by the requirement of maintaining perfusion pressure and cardiac output especially toward preserving renal homeostasis.

Strength: strong consensus

Score: 90%

13. Recommendations for management of bleeding

In patients with prior thoracic surgery physical methods (such as argon plasma diathermy) or locally active hemostatic measures (aerosolized fibrin or collagen sheets) may be of benefit to reduce bleeding and should be considered.

Strength: strong consensus

Score: 84%

The antifibrinolytic aprotinin is effective in reducing postoperative transfusions in lung transplantation and is recommended in countries where it is approved and available. Its use is associated with postoperative renal dysfunction but not failure. Its potential to affect potential early graft dysfunction is controversial and requires investigation. Higher doses of tranexamic acid have been associated with increased seizure activity.

Strength: agreed consensus

Score: 70%

The potential for adverse immune effects in this population suggests red cell transfusions should be minimized. Transfusion in the absence of major bleeding should be based on clinical criteria rather than a hemoglobin trigger. Mixed and/or central venous oxygen saturation may be used to guide red cell transfusion.

Strength: strong consensus

Score: 87%

Frozen plasma transfusion is not indicated unless hemorrhage is uncontrolled.

Strength: agreed consensus

Score: 78%

Prothrombin Complex Concentrates (PCC) may be administered if there is concern about right heart failure or volume overload.

Strength: strong consensus

Score: 85%

Use of cryoprecipitate or fibrinogen concentrate is based on availability. A fibrinogen trigger of 1.2 g/L aiming for a concentration of 2.8 g/L is recommended. Monitoring plasma concentration appears more accurate than viscoelastic testing.

Strength: agreed consensus

Score: 79%

Recombinant Factor VIIa has demonstrated adverse thrombotic events when used in cardiac surgery and cannot be recommended.

Strength: agreed consensus

Score: 77%

Platelet transfusion based on counts alone is not recommended. If there is active bleeding, transfusion based on point-of-care testing may minimize the dose. In the absence of evidence, catastrophic surgical bleeding may be replaced in the 1:1:1 ratio for red cells platelets and plasma, based on the major trauma setting.

Strength: strong consensus

Score: 84%

14. Recommendations for second lung implantation

Unexpected high pulmonary artery pressure upon clamping the second native pulmonary artery may indicate problems with the vascular anastomoses of the firstly transplanted lung allograft and needs to be rectified before second pneumonectomy.

Strength: strong consensus

Score: 88%

Left lung implantation generally requires more extensive surgical manipulations and displacement of the heart with consequent hemodynamic compromise. Communication between surgeon and anesthetist, aggressive multimodal monitoring, and timely stabilization measures are paramount.

Strength: strong consensus

Score: 93%

Protective pulmonary perfusion and ventilation should be employed throughout the implantation of the second allograft with constant assessment for signs of early primary graft dysfunction.

Strength: strong consensus

Score: 92%

15. Recommendations for conclusion of the transplant operation

If substantial size mismatch is encountered intra-operatively, this should be addressed with delayed chest closure and diuresis or lung reduction surgery.

Strength: strong consensus

Score: 88%

If iNO therapy is to be continued in the ICU, its administration should be uninterrupted during transit. The level of early postoperative mechanical and/or inotropic support and rate of weaning should be decided by the principal surgeon and anesthetist. Weaning should only proceed in the presence of senior clinical staff, preferentially during the daytime. Bridging therapy should be implemented to avoid rebound pulmonary hypertension and associated potential cardiorespiratory instability.

Strength: strong consensus

Score: 83%

Changing from double lumen tube to single lumen tube should be considered as potentially difficult. Use of tube exchanger is recommended to ensure maintenance of a secure airway.

Strength: strong consensus

Score: 83%

Keeping the double lumen tube and differential lung ventilation should be considered in emphysema patients following single-lung transplantation if they cannot be extubated and do not tolerate ventilation of both lungs with the same ventilation settings.

Strength: strong consensus

Score: 83%

Assessment of the vascular anastomoses with TEE should be performed on all patients before leaving the operating room and should be reassessed in the ICU if unexplained hypoxemia or hemodynamic instability is present.

Strength: strong consensus

Score: 87%

TEE is recommended during hypotension in the postoperative setting of lung transplantation when transthoracic echocardiogram (TTE) provides poor echocardiographic windows for a complete cardiac exam (right and/or left ventricular dysfunction, presence of tamponade, RVOT and/or LVOT obstruction, valvular disorder)

Strength: strong consensus

Score: 93%

6. Pain management

A multi-modality approach to analgesia following lung transplantation is recommended to ensure better postoperative outcomes.

Strength: strong consensus

Score: 94%

Thoracic epidural anesthesia is recommended as a technique for pain relief after lung transplantation.

Strength: strong consensus

Score: 80%

NSAIDS should be avoided in the postoperative period due to increased risk of renal failure.

Strength: strong consensus

Score: 86%

Unless specifically indicated for surgical issues, the use of bilateral thoracotomies or median sternotomy over the

thoraco-sternotomy or "clamshell" approach is likely to be associated with less post-operative pain.

Strength: strong consensus

Score: 84%

7. Post operative and/or intensive care management

1. Recommendations for sedation and/or *early extubation*

Deep sedation in the intensive care unit should be avoided whenever is possible as it is associated with prolonged mechanical ventilation and increased mortality.

Strength: strong consensus

Score: 92%

Sedation with benzodiazepine should be avoided as it may increase early onset delirium in lung transplant recipients.

Strength: strong consensus

Score: 90%

Early extubation in the intensive care unit is recommended after an uncomplicated intraoperative course and in the absence of graft dysfunction if hemodynamic stability, hemostasis, and adequate pain control is achieved.

Strength: full consensus

Score: 96%

Early extubation in the operating room is feasible but cannot be recommended as a routine practice.

Strength: strong consensus

Score: 89%

2. Recommendations for mechanical ventilation in the ICU

These recommendations are identical to those for intraoperative ventilation of allograft and not repeated here.

3. Recommendations for antimicrobial prophylaxis and/or *treatment*

In uncomplicated lung transplantation with low risk for donor and recipient-derived infection, a short antibacterial prophylaxis, primarily aimed at preventing surgical site infections, should be administered. First and second-generation cephalosporins are considered equally efficacious.

Strength: strong consensus

Score: 86%

In case of positive cultures from donor or recipient, postoperative antimicrobial treatment should be modified according to the isolated microorganism and the duration should be 7 to 14 day's or longer, especially for patients with cystic fibrosis colonized by P. Aeruginosa or other multi drug resistant infections.

Strength: strong consensus

Score: 90%

Antifungal prophylaxis should be considered, to reduce the risk of invasive aspergillosis. A lipid formulation of amphotericin-B should be preferred with aerosolized administration, to minimize the side effects.

Strength: agreed consensus

Score: 80%

A routine prophylaxis with intravenous fluconazole for Candida should be discouraged, to avoid increase of resistance profile or the selection for Candida non−Albicans species.

Strength: strong consensus

Score: 87%

Pretransplant donor and recipient serology should be performed. If pretransplant serology of the recipient is negative, a retest at the time of transplant is mandatory. If the result is equivocal in the recipient, it should be assumed negative. If the pretransplant serology is equivocal in the donor, it should be assumed positive.

Strength: strong consensus

Score: 91%

Prophylaxis should be considered in CMV seronegative recipients who receive an organ from a CMV seropositive donor (D+/R-) and in seropositive recipients, independently from the donor.

Strength: strong consensus

Score: 90%

Both CMV antigenemia and quantitative nucleic acid testing (QNAT) viral load tests are acceptable options in diagnosing, and decision making regarding preemptive therapy, and monitoring the response to therapy.

Strength: strong consensus

Score: 87%

Combined prophylaxis comprising of CMV-IG and antiviral treatment reduces CMV infection and disease burden and may improve recipients' outcome.

Strength: strong consensus

Score: 85%

4. Recommendations for perioperative immunosuppression

Preoperative, intraoperative, and early postoperative immunosuppression is an essential component of perioperative management of lung transplantation. However, there is no international consensus on exact immunosuppression regimes and there is variation in center specific protocols.

Strength: strong consensus

Score: 92%

Pre- and postoperative immunosuppression is primarily the responsibility of the transplant physician. However, as part of the multidisciplinary team, it is mandatory that the intensive care physician reviews and confirms on a daily basis that appropriate immunosuppression is prescribed and delivered. Moreover, to optimize immunosuppression, they should consider multiple drug interactions, review measured levels and various organ dysfunctions and communicate with the transplant physician.

Strength: strong consensus

Score: 92%

Induction therapy with antibodies against T-cells remains controversial. Current evidence suggests that induction therapy does not reduce acute rejection grade II or higher and it does not appear to improve survival.

Strength: strong consensus

Score: 82%

5. Recommendations regarding postoperative mechanical extracorporeal support

Lung transplantation centers should use a point-of care coagulation transfusion protocol according to the target guideline of the extracorporeal life support organization (ELSO).

Strength: strong consensus

Score: 82%

In case of severe primary graft dysfunction (PGD), extracorporeal circulation support should be initiated early to provide lung-protective ventilation.

Strength: strong consensus

Score: 91%

Protective mechanical ventilation should be maintained during post-transplant ECMO support, in order of avoiding ventilator- induced lung injury in patients recovering from primary graft dysfunction.

Strength: strong consensus

Score: 93%

TEE assessment is crucial in evaluating the recovery progress while on ECMO and assisting in weaning from it.

Strength: strong consensus

Score: 88%

Interatrial septum should be interrogated with TEE for occurrence of persistent foramen ovale if unexplained hypoxemia is present.

Strength: strong consensus

Score: 92%

Weaning from ECMO support in a lung transplant patient should be started when following criteria are found: hemodynamic stability with SvO_2> 75%; •PaO_2/FiO_2 > 100 and $PaCO_2$ < 45 mm Hg: •the improvement of lung compliance and chest X-ray and/or CT-scan. During trial off, protective ventilation should be increased to a maximum Peak Inspiratory Pressure (PIP) of 29 cm H_2O and FiO_2 = 60%.

Strength: strong consensus

Score: 85%

In case of VA-ECMO, weaning should be performed reducing pump flow by 0.5 L/min every 12 hours, adjusting heparin infusion to keep Activated Clotting Time (ACT) >200 sec. In case of VV-ECMO, weaning should be performed reducing gas flow; no adjustment in heparin infusion is needed.

Strength: agreed consensus

Score: 76%

6. Recommendations for airway complications

Bronchoscopic surveillance of bronchial anastomoses is recommended in the early post-operative period.

Strength: strong consensus

Score: 93%

Brushings or biopsies (if exuberant tissue) for culture should be obtained from the bronchial anastomotic site if infection is suspected.

Strength: strong consensus

Score: 87%

Despite low level of evidence, members of the Task Force recommend fungal prophylaxis to decrease the risk for fungal colonization or infection in patients with known anastomotic problems.

Strength: agreed consensus

Score: 80%

Antimicrobial therapy targeting the isolated pathogen is recommended for bronchial anastomotic infection.

Strength: strong consensus

Score: 93%

Bronchial dehiscence should be suspected in lung transplant recipients with a prolonged or large airleak, pneumothorax or pneumomediastinum.

Strength: strong consensus

Score: 94%

CT may be used to screen for suspected bronchial dehiscence.

Strength: strong consensus

Score: 89%

Bronchoscopy is required to confirm and grade the severity of bronchial dehiscence.

Strength: strong consensus

Score: 93%

Low grade, partial bronchial dehiscence can be managed conservatively with frequent surveillance bronchoscopy, and antimicrobials.

Strength: strong consensus

Score: 87%

High grade bronchial dehiscence requires bronchoscopic or surgical intervention, preferably bronchoscopic if feasible given the poor outcomes associated with surgical intervention.

Strength: strong consensus

Score: 91%

Bronchopleural fistulae may present as persistent air leak, pneumothorax, or subcutaneous air.

Strength: strong consensus

Score: 94%

Treatment of bronchopleural fistulae includes tube thoracostomy when required for pneumothorax or empyema, minimizing of ventilator pressures, and consideration of bronchoscopic or surgical closure.

Strength: strong consensus

Score: 92%

Bronchovascular fistulae should be addressed with prompt surgical intervention.

Strength: strong consensus

Score: 91%

7. Recommendations for pleural complications

Hemothorax should be suspected in patients with dropping hemoglobin, worsening oxygenation, increasing (dense) effusion on chest radiograph, or hemodynamic instability.

Strength: full consensus

Score: 95%

CT scan is useful in screening for hemothorax if the diagnosis is suspected but the chest radiograph is unrevealing.

Strength: strong consensus

Score: 92%

Correction of coagulopathy, tube thoracostomy drainage, and resuscitation with blood products are the first line treatment of hemothorax.

Strength: strong consensus

Score: 91%

Surgical re-exploration should be considered in patients with ongoing blood loss despite correction of coagulopathy, hemodynamic instability, and profound hypoxia with associated mechanical compression of the lungs.

Strength: strong consensus

Score: 95%

Efforts should be made to clear residual blood from the pleural space to prevent development of fibrothorax and trapped lung. This can be accomplished with chest tube drainage, pleural thrombolytic instillation, or VATS.

Strength: strong consensus

Score: 91%

Chylothorax should be suspected in patients with persistent or high output from pleural drains after lung transplant. Chylous effusions might not have the characteristic "milky" appearance.

Strength: strong consensus

Score: 93%

Initial treatment of chylothorax is typically dietary modification in an effort to spontaneously close the leak by decreasing lymph production.

Strength: strong consensus

Score: 90%

Chylothoraces which fail to respond to conservative treatment can be addressed with surgical thoracic duct ligation or thoracic duct embolization by interventional radiology.

Strength: strong consensus

Score: 92%

Lung transplant recipients with a persistent air leak should undergo bronchoscopy to assess for bronchial dehiscence or bronchopleural fistula.

Strength: full consensus

Score: 95%

Post-lung transplant empyema is suggested by a pleural neutrophil count >21%.

Strength: agreed consensus

Score: 80%

Pleural space infection with simple effusion can be addressed with antimicrobials and thoracentesis or chest tube drainage.

Strength: strong consensus

Score: 89%

Complicated pleural effusions should be addressed with either a chest tube and instilled pleural thrombolytic therapy or surgical decortication.

Strength: strong consensus

Score: 88%

8. Recommendations for vascular complications

Pulmonary vascular anastomotic complications should be entertained in post-lung transplant patients with unexplained hypoxemia, particularly if it occurs in concert with pulmonary hypertension.

Strength: strong consensus

Score: 89%

CT angiography or transesophageal echocardiography can be used to diagnose pulmonary vascular anastomotic complications. Bronchoscopy should be diagnostic in the setting of torsion. In the operating room, direct assessment of the pressure gradient across the left atrial anastomosis can be performed.

Strength: strong consensus

Score: 90%

Significant pulmonary vascular anastomotic stenosis should be corrected surgically if discovered intra-operatively or immediately post operatively.

Strength: strong consensus

Score: 93%

Late diagnosed (>2 weeks post-operative) pulmonary vascular anastomotic stenosis should be addressed with angioplasty and stenting if anatomically feasible.

Strength: strong consensus

Score: 89%

In patients with pulmonary vascular anastomotic stenosis diagnosed within 2 weeks of surgery, clinicians must weigh the relative risks of surgical intervention vs endovascular intervention on a fresh anastomosis.

Strength: strong consensus

Score: 90%

Diagnosis of torsion requires a high index of suspicion and emergent surgical exploration and correction if suspected due to the risk for rapid progression to irreversible graft infarction.

Strength: strong consensus

Score: 94%

An undiagnosed venous anastomotic thrombosis may result in infarction and gangrene of the pulmonary allograft (entire lung or lobe) leading to sepsis and possible death of the recipient. Urgent transplantectomy is then indicated.

Strength: strong consensus

Score: 91%

9. Recommendations for wound infections

Clinicians should remain vigilant for development of surgical site infections.

Strength: full consensus

Score: 95%

Meticulous infection control, glucose control, and appropriate peri-operative antimicrobial prophylaxis should be instituted to prevent surgical site infection.

Strength: strong consensus

Score: 95%

Compered to thoracosternotomy (clam-shell incision), bilateral (anterior) thoracotomies may be associated with reduced incidence of wound infections with chondritis and sternal non−union, and should be considered whenever possible or appropriate.

Strength: strong consensus

Score: 83%

10. Recommendations for nerve injury

Lung transplant recipients with post-operative elevation of the hemidiaphragm, ventilatory insufficiency, or unexplained basilar atelectasis should be assessed for diaphragmatic paralysis.

Strength: strong consensus

Score: 93%

Non−invasive ventilatory support can be used to assist ventilation or aid liberation from mechanical ventilation in patients with diaphragmatic paralysis.

Strength: strong consensus

Score: 91%

Post-operative gastroparesis requires a multi-faceted treatment approach including small, frequent meals,

prokinetic medications, and nutritional support with jejunal enteral feeds in patients unable to meet caloric demands.

Strength: strong consensus

Score: 92%

Refractory gastroparesis may benefit from gastric electrical stimulators or intrapyloric injections of botulinum toxin.

Strength: agreed consensus

Score: 78%

Patients with dysphonia, dysphagia, inefficient cough, or stridor following LT should be evaluated for vocal cord injury with fiberoptic laryngoscopy or transcutaneous laryngeal ultrasound.

Strength: strong consensus

Score: 91%

If vocal cord paralysis fails to improve spontaneously, consideration should be given to gel injections of the vocal cord.

Strength: strong consensus

Score: 88%

8. E-supplements

1. Preoperative evaluation for lung transplantation
2. Perioperative monitoringnduring lung transplantation
3. General intraoperative management in lung transplantation
4. Management of pulmonary hypertension in lung transplantation
5. Hemostasis management during lung transplantation
6. The role of transesophageal echocardiography during lung transplantation
7. Intensive care management in lung transplantation
8. Mechanical respiratory and circulatory support during lung transplantation
9. Pain management for lung transplantation
10. Surgical complications

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Supplementary materials

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