REVIEW ARTICLE

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Lung Transplantation

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CME

Lung transplantation has evolved over 60 years from an experimental to an accepted standard treatment for life-threatening lung disease. Suitable recipients can expect improved survival and quality of life despite commonly observed problems such as primary graft dysfunction, chronic lung allograft dysfunction (CLAD), increased risk for opportunistic infections, cancer, and chronic immunosuppression-related health issues. Although lung transplantation is becoming more common worldwide, the number of procedures performed is not keeping pace with growing demand. This review focuses on the current status of and recent developments in lung transplantation and on future opportunities in the effective delivery of this challenging but potentially life-transforming therapy.

Candidate Assessment and Selection

Because of the relative scarcity of suitable donor lungs, centers are ethically bound to allocate donor organs to candidates who are most likely to derive a net benefit from transplantation.[1] Such candidates have been traditionally defined as having an estimated risk of dying from their lung disease within 2 years of greater than 50% and, with the assumption of adequate allograft function, a likelihood of being alive 5 years after transplantation of greater than 80%.[2] The most common indications for lung transplantation are pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary vascular disease, and cystic fibrosis.[3] Patients are referred on the basis of a decline in pulmonary function, a decline in physical functioning, and disease progression despite the maximal use of medical and surgical therapies; additional disease-specific criteria are also considered.[2] Challenges in prognostication support an early referral strategy, which allows for better risk–benefit counseling to improve informed shared decision making and provides the opportunity to modify potential barriers to successful transplantation outcomes.[4] A multidisciplinary team assesses the need for lung transplantation, as well as the individual patient's risk of post-transplantation complications associated with the use of immunosuppression, such as the risk of potentially life-threatening infections (Fig. 1). Screening for extrapulmonary organ dysfunction, physical fitness, mental health, systemic immunity, and cancer is essential. Specific assessments of coronary and cerebral arteries, kidney function, bone health, esophageal function, psychosocial capacity, and social support are important while noting the need for transparency to avoid inequities in decisions regarding suitability.[5]

Consensus-based contraindications and risk factors for adverse outcomes are described in Table 1.[2] Multiple risks factors are seen as more detrimental than single risk factors.[6] Traditional barriers to transplantation including older age, obesity, history of cancer, critical illness, and coexisting systemic disease have been recently challenged.[7] A steady increase in the age of recipients, with 34%

KEY POINTS

LUNG TRANSPLANTATION

- Lung transplantation is growing worldwide as a recognized treatment method for advanced lung diseases.
- Candidate selection for lung transplantation has evolved from the use of previously strict criteria to a more flexible assessment, with greater allowance for relative contraindications (for which the benefit of the procedure may outweigh the risk, as determined on a case-by-case basis) and active management to minimize their effects to facilitate the candidate's potential for recovery.
- Methods for donor-organ preservation are changing with the availability of emerging technological innovations, such as those enabling ex situ and in situ assessments, with the potential for preimplantation therapeutics to extend preservation time while potentially reducing the risk of primary graft dysfunction, which is the major cause of early complications and death.
- Maintaining graft function and the overall health of the recipient involves careful monitoring and striking a balance between the protective and adverse effects of long-term immunosuppression.
- Chronic lung allograft dysfunction remains the main obstacle to long-term survival, and further research into its mechanisms and multicenter clinical trials of preventive and therapeutic strategies are urgently needed.
- The assessment and care of lung-transplant recipients involves a team approach with a holistic focus on improving function and quality of life.

of recipients being older than 65 years in the United States in 2021, shows an increasing emphasis on physiologic over chronologic age.[3] The 6-minute walk distance is now often complemented by more formal assessments of frailty that focus on physical reserve and anticipated response to stressors. Frailty has been associated with poor outcomes after lung transplantation and is often tied to body composition.[8] Approaches to account for obesity and body composition are evolving, with less focus on body-mass index and more on adiposity and underlying muscle mass.[9] Promising tools are being developed to quantify frailty, sarcopenia, and resilience to better predict recoverability from lung transplantation.[8,10] Both body composition and frailty might be modifiable through preoperative pulmonary rehabilitation to potentially improve outcomes.[2]

Determining frailty and recoverability is particularly challenging in the setting of acute critical illness. Transplantation in patients who are receiving mechanical ventilation was formerly rare but has become more common.[11] Furthermore, the use of extracorporeal life support as a bridge to transplantation has increased in recent years.[12] Advances in technology and vascular access have made it possible for carefully selected awake patients who are receiving extracorporeal life support to participate in the consent process and in physical rehabilitation and to have post-transplantation outcomes that are similar to those in patients who do not require extracorporeal life support before transplantation.[4]

Coexisting systemic illnesses, previously considered to be absolute contraindications, are now individually assessed for their effect on post-transplantation outcomes. Early guidelines on preexisting malignant conditions focused on a requisite of a patient being cancer-free for 5 years before being listed for transplantation, given that transplant-related immunosuppression increases the likelihood of cancer recurrence.[13] However, as cancer therapies have become more effective, an assessment of the likelihood of recurrence that is specific to the individual patient is now recommended.[13] Systemic autoimmune disease was traditionally viewed as a contraindication, which was problematic, given that advanced lung diseases often limit the life expectancy in such patients. Recent guidelines recommend that before lung transplantation, a more disease-specific evaluation be performed, with treatment to reduce any disease manifestations that have potential detrimental effects on outcomes, such as esophageal issues associated with scleroderma.[14]

The presence of circulating antibodies to specific HLA subclasses makes some candidates sensitized to certain donor organs, which leads to longer wait times, a lower likelihood of transplantation, and a higher risk of acute organ rejection and CLAD.[15] However, similar outcomes have been achieved despite transplantations being performed across some candidate antibody and donor types with the use of preoperative desensitization protocols including plasma exchange, intravenous immune globulin, and anti–B-cell therapies.[16]

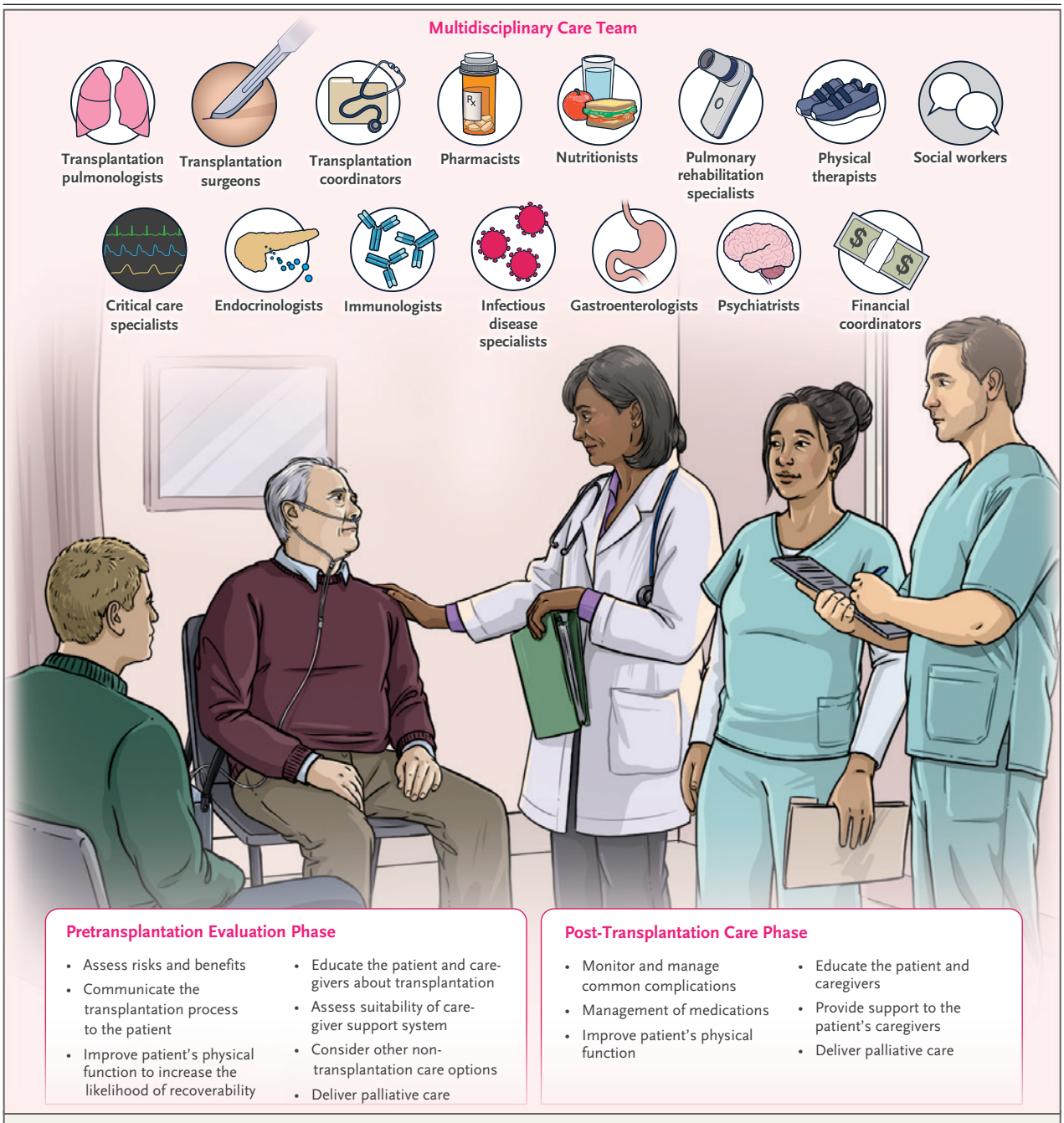


Figure 1. The Lung Transplantation Multidisciplinary Team.

Each member of the team follows and supports the patient as needed through the evaluation, pretransplantation care, immediate post-transplantation care, and long-term care.

DONOR-LUNG SELECTION AND UTILIZATION

Organ donation is an altruistic act. Consent and respect for donor autonomy are the foremost ethical considerations.[1] Donor lungs can sustain injuries related to chest trauma, resuscitation maneuvers, aspiration, embolism, ventilator-associated injury or infection, or neurogenic injury, thereby making many donor lungs unsuitable for trans-

plantation.[17] Generally acceptable donor criteria have been defined by the International Society for Heart and Lung Transplantation (ISHLT), although criteria vary among transplantation centers[17]; in fact, very few donors meet "ideal" criteria for lung donation (Fig. 2). Donor-lung utilization continues to increase with the use of extended-criteria donors (i.e., those not meeting the standard ideal criteria), careful evaluation, active donor care, and ex vivo assessment (Fig. 2).[18] Donor history of active cigarette smoking is a risk factor for primary graft dysfunction in the recipient,[19] yet the risk of death with the use of such organs is limited and should be balanced against the mortality-related consequence of longer wait times for lungs from never-smokers.[20] The use of highly selected lungs from older (>70 years of age) donors with no other risk factors has been associated with survival and allograft function outcomes that are similar to those with lungs from younger donors.[21]

The use of lungs from controlled donation after circulatory death (DCD) has risen to between 30 and 40% in some countries, with similar rates of acute organ rejection, CLAD, and survival.[22] Traditionally, transplantation of organs from donors infected with transmissible viruses has been avoided in uninfected recipients; however, in recent years, direct-acting antiviral agents against hepatitis C virus (HCV) have enabled safe transplantation of HCV-positive donor lungs into recipients who are negative for HCV.[23] Likewise, human immunodeficiency virus (HIV)–positive donor lungs can be transplanted into recipients who are positive for HIV, and hepatitis B virus (HBV)–positive donor lungs can be transplanted into recipients who have been vaccinated against HBV and those with existing immunity. Transplanting lungs from donors with active or past severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been reported.[24] More evidence is needed to determine the safety of transplanting lungs from donors infected with transmissible viruses.

Evaluation of lung quality in the donor can be challenging owing to the complexities of multiorgan procurement. Evaluation with ex vivo lung perfusion systems may allow for more detailed functional assessment of donor lungs and potential reconditioning before they are used (Fig. 2).[25,26] Because donor lungs are highly susceptible to injury, ex vivo lung perfusion systems provide a platform for administering specific biologic treatments to repair injured donor lungs (Fig. 2).[25] Two randomized trials showed that normothermic ex vivo lung perfusion for standard-criteria donor lungs is safe and allows transplantation teams to extend preservation times.[25] Preserving donor lungs at elevated hypothermic temperatures (6 to 10°C) rather than 0 to 4°C on ice has been reported to provide better mitochondrial health, result in less injury, and improve pulmonary function.[27,28] Promising post-transplantation outcomes have been reported with longer overnight preservation for semielective daytime transplantation.[29] A large noninferiority safety trial comparing preservation at 10°C with standard cold storage is under way (ClinicalTrials.gov number, NCT05898776). There is growing use of multiorgan donor-care centers to facilitate the timely recovery of organs and organ-repair centers to support the process of improving organ function to enable transplantation with better-quality organs. The effects of these transplant ecosystem changes continue to be evaluated.[30]

In situ normothermic regional perfusion with extracorporeal membrane oxygenation (ECMO) to preserve controlled DCD organs can be used in the functional assessment of abdominal organs and to support direct procurement and preservation of thoracic organs, including lungs. Experience with lung transplantation after thoracoabdominal normothermic regional perfusion is limited and has mixed results.[31] There are concerns that the procedure may compromise the deceased status of the donor and break a fundamental ethical principle of organ procurement; as such, normothermic regional perfusion is not yet permitted in many countries.[32]

LUNG ALLOCATION

In 2005, the United States transitioned from an accumulated wait-time allocation system to an urgency-weighted lung allocation score, which involved a ratio of the estimated 1-year survival with lung transplantation and without lung transplantation. Subsequently, other nations adopted similar approaches, with a goal of reducing wait-list mortality (the rate of death that occurs after being listed for an organ transplant but before receiving it) and increase transplantation activity.[33] In March 2023, the United States adopted a new composite allocation score, which prioritizes five domains: medical urgency (based

Table 1. Consensus-Based Contraindications to Lung Transplantation and Risk Factors for Poor Outcomes.*

Contraindications and Risk Factors	Comments
Absolute contraindications	
Lack of patient willingness or acceptance to undergo transplantation Malignant condition with a high risk of recurrence or death related to cancer Glomerular filtration rate of <40 ml/min/1.73 m^2 of body-surface area (unless being considered for multiorgan transplantation) Acute coronary syndrome or myocardial infarction in the past 30 days (excluding demand ischemia) Stroke in the past 30 days Liver cirrhosis with portal hypertension or synthetic dysfunction (unless being considered for multiorgan transplantation) Acute liver failure Acute kidney failure with a rising creatinine level or that is being treated by dialysis, with a low likelihood of recovery (unless being considered for multiorgan transplantation) Septic shock Active extrapulmonary or disseminated infection Active tuberculosis infection HIV infection with detectable viral load Limited functional status (e.g., nonambulatory) with poor potential for post-transplantation rehabilitation Progressive cognitive impairment Repeated episodes of nonadherence without evidence of improvement† Active substance use or dependence (e.g., current tobacco use, vaping, marijuana smoking, or intravenous drug use) Other severe uncontrolled medical condition expected to limit survival after transplantation	Candidates with these conditions are considered to be at too high risk to achieve successful outcomes after lung transplantation. These factors or conditions substantially increase the risk of an adverse outcome after transplantation, would make transplantation most likely harmful for a recipient, or both. Most lung transplantation programs should not perform transplantation in patients with these risk factors, except under very exceptional or extenuating circumstances.
Traditional relative contraindications: factors associated with substantially increased risk	
Age >70 years Severe coronary artery disease that warrants coronary-artery bypass grafting at transplantation Reduced left ventricular ejection fraction of <40% Substantial cerebrovascular disease Severe esophageal dysmotility Untreatable hematologic disorders (e.g., bleeding diathesis, thrombophilia, or severe bone marrow dysfunction) BMI >35 BMI <16 Limited functional status with potential for post-transplantation rehabilitation. Psychiatric, psychological, or cognitive conditions with potential to interfere with medical adherence without sufficient support systems Unreliable support system or caregiving plan Lack of understanding of disease or transplantation (or both) despite having been provided adequate education *Mycobacterium abscessus* infection *Lomentospora prolificans* infection *Burkholderia cenocepacia* or *B. gladioli* infection Hepatitis B or C virus infection with detectable viral load and liver fibrosis Chest wall or spinal deformity expected to cause restriction after transplantation Extracorporeal life support Retransplantation <1 year after initial lung transplantation Retransplantation for restrictive CLAD Retransplantation for AMR as the cause of CLAD	Candidates with these conditions may be considered in centers with expertise specific to the condition. Data may not be available to support performing transplantation in patients with these risk factors or there is substantially increased risk on the basis of currently available data; further research is needed to better inform future recommendations. When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing the risk of adverse outcomes. Modifiable conditions should be treated to mitigate risk when possible.

Table 1. (Continued.)

Contraindications and Risk Factors	Comments
Additional factors associated with increased risk	
Age of 65 to 70 years Glomerular filtration rate of 40 to 60 ml/min/1.73 m^2 Mild-to-moderate coronary artery disease Severe coronary artery disease that can be revascularized through percutaneous coronary intervention before transplantation Patients with prior coronary-artery bypass grafting Reduced left ventricular ejection fraction of 40 to 50% Peripheral vascular disease Connective-tissue diseases (scleroderma, lupus, or inflammatory myopathies) Severe gastroesophageal reflux disease Esophageal dysmotility Thrombocytopenia, leukopenia, or anemia with a high likelihood of persistence after transplantation Osteoporosis BMI of 30.0 to 34.9 BMI of 16.0 to 17.0 Frailty Hypoalbuminemia Diabetes that is poorly controlled Edible marijuana use *Scedosporium apiospermum* infection HIV infection with undetectable viral load Previous thoracic surgery Prior pleurodesis Mechanical ventilation Retransplantation >1 year for obstructive CLAD	Risk factors with unfavorable implications for short- or long-term outcomes after lung transplantation. Although acceptable for lung transplantation programs to consider patients with these risk factors, multiple risk factors together may increase the risk of adverse outcomes after lung transplantation.

* Adapted from Leard et al.[2] Risk factors can change over time and may not be a contraindication for referral, but when present at or during the time of listing for lung transplantation, they may increase the risk of poor transplantation outcomes. AMR denotes antibody-mediated rejection, BMI body-mass index (the weight in kilograms divided by the square of the height in meters), CLAD chronic lung allograft dysfunction, and HIV human immunodeficiency virus.
† For pediatric patients this is not an absolute contraindication, and ongoing assessment of nonadherence should occur as patients progress through different developmental stages.

on the expectation of a candidate to survive for 1 year without a transplant), post-transplantation outcomes (based on 5-year survival), biologic disadvantages (based on blood type, height, and sensitization), patient access (based on pediatric status and history of living-organ donation), and transplantation efficiency (based on travel distance, cost, and efficiency of transportation mode).[34] In current lung-allocation practice, donor organ–associated risks of poor outcomes are not formally quantified, which is an opportunity for future refinement.

SURGICAL APPROACHES

Bilateral, sequential lung transplantation is the most common procedure for all disease indications.[11] The use of single-lung transplantation has decreased over time, although it is a valuable option, with similar outcomes and fewer postoperative complications, especially in older patients.[35] Debate regarding the benefit of bilateral as compared with single-lung transplantation continues, with data hampered by selection and indication bias that is inherent in these observational studies.[36] The use of heart–lung transplantation has also decreased over time, and the procedure is reserved for patients with both end-stage heart and lung failure whose underlying cardiac pathophysiologic state cannot be corrected by bilateral lung transplantation with concomitant cardiac repair.[2,37]

Surgical approaches vary among centers according to preference and experience. Bilateral thoracotomy with transverse sternotomy, also known as "clamshell" incision, facilitates good

Donor

Ideal Selection Criteria

- Age <55 years
- Clear serial chest radiograph
- Normal gas exchange (Pao_2–FIo_2 >300 mm Hg)
- Absence of chest trauma
- No evidence of aspiration or sepsis
- Absence of purulent secretions on bronchoscopy
- Absence of organisms on sputum gram stain
- No history of primary pulmonary disease
- No active pulmonary infection
- Tobacco history of <20 pack-years
- ABO compatibility
- No previous cardiopulmonary surgery
- Appropriate donor–recipient size match

Type

Donation after Brain Death

Donation after Circulatory Death

- Controlled
- Uncontrolled

Discontinuation of Life-Sustaining Therapies in Controlled DCD

- Direct procurement and preservation
- Normothermic regional perfusion

Management

- PEEP of 8–20 cm of water
- Tidal volume of 6–8 ml/kg of body weight
- Lung recruitment once per hour after disconnection from ventilator
- Bronchoscopy and lavage after brain death
- PiCCO: EVLW of <10 ml/kg and CVP of <8 mm Hg
- Methylprednisolone, 15 mg/kg
- Alveolar recruitment with plateau air pressure of 35 mm Hg and PEEP of 18–20 cm of water
- Pao_2–FIo_2 <300 mm Hg, semilateral decubitus

Lung Preservation

- Extracellular solution
- Anterograde flush, 60 ml/kg through pulmonary artery
- Retrograde flush, 250 ml through each of 4 pulmonary veins
- Pulmonary arterial pressure of 10–15 mm Hg
- Tidal volume of 10 ml/kg or 50% total lung capacity
- PEEP of 5 cm of water
- FIo_2 of 50%
- Airway pressure of 15–20 cm of water

Lung Storage and Transport

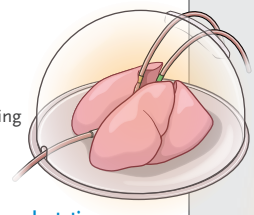
- Ice box (0–4°C)
- Hypothermic (6–10°C)
- Normothermic (37°C)

Lung Transplant Procedure

Interim Care and Preparation

Ex Vivo Lung Perfusion

- Evaluation
- Reconditioning
- Preservation

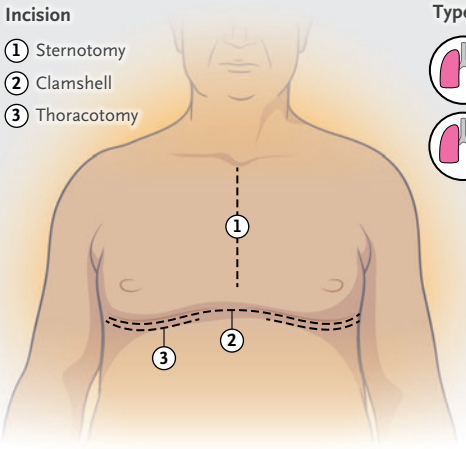


Bridging to Transplantation with Extracorporeal Life Support

Use in select candidates whose condition deteriorates dramatically

Incision

1. Sternotomy
2. Clamshell
3. Thoracotomy



Type of Transplantation


Single lung


Heart–lung


Both lungs

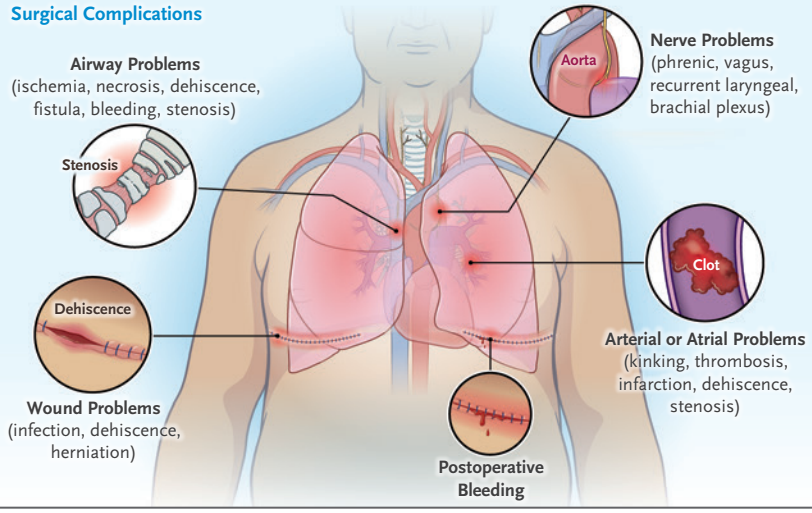

Lobar lung

Extracorporeal Lung Support

- Off-pump
- ECMO (vein–artery, vein–vein–artery, or vein–vein)
- Cardiopulmonary bypass

Recipient

Surgical Complications



Airway Problems (ischemia, necrosis, dehiscence, fistula, bleeding, stenosis)

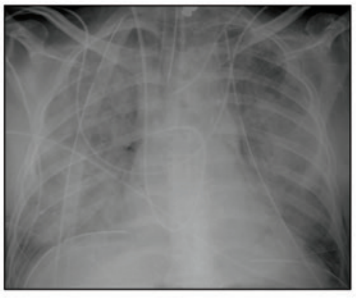
Nerve Problems (phrenic, vagus, recurrent laryngeal, brachial plexus)

Arterial or Atrial Problems (kinking, thrombosis, infarction, dehiscence, stenosis)

Wound Problems (infection, dehiscence, herniation)

Postoperative Bleeding

Primary Graft Dysfunction



Management

- Lung-protective ventilation
- Vasodilators
- Diuresis
- ECMO (vein–artery or vein–vein)

Figure 2 (facing page). The Lung Transplantation Process.
Appropriate care for multiorgan donors with consideration for potential lung donation is essential to ensure a high likelihood that the donor lungs will be suitable for transplantation. Although few lungs currently offered satisfy the historical definition of an ideal donor lung, extension of the criteria beyond these traditional criteria can allow successful utilization of organs without compromising outcomes. A standardized approach to lung preservation helps protect organ integrity before implantation into the recipient. Transport of organs to the transplantation unit can be performed under different conditions, such as cold static storage or as machine perfusion at hypothermic or normothermic temperatures. Lungs not thought to be suitable for immediate transplantation can be further objectively assessed and potentially treated by ex vivo lung perfusion (EVLP) or preserved for longer to allow logistic barriers to transplantation to be overcome. The type of lung-transplant operation offered, the surgical approach, and the intraoperative support used are determined by patient needs as well as by the surgeon's experience and preference. Selected lung transplantation candidates whose condition dramatically deteriorates while waiting can be considered for bridging to transplantation by means of extracorporeal life support. Early postoperative complications may include bleeding, airway, or vascular anastomoses dysfunction and wound infection. Intrathoracic phrenic or vagus nerve damage can cause additional complications affecting diaphragm function and gastric emptying, respectively. The donor lungs are at risk of early acute lung injury after implantation and reperfusion, termed primary graft dysfunction. Classification of primary graft dysfunction severity and management is supportive, but severe primary graft dysfunction carries a high risk of early death. Because lungs get injured early on in the hours after initial brain insult in the potential donor, lung management should include correct ventilatory settings, alveolar recruitment, bronchoscopy with suctioning and lavage for culture sampling, management of patient fluids, and chest repositioning. ABO denotes blood groups A, B, AB, and O, CVP central venous pressure, DCD donation after circulatory death, ECMO extracorporeal membrane oxygenation, EVLW extravascular lung water, Pao_2–Fio_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen, PEEP positive-end expiratory pressure, and PiCCO pulse index contour cardiac output.

access to both lungs, mediastinal structures, and the heart for central cannulation for extracorporeal life support. A median sternotomy supported by venoarterial ECMO or cardiopulmonary bypass allows better decompression of the heart but requires more anticoagulation, whereas a bilateral anterior sternal-sparing thoracotomy results in fewer sternal healing complications.[38] Many centers have now moved to ECMO as opposed to cardiopulmonary bypass in cases when intraoperative support is needed.[39] Routine ECMO use is proposed by some; however, performance of lung transplantation without any mechanical support when technically feasible yields lower rates of primary graft dysfunction.[40] Oversized donor lungs can be made smaller for allocation to recipients with smaller or deformed chests by means of nonanatomical lung-volume reduction or anatomical lobectomy; refining donor–recipient size-matching may improve outcomes with this approach.[41] Living-donor lobar lung transplantation is an uncommon procedure and is currently mainly practiced in Japan.[42]

EARLY POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Primary graft dysfunction is an acute lung injury that occurs immediately after lung transplantation and is characterized by pulmonary edema and hypoxemia.[43] The pathophysiologic mechanisms of primary graft dysfunction begin with donor brain death and critical illness and are compounded by lung ischemia–reperfusion injury with characteristic activation of an early innate immune response in both the donor lung and the recipient.[43] Severe primary graft dysfunction occurs in 15 to 25% of transplants and has a major effect on the length of stay in the intensive care unit and on 90-day and 1-year mortality.[12] CLAD is more likely to develop in survivors of primary graft dysfunction, who have higher long-term mortality.[19,20] Therefore, strategies aimed at preventing primary graft dysfunction could have a major effect on longer-term outcomes. Elevated risk of primary graft dysfunction occurs with greater recipient adiposity, pretransplantation lung fibrosis, and pulmonary hypertension.[19,20] Donor smoking history is associated with a milder form of primary graft dysfunction, without increased mortality.[20] Treatment is supportive, with early ECMO commonly used in patients with severe primary graft dysfunction.[12,44]

Ventilation strategies after lung transplantation aim to reduce lung injury through the use of lung-protective ventilation.[44] Infections are common in the early post-transplantation period, and the use of prophylactic antimicrobial agents tailored to donor and recipient cultures is routine. Acute kidney injury due to the physio-

logical effects of surgery and critical illness, as well as the nephrotoxic effects of immunosuppression and antimicrobials, contributes to early complications and may lead to chronic kidney disease.[44]

Vascular complications at the level of the pulmonary artery or left atrial anastomoses, such as kinking, stenosis, thrombosis, and infarction, are rare but may result in graft loss or death if not recognized early (Fig. 2). Partial dehiscence of the airway anastomoses affects up to 10% of lung-transplant recipients. Acute airway ischemia and secondary infection of the anastomotic site are risk factors, with fungal infection often being a serious complication.[45] Airway stenosis typically occurs later in watershed areas of the airways and can cause mucus retention, recurrent infection, breathlessness with wheezing and stridor, and even complete airway occlusion in severe cases. Bronchial dilation and stenting can improve function. Malacia, defined as dynamic collapse of the airway to less than 50% of its diameter on expiration, is difficult to treat, and its management includes infection prevention, use of continuous positive airway pressure, stenting in selected patients, and relief of symptoms.[46]

IMMUNOSUPPRESSION STRATEGIES

Benefits of induction therapies that deplete or inhibit lymphocytes in the peritransplantation period have historically been equivocal in lung transplantation. The use of induction therapy is inconsistent and center-specific and is frequently tailored to a candidate's risk of infection and immune status.[47] Any use of induction therapy occurs in 64% of recipients, with basiliximab, a monoclonal interleukin-2–receptor antagonist, being the most common agent used and having the most evidence of benefit.[48] Alemtuzumab and antithymocyte globulin are alternative therapies.[49]

A three-drug maintenance immunosuppression regimen comprising a calcineurin inhibitor (cyclosporine or tacrolimus), a low-dose glucocorticoid, and a cell-cycle inhibitor (azathioprine or mycophenolate mofetil) is used almost universally; mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus) and nondrug immunomodulatory therapies, such as antibodies directed against lymphocytes, total lymphoid irradiation, and extracorporeal photopheresis, have been reported either alongside or as replacements for traditional agents in specific circumstances.[47] Primary use of tacrolimus rather than cyclosporine A is associated with reduced incidence of CLAD.[50] The use of everolimus instead of mycophenolate mofetil showed a reduction in the incidence of bronchiolitis obliterans syndrome, biopsy-proven acute rejection, and infections but did not show any difference with respect to bronchiolitis obliterans syndrome–free survival.[51] Belatacept, which blocks T-lymphocyte costimulation, was associated with excess mortality among patients who had undergone lung transplantation, which shows the importance of evaluating agents in the lung transplantation population rather than extrapolating from reported findings of effectiveness in other organ transplantations.[52] The role of adjunctive inhaled cyclosporine in protecting against CLAD has not been established, and further studies are warranted.[53]

ACUTE LUNG ALLOGRAFT DYSFUNCTION (ALAD)

Lung allograft health is monitored with longitudinal spirometry; a fall in the forced expiratory volume in 1 second (FEV_1) of greater than 10% triggers investigation, even in the absence of symptoms. Allograft function can deteriorate considerably before symptoms manifest, and home spirometry with interactive technology may improve patient engagement with self-monitoring outside the clinic.[54] ALAD occurs because of a variety of reasons (Fig. 3), among which treatment differs widely. Early diagnosis is performed through history and examination alongside radiologic imaging, diagnostic blood tests, and bronchoscopy with bronchoalveolar lavage and endomucosal or transbronchial biopsies (or both). The advantages of routine bronchoscopic surveillance for up to 2 years after transplantation to aid early ALAD detection remain equivocal, yet it is common practice at many centers.[55] In many cases, ALAD can be effectively treated, and allograft function can return to baseline levels.[55]

Acute cellular rejection affects 20 to 50% recipients in the first year and is thought to be mostly driven by T-cell infiltration into the allograft.[56] In most cases, acute cellular rejection

resolves with glucocorticoid augmentation.[57] Recurrent or glucocorticoid-resistant acute rejection can be treated with antithymocyte globulin, total lymphoid irradiation, or extracorporeal photopheresis. Acute cellular rejection is diagnosed on the basis of transbronchial biopsies with ISHLT pathology scoring.[58] An A2 (mild rejection) or higher is almost universally treated, even in asymptomatic patients, whereas the need to treat asymptomatic A1 (minimal rejection) remains contentious. Careful monitoring may be appropriate if lung function remains stable, since studies have shown no clear increased risk of CLAD or death with A1 rejection.[59]

Antibody-mediated rejection, driven by recipient antibodies against donor HLA or non-HLA antigens, can occur in isolation or alongside acute cellular rejection. A combination of symptom recognition, the detection of new donor-specific antibodies, and changes in features of graft injury on radiologic and pathological examination increases confidence in a diagnosis of antibody-mediated rejection. Complement (C4d) staining is much less specific for antibody-mediated rejection in lung tissue, as compared with kidney tissue. Treatment includes antibody removal through plasma exchange and intravenous immune globulin, as well as immune-cell–targeted therapy with rituximab and proteasome inhibitors, bortezomib, or carfilzomib.[60] It is uncertain whether asymptomatic recipients with newly detected donor-specific antibodies and no radiologic or pathological evidence of antibody-mediated rejection should be treated.[61] Organizing pneumonia can occur early or late after lung transplantation and is associated with impaired function and increased mortality.[62]

Bacterial, fungal, and viral infections are a major cause of illness and death, with specific opportunistic organisms causing major challenges.[63] Primary infection with or reactivation of latent cytomegalovirus (CMV) is common and leads to systemic illness, graft injury, and an increased risk of CLAD. Approaches to limit CMV infection vary, ranging from universal prophylaxis to targeted risk-based approaches alongside monitoring for CMV viremia. Extending the duration of CMV prophylaxis to 12 months[64] or guiding the duration of prophylactic treatment through the measurement of CMV-directed immunity has shown promise in reducing late breakthrough infections.[65] Nontuberculous mycobacterial infections may cause substantial illness depending on the species, and if nontuberculous mycobacterial lung disease develops, the risk of death increases. *Mycobacterium abscessus* infection is especially challenging to manage post-transplantation because treatment involves a very long-term multiple antibiotic regimen and may include surgical débridement.[66]

Community-acquired respiratory viruses have a major effect on lung-transplant recipients. Severe infection with community-acquired respiratory viruses is associated with early CLAD development.[67] Ribavirin therapy has not been shown to protect against CLAD. Secondary infections such as invasive fungal disease after infection with a community-acquired respiratory virus substantially increases the risk of CLAD, progression, and death.[68] Long-term consequences of the SARS-CoV-2 infection are still emerging.[69]

Fungal infections, either intrathoracic or systemic, can cause major complications that warrant prolonged antifungal treatment. Aspergillus species are the most common cause, and universal or targeted prophylaxis is widely used to help reduce the risk. Pulmonary aspergillosis in lung-transplant recipients has been associated with an increased risk of subsequent CLAD development.[70]

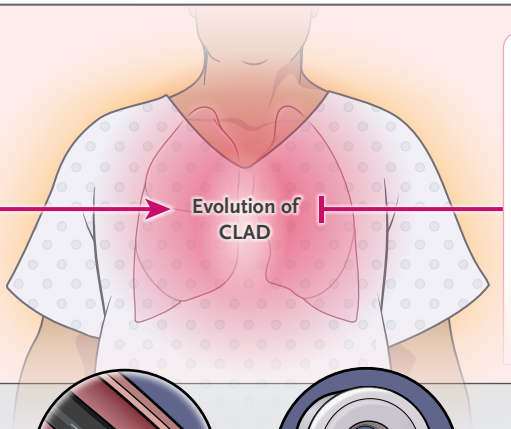
CHRONIC LUNG ALLOGRAFT DYSFUNCTION

Within 5 years, chronic rejection will develop in half the lung-transplant recipients, which substantially increases morbidity, restricts activities, and raises the risk of death. The umbrella term CLAD is now used. CLAD has two distinct but potentially overlapping phenotypes — bronchiolitis obliterans syndrome and restrictive allograft syndrome — which have improved the classification, understanding, and treatment of chronic rejection (Fig. 3).[71]

CLAD is the physiological manifestation of a complex interplay between innate and adaptive alloimmune responses in the lung allograft, leading to the final common pathway of dysregulated repair and fibrosis in airway (bronchiolitis obliterans syndrome) and parenchymal (restrictive allograft syndrome) compartments. The pathophysiologic mechanisms of CLAD involve early innate responses with neutrophils, macrophages,

Risk Factors for CLAD

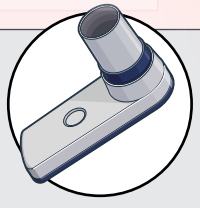
- Primary graft dysfunction (grade 3 within 72 hours after transplantation)
- Cellular rejection
- Antibody-mediated rejection
- Air pollution and smoking
- Gastroesophageal reflux
- Infections (pseudomonas, aspergillus, respiratory viruses, cytomegalovirus)

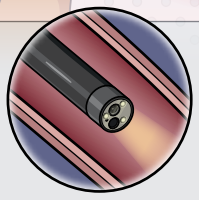


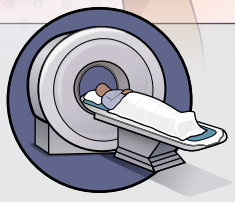
Preventive Strategies

- Induction therapy
- Maintenance immunosuppression
- Azithromycin prophylaxis
- Augmented corticosteroids
- Plasmapheresis, rituximab, IVIG, cyclophosphamide
- Medication and antireflex surgery for GERD
- Infection prophylaxis and treatments

Monitoring


Clinic and Home Spirometry


Surveillance, Responsive Bronchoscopy, or Both


Radiologic Surveillance


Molecular Diagnostics

Progression to CLAD

Diagnostic

Persistent **>20% decline in FEV_1 or FVC** from post-transplantation baseline value after exclusion of **non-CLAD** causes and treatment of all reversable causes

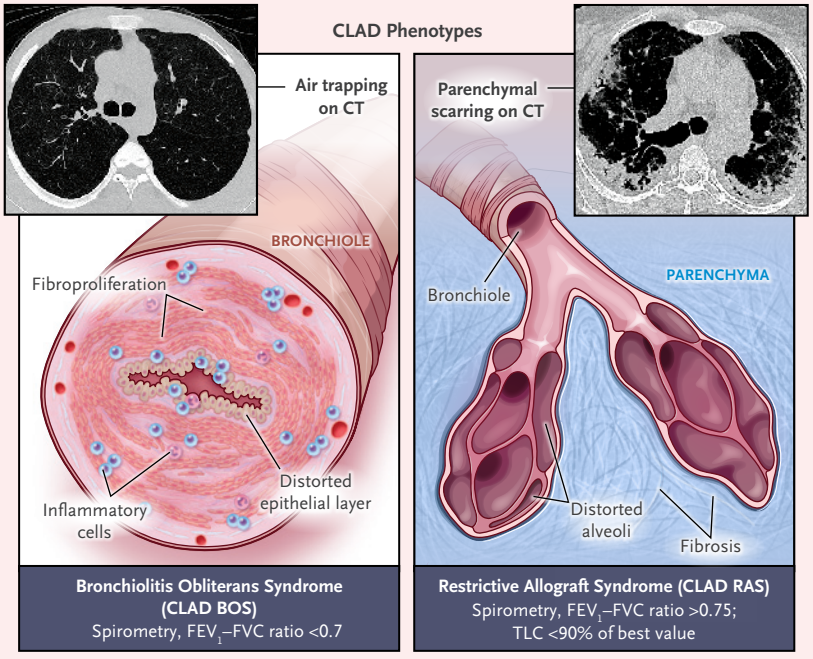
CLAD Stage	Current FEV_1 (% of baseline value)
0	>80%
1	>65 to 80%
2	>50 to 65%
3	>35 to 50%
4	≤35%

Non-CLAD Signs and Symptoms

Graft-related: acute cellular or antibody-mediated rejection, bronchial stenoses, infections, GERD with aspiration, disease recurrence, lung tumor

Extrapulmonary: weight gain, neuromuscular disease, diaphragm palsy, chest-wall injury or surgery

CLAD Phenotypes



Bronchiolitis Obliterans Syndrome (CLAD BOS)
Spirometry, FEV_1–FVC ratio <0.7

Restrictive Allograft Syndrome (CLAD RAS)
Spirometry, FEV_1–FVC ratio >0.75; TLC <90% of best value

CLAD Mixed
(BOS and RAS characteristics)

Management

Interventions

- Clinical trials
- Extracorporeal photopheresis
- Total lymphoid irradiation
- Lymphocyte-depleting therapy
- Antileukotriene therapy
- Inhaled cyclosporin
- Antifibrotic therapy
- Lung retransplantation

Supportive Approaches

- Supplemental oxygen
- Nutritional support
- Pulmonary rehabilitation
- Psychological support
- Palliative care
- Opioids
- Benzodiazepines
- Hospice

Figure 3 (facing page). Evolution of Chronic Lung Allograft Dysfunction (CLAD).

The lung allograft is exposed to a range of innate and alloimmune insults. Severe primary graft dysfunction, acute rejection, pulmonary infections, gastroesophageal reflux, and air pollution are all associated with an increased risk of CLAD. Preventive strategies are designed to minimize graft injury and protect function. Lung function testing, lung imaging, molecular diagnostics, and bronchoscopy with bronchoalveolar lavage and lung biopsy allow a comprehensive assessment of the allograft and helps identify any lung-related or extrapulmonary causes of acute lung allograft dysfunction (ALAD). CLAD is diagnosed when the forced expiratory volume in 1 second (FEV_1) decreases more than 20% from the best post-transplantation level with no reversible causes identified or if dysfunction is not corrected despite adequate treatment of any cause for ALAD. CLAD phenotypes of bronchiolitis obliterans syndrome (BOS), restrictive allograft dysfunction (RAS), or mixed are classified on the basis of the pattern of the lung function defect and the presence or absence of radiological lung infiltrates. Treatment of CLAD falls into two broad strategies: supportive care aimed at symptom relief and suppression of ongoing alloimmune injury. These include pharmacologic approaches that target effector immune-cell function[29] and also more generalized immunomodulation through extracorporeal photopheresis[30] or total lymphoid irradiation.[31] Participation in clinical trials that robustly evaluate interventions is to be strongly encouraged. Retransplantation is an option for highly selected recipients with very severe CLAD, but palliative care should be initiated as disease progresses. CT denotes computed tomography, FVC forced vital capacity, GERD gastroesophageal reflux disease, IVIG Intravenous immune globulin, and TLC total lung capacity.

and eosinophils and later adaptive responses with T and B lymphocytes alongside cytokine, immunoglobulin, and complement activation.[72] The diagnostic and therapeutic approach to CLAD is detailed in Figure 3. Current treatments for CLAD, at best, slow or temporarily halt the loss of lung function. The evidence base consists mainly of small, uncontrolled, and single-center studies, thereby leaving it unclear if reported benefits reflect the treatment or the natural history of CLAD, which can, in some recipients, stabilize for many years.[73] Lung retransplantation is considered in selected recipients with CLAD, but the second procedure accounts for less than 5% of the worldwide lung transplantation activity. Although it is associated with outcomes that are inferior to those with primary lung transplantation, late bilateral retransplantation for CLAD has better outcomes than early retransplantation for severe primary graft dysfunction or with single-lung retransplantation.[74]

CANCER

Cancer is more common in the post–lung transplantation population than in the general population and frequently has a worse prognosis, accounting for up to 17% of deaths. Lung cancer and post-transplantation lymphoproliferative disease (PTLD) are the most common causes of cancer-related mortality.[75] Chronic immunosuppression, effects of previous cigarette smoking, or risk from underlying lung disease contribute to the risk of lung cancer in the native lung of single-lung recipients, although in rare cases, donor transmission of subclinical lung cancer can occur with transplanted lungs. Nonmelanoma skin cancers are the most common cancers among transplant recipients, and regular dermatologic cancer surveillance is mandated. Epstein–Barr virus–driven B-cell PTLD is a major cause of illness and death. Although PTLD can regress with immunosuppression minimization, targeted B-cell therapy with rituximab, systemic chemotherapy, or both is often warranted.[76]

SURVIVAL AND LONG-TERM OUTCOMES

Survival after lung transplantation, as compared with other organ transplantations, remains limited at a median of 6.7 years, with little progress with respect to long-term outcomes over three decades.[11] However, many patients have substantial improvements in quality of life, physical performance, and other patient-reported outcomes; more focus on these patient-reported outcomes is warranted in order to provide a more holistic assessment of the therapeutic benefit of lung transplantation.[8,10,77] Addressing recipient mortality due to either late graft failure or fatal complications of long-term immunosuppression remains an important unmet clinical need. The long-term care of lung-transplant recipients is active and involves a team approach with careful balance between monitoring and maintaining graft function while also protecting the overall health of the recipients by minimizing the adverse effects of immunosuppression and supporting their physical and psychological well-being (Fig. 1).[4,77]

FUTURE DIRECTIONS

Lung transplantation has progressed substantially as a therapeutic method in a short time but has yet to reach its full potential. The shortage of suitable donor lungs remains a major challenge, and new methods for assessing and caring for donors, delivering therapies to treat and modify donor lungs, and enhancing preservation continue to be developed. The refinement of organ-allocation policies through enhanced donor–recipient matching is needed to further increase the net benefit. Interest in molecular diagnostics for rejection or infection or in guiding the minimization of immunosuppression is growing, especially with the use of donor-derived cell-free DNA; however, their utility as adjuncts to current clinical approaches to graft monitoring are still to be established.[78]

Working together as a lung transplantation community through the formation of consortia (e.g., ClinicalTrials.gov number, NCT04787822; https://lungtransplantconsortium.org) will facilitate faster progress with respect to the prevention of primary graft dysfunction and treatment, prediction of CLAD, early diagnosis and endotyping, syndrome refinement, and mechanistic understanding of primary graft dysfunction, antibody-mediated rejection, ALAD, and CLAD. Individualization of immunosuppression to minimize side effects and reduce the risk of ALAD and CLAD, along with defining and incorporating patient-centric outcomes into outcome measures, are key foci to improve the long-term success of lung transplantation.

The views expressed are those of the authors and not necessarily those of the National Institute of Health, the Cystic Fibrosis Foundation, the National Institute for Health and Care Research, National Health Service Blood and Transplant or the U.K. Department of Health and Social Care.

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