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REVIEW

PEDIATRIC PULMONOLOGY WILEY

Disparities in lung transplantation in children

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Abstract

Lung transplantation is a recognized therapy for end-stage respiratory failure in children and young people. It is only available in selected countries and is limited by access to suitable organs. Data on disparities in access and outcomes for children undergoing lung transplantation are limited. It is clear from data from studies in adults, and from studies in other solid organ transplants in children, that systemic inequities exist in this field. While data relating specifically to pediatric lung transplantation are relatively sparse, professionals should be aware of the risk that healthcare systems may result in disparities in access and outcomes following lung transplantation in children.

KEYWORDS
lung transplantation, social dimensions of pulmonary medicine

1 | INTRODUCTION

There are almost 70,000 episodes of lung transplantation recorded to date in the International Society of Heart and Lung Transplantation (ISHLT) registry,[1] of which 2777 are recorded as pediatric procedures.[2] The approximate incidence of pediatric lung transplantation is around one procedure per 10 million of total population per annum in developed countries with an established pediatric program. Pediatric lung transplantation is thus a rare event, and while readers will be familiar with the pathologies that may lead to a need for transplantation, many respiratory pediatricians will only care for one or two patients who have been listed, or successfully transplanted, during their careers.

Measuring disparities in care for rare events is challenging, as data are scarce. The only systematic review of social determinants of health in pediatric solid organ transplants includes 93 studies, of which only one mentions any data on lung transplantation.[3] As healthcare professionals, however, we should be mindful of the risk that external factors may play a role in determining who eventually receives donor lungs. By examining the pathway to transplantation, and by describing data from adult lung transplantation as well as from other solid organ transplant activity, we will outline the potential risks to disparity in this small group of patients, and describe the current system and technological approaches that seek to mitigate these risks.

2 | LUNG TRANSPLANTATION AS A THERAPY FOR END-STAGE RESPIRATORY FAILURE IN CHILDREN

The first successful pediatric lung transplant was performed in 1987, at the University of Toronto, for a 16-year-old patient with pulmonary fibrosis.[4] Since then, lung transplantation has become established as a treatment for end-stage respiratory failure in children and young people. The commonest disorders resulting in listing for pediatric lung transplantation in the era 2010–2018 are cystic fibrosis (CF, 51%), pulmonary vascular disease (21%), and

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childhood interstitial lung diseases (chILD, 11%)[2]; the impact of CF transmembrane regulator (CFTR) modulators is predicted to decrease transplantation for CF, whereas pulmonary vascular diseases and chILD appear to be increasingly recognized.[5]

Following referral to transplant teams, patients undergo a series of investigations as part of a structured assessment. As well as assessments of respiratory efficiency (lung function, exercise tests, polysomnography), imaging (computed tomography [CT] scan and plain radiograph, abdominal ultrasound, echocardiography, dual energy X-ray absorptiometry scan), and renal function, a detailed psychosocial history including adherence/concordance to therapies, schooling, and family support is a key part of the assessment.[6] Neuropsychological outcomes are reported as improved following transplantation.[7]

Surgery is via a transverse thoracotomy ("clamshell incision") or median sternotomy, with bilateral bronchial and pulmonary artery anastomoses. Historically, breakdown of the airway anastomoses was a repeated concern postoperatively,[4] modern surgical techniques and immunosuppressive agents have made this a rarer event.[6] Post-operatively, patients remain in intensive care for approximately 7 days and are discharged around 3 weeks following the operation. There is initially a period of frequent follow-up; monitoring for rejection, opportunistic infection, and side effects of life-long immunosuppression. Patients transition to specialist adult centers for ongoing care once they reach late adolescence. International data demonstrate a median conditional survival (those alive at 1 year postprocedure) of around 9 years.[2]

3 | INDICATIONS FOR REFERRAL TO LUNG TRANSPLANTATION TEAMS

The ISHLT International Guidelines for the Selection of Lung Transplant Candidates were first published in 1998 with updates in 2006, 2014, and 2021,[8] new pediatric-specific guidelines are currently in preparation. Children and young people should be referred if they have a progressive lung disease on maximal medical therapy, with a short predicted lifespan and/or poor quality of life. As waiting times are longer, particularly for smaller children, early referrals are advised. These consensus statements play out in day-to-day practice depending on the underlying disease and the age of the child, and additional factors including donor organ availability (predominantly relating to recipient height and blood group), existing sensitization to human leucocyte antigen (HLA) types carried by potential donors, and rate of disease progression. To assess the factors that may introduce disparities into the system, it is first important to understand those pathways, which may differ from country to country in specific aspects but are broadly similar overall.

Children and young people with significant respiratory disease first need to come to the attention of medical teams. Patients with repeated chest infections, with significant symptoms of breathlessness and wet cough, are likely to come to medical attention, whereas those with idiopathic pulmonary hypertension depend on physicians recognizing the possibility of the diagnosis and having access to echocardiography, as well as to pediatric cardiologists with expertize in this area. Children with failure to thrive, or wheeze not responding to usual medical therapy, as seen in some presentations of interstitial lung disease, again depend on diagnosis by experienced clinicians, as well as access to CT scans and lung biopsies, and radiologists and histopathologists who can support the diagnostic process.

Once a disorder is recognized and medical treatment started, the progression of the disease depends both on the ability of medical teams to deliver appropriate therapies and the access that patients have to those therapies. For example, before September 2022, patients in Canada with CF would be eligible for referral for lung transplantation at one of a number of highly experienced centers, yet may not have had access to elexacaftor/tezacaftor/ivacaftor (ETI; "Trikafta", "Kaftrio") on the basis of local funding decisions,[9] these CFTR modulators are projected to decrease the number of patients with severe CF lung disease by 60%.[10] At the time of writing, age cut offs for access to ETI differ around the world (12 years and above in Canada and Australia, 6 years and above in the United Kingdom and Ireland). Wider access to these medications should result in a large proportion of patients with CF being removed from active listing, following an existing trend of fewer patients with CF requiring transplantation over the last decade.[5] These medications are expensive,[11] and it is notable that they are predicted to improve the median age of survival by 9.2 years,[10] which is 0.1 years longer than conditional median survival following pediatric lung transplantation.[12] Lack of access to these medications in some parts of the world is an obvious source of disparity for children who are potentially on a transplant pathway. "Disparity" can act in both directions, and a situation where funding decisions affect access to maximal medical therapy, meaning that referral to transplant occurs earlier in one patient group compared to another lacks equity, no matter how "good" the access to a transplant service. A treatment course where the provision of ETI provides an additional 9 years of survival before listing for lung transplantation appears preferable overall to lung transplantation earlier in life.

Pediatricians working in teams caring for children with end-stage lung disease need the knowledge and experience to recognize when a transplant referral is indicated. This is a challenging time for patients and families as it may be a point at which the severity of their condition is acknowledged openly by referral to an external team. Early referral where possible is repeatedly stressed in consensus documents,[8] but some of the terminology in these documents is less specific than a clinician may need at the point of decision making; how to define a "short life expectancy" or a "poor quality of life"? As transplantation services are highly centralized in many countries, only a minority of pediatric respiratory physicians will be exposed to transplant assessments during their training. In our center, we consider a short life expectancy to be less than 2 years (with all the inherent uncertainty in trying to predict this) and would judge a "poor quality of life" to be one where significant breathlessness with/or hypoxia limit children to being housebound, or only able to attend school for limited periods in a wheelchair with supplemental oxygen.

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Although specific criteria for referral are agreed in consensus for both CF[13] and pulmonary hypertension,[14] outside of these diagnoses the decision to list comes down to subjective judgments, which it is important to be open about with children and families as well as referrers.

Transplant teams seek to avoid, where possible, referrals where the patient is felt to be less likely to survive the probable time that they may wait for a suitable organ offer, and, therefore, erring on the side of earlier referral is advised.[8] Early discussions are certainly helpful, and may postpone or avoid the need to go on to a formal referral at that stage following a discussion between teams, we encourage this approach in our practice in the United Kingdom.

Evidence to support current practice in this area can be extrapolated from adult lung transplant services in the United Kingdom. The second Atlas of variation in risk factors and healthcare for respiratory disease in England examined the variation in rate of lung transplants per population by the Strategic Health Authority in England for 2017/2018.[15] For 284 new registrations to the adult lung transplant list in the time period, the National Health Service Blood and Transplant Annual Report on Cardiothoracic Transplantation found no evidence of geographical variation between Strategic Health Authorities (geographical areas in England by which healthcare is organized) beyond what would be expected at random. This suggests that referrals are evenly distributed across England by adult respiratory physicians. This study has not been repeated for pediatric lung referrals, but evidence from referrals for children with transplant-eligible end-stage kidney disease in the United Kingdom[16] suggests that neither geographical location nor socioeconomic deprivation is associated with late presentations to services. While renal services differ to lung transplant services in that there is a long-term alternative to transplantation (via dialysis), this study assessed data on 2160 children aged 3 months to 16 years, and did not see an effect of distance to center, or socioeconomic status,[17] and, therefore, it could be postulated that there may be a protective effect from universal healthcare systems. However, a study of adult renal patients encompassing all 71 renal centers in the United Kingdom[18] did show socioeconomic status was associated with a lower incidence of pre-emptive listing for transplantation. Taking a wider view, a recent systematic review of pediatric solid organ transplant care related to social determinants of health, predominantly reviewing data from studies including kidney and liver patients in multiple countries,[3] demonstrated consistent disparities in outcomes related to ethnicity including timing and likelihood of transplant, as well as posttransplant outcomes including rates of rejection, incidence of graft failure, and overall mortality. In those with renal disease, Black children had a longer wait for transplant,[19] and Black and Hispanic children were more likely to spend at least 12 months on dialysis before transplant.[20,21] Findings related to insurance status, location, and socioeconomic status varied[3] but financial issues were highlighted as the primary barrier to transplantation in studies in the United States.[22,23]

4 | DISPARITIES WITHIN LUNG TRANSPLANT SERVICES

This is a contentious area, within which the main debate is about how services are arranged. Lung transplant services for children and young people can either be embedded within larger adult services or delivered by services specializing in pediatric care alone. The benefits of embedding with adult teams are those of greater experience due to volume (around 20 times more adult than pediatric lung transplants take place per annum in the United Kingdom),[24] and although it appears intuitive that higher center volume should result in improved outcomes this is not necessarily the case for pediatric patients and may be disease-specific.[25] In one registry study,[26] younger patients (<12 years) who had their surgery in a high-volume pediatric center (>4 transplants/year) had better 30-day graft survival than those operated on in a combined adult–pediatric center, with trends toward better overall survival, and 1-year conditional survival versus low-volume pediatric centers (<4 transplants/year) and adult centers. In children aged under 12 years, those undergoing surgery in a high-volume center had a median survival of 7.6 versus 2.9 years for those in a low-volume center ($p = .002$). Similar trends were seen in older children (12–17 years).

Adult physicians and multidisciplinary teams will be less experienced in pediatric-specific diseases (such as childhood ILD), consent, safeguarding, and adherence issues relevant to pediatric practice, growth and nutrition, and medical care of children following transplantation. These aspects are particularly relevant in infants and young children undergoing transplantation. Services delivered by pediatricians benefit from these strengths, and the surgeons working in these teams will be more experienced in performing operations on younger children, including highly specialized procedures such as "trimming" (selective lobectomy or partial lobectomy of donor lungs to fit the recipient thorax). Due to the infrequent nature of the surgery, however, surgeons will perform fewer transplants per annum and opportunities for training will be limited by this. In a resource-limited environment, it is possible that surgeons with varying practice and experience in highly specialized surgery may not always be immediately available (e.g., if another thoracic organ offer has come in immediately before a current offer). Potential novel approaches to these challenges include organizing regional rotas for on-call surgeons (mirroring the model used by organ retrieval teams) to avoid supra-regional disparities in access to emergency surgery.

5 | DISPARITIES IN PEDIATRIC TRANSPLANTATION OF OTHER SOLID ORGANS

The is a growing body of evidence that children who require transplantation of other solid organs (kidney, liver, and heart) face disparities at various points in the transplantation pathway; from accessing the waiting list through to posttransplant outcomes. Examining this evidence demonstrates several common themes that

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are likely to become increasingly relevant to the field of pediatric lung transplantation as lung transplant programs continue to develop and expand around the world.

5.1 | Sex and gender

There is disparity in access to solid organ transplantation, and in outcomes posttransplantation, with respect to sex and gender.[27] Across adult and pediatric practice, women and girls have less access to organs and poorer outcomes; the reasons for these are multifactorial and depend on health systems as well as differences in the prevalence between sexes in diseases resulting in end-stage organ failure, and biological factors, and are extensively reviewed.[27] For lung transplantation overall, it appears that women have better outcomes than men in terms of graft survival.[28] Specific to pediatric lung transplantation, one single-center study (n = 58) reported poorer outcomes with respect to the female sex, sex-mismatched transplants, and particularly male donor to female recipient,[29] these analyses are based on comparisons between 12 and 18 transplants and the authors highlight the need for further studies to investigate this further. A preceding single-center study (n = 53) did not find an association between sex and outcomes.[30]

5.2 | Ethnicity

Ethnicity is perhaps the most widely studied variable in the context of transplant inequity. In kidney transplantation, children from minority ethnic backgrounds are significantly disadvantaged at every stage of the treatment pathway with late referral to specialist services,[31] reduced access to the waiting list,[32] longer waiting times,[19,33–35] a lower likelihood of receiving a kidney transplant from both deceased and living donors,[31,33,34,36–38] decreased rates of pre-emptive transplantation,[31,34] and significantly poorer long-term graft survival.[20,39,40] These disparities are widespread across many different countries and have predominantly been reported among Black and Hispanic patients in the United States, Black and Asian patients in Europe, and Indigenous and Aboriginal patients in Canada, New Zealand, and Australia. Several studies from the United States show that ethnic minority children undergoing heart transplantation experience higher waiting list mortality,[41,42] increased rejection episodes[41,43] and two to three times higher rates of graft loss and patient death posttransplantation.[43] Interestingly, ethnicity has not been shown to be a major determinant of transplant outcomes in pediatric liver transplantation, except for being associated with a reduced likelihood of living donor liver transplantation.[44–47] There are many potential complex reasons for these concerning differences in care. Biological factors such as HLA and blood group types of minority ethnic patients can contribute to a reduced likelihood of receiving a donor organ due to scarcity of compatible donors. Organ donation is less accepted in ethnic minority communities and data from the United Kingdom show that the family authorization rate for organ donation in potential pediatric donors is considerably lower amongst Black, Asian, and Minority ethnic families compared with White families (37% vs. 61%).[48] This leads to underrepresentation of minority ethnic groups in the donor pool. There may be reduced awareness or acceptance of transplantation as a treatment option in specific communities, where cultural or religious beliefs and language barriers are contributing factors. Similarly, clinicians and healthcare providers may themselves hold preconceived ideas or biases toward specific ethnic groups. Certain hereditary diseases or comorbidities such as obesity, diabetes, and hypertension are more common in patients from ethnic minorities[49] which can not only affect their own suitability for transplantation but also the suitability of their relatives to become living donors. This also prolongs the transplant evaluation period. Furthermore, all of the above issues may result in patients having more severe disease by the time they are listed or transplanted, leading to higher waiting list mortality and worse posttransplant outcomes. The intricate relationship between ethnicity and socioeconomic deprivation is another important consideration which may impede access to optimal care such as adherence to immunosuppressive medications or attending specialist services for follow-up. Several studies demonstrate an interaction between ethnicity and socioeconomic deprivation whereby disparities for certain ethnic minorities in pediatric transplantation are somewhat mitigated by socioeconomic status.[32,50]

5.3 | Socioeconomic deprivation

The association between socioeconomic deprivation and child health outcomes is well established and has been reported in the context of both public and private healthcare systems. Socioeconomic deprivation can be measured by lack of health insurance, low income, or socioeconomic deprivation scores. In pediatric kidney transplantation socioeconomic deprivation appears to mostly affect the earlier stages of the transplantation pathway including referral to specialist services,[51,52] activation on the waiting list,[32,53] and pre-emptive transplantation.[16,52] This is particularly concerning for children with renal failure, where early diagnosis and access to pre-emptive transplantation confers significant benefits on growth, development, and survival by avoiding the detrimental effects of dialysis. Children from more socioeconomically deprived backgrounds are at higher risk of mortality on the liver transplant waiting list,[47] long-term graft failure and death after liver transplantation,[50,54] and have poorer survival both on the waiting list and after heart transplantation.[55] The mechanisms by which social deprivation affects access to and outcomes from transplantation for children are complex and closely related to parental disadvantages and the community in which they live. Financial disadvantage may significantly impact a child's ability to access healthcare services and treatment, particularly in private healthcare systems. However, other hidden costs such as transport to frequent hospital appointments, ability for parents to take time off work or costs of staying near to specialist transplant centers may all provide significant barriers for families from low-income

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backgrounds. Socioeconomic deprivation is strongly associated with lower educational attainment and reduced health literacy, which may influence parent's perception and understanding of transplantation and subsequent decisions they make on behalf of their child.[56–58] For example, many of the concepts and discussions in the transplant space depend on written materials and internet resources to support the face-to-face clinic discussions, and parents with literacy or financial challenges may find it difficult to understand (or access) these materials. The immunosuppression regimes after transplant involve multiple medications, with doses that may change frequently depending on drug levels and if parents find it hard to access, retain, or act on changing information then this may disadvantage their child. Parents with reduced confidence and ability to participate in medical discussions are less engaged with the transplantation process, resulting in lower motivation and capacity to be an advocate for their child through, for example, recruiting potential living donors. This is compounded by lack of social support in deprived families. Children living in poverty-stricken areas may also be affected by inadequate and stretched healthcare services leading to poorer care compared to more affluent areas.

5.4 | Geography

Where a child lives has been shown to significantly affect their access to and outcomes from organ transplantation. However, these associations vary widely between different countries. In the United States, living further away from the child's transplant center is associated with increased mortality on the kidney and liver waiting list, but is not related to the likelihood of receiving a transplant, that is, the higher risk of death is not a result of a lower chance of transplantation and other factors are at play.[37,47] There is also significant inter-center and interregional variation in the United States in access to transplantation and waiting list mortality for children who need a liver or heart transplant.[55,59] In Canada, further distance from the renal transplant center is associated with a lower likelihood of transplantation[33] and in Australia, children from remote regions are less likely to undergo pre-emptive transplantation.[60] In the United Kingdom, distance to center is not associated with kidney transplantation after adjusting for other factors.[16] In France, children treated in a pediatric versus adult renal transplant center have a lower likelihood of transplantation, which is felt to be due to differences in center practices where pediatric centers use stricter HLA matching requirements.[61] Geographical disparities can be caused by a number of different factors. Wide variation in center practices have developed, often within the same country, due to lack of evidence-based guidelines on patient assessment processes and acceptance criteria for transplantation. Regional differences in transplantation outcomes may also be related to variations in donor availability, in countries that do not employ national organ allocation systems. Differences in the availability of resources can also lead to a postcode lottery in care. Children who live further away from tertiary centers are likely to experience greater challenges in accessing specialist centers and receiving follow-up care, and in some cases, the family will need to take into account the need to move house for the uncertain duration of time while their child is on the waitlist. Although this problem is also seen in the adult transplant population, the problem is magnified for pediatric patients where the number of pediatric transplant centers is even smaller. Where a child lives is closely linked with socioeconomic deprivation. In the United Kingdom, a higher number of affluent children live remotely, whereas for Australian children, the inverse is true.[60]

There is currently a paucity of research and understanding of the underlying mechanisms behind the disparities in pediatric transplantation and consequently a lack of effective solutions. More needs to be done to ensure that all children have equitable access to transplantation with optimal outcomes.

6 | ORGAN OFFERS AND ALLOCATION POLICIES

Wait times for suitable organ offers vary from country to country. This is related to a number of factors including rates of accidental deaths in children and young adults[62] (as way of illustration, in 2010, children in the United States were five times more likely to die in a road traffic accident than children in the United Kingdom),[63] as well as rates of organ donation, approaches to donor management in the intensive care unit, and technological approaches to increasing the utility of potential organs. Many of the factors that are key to accepting organ offers are nonmodifiable (donor age, donor height—as a surrogate for organ size, donor co-morbidities, and smoking status), but newer technologies mean that some of the other factors (donor blood group epitope status, organ function, organ size and distance to transplant center) may be modifiable now, or in the future.

In adults, the median time to lung transplant following listing in the United States is 42 days,[64] in the United Kingdom it is 422 days.[24] Directly comparable data for pediatric patients is less available, in the United States 45.4% (six of 14 patients) had been on the waitlist less than 6 months at the time of reporting for the 2020 data,[64] median waiting time in the United Kingdom from 2015 to 2018 for pediatric patients was 210 days (17 transplanted from 23 registrations).[24] Waitlist mortality varies due to fluctuations in small numbers but is around 25% in the United States[65] and United Kingdom.[24] Waitlist times are shorter and waitlist mortality is lower for pediatric patients in Australia.[66]

Countries differ in their approach to allocating organs to specific recipients.[67] In the United Singdom, and countries in Europe that participate in Eurotransplant, previously a “lung allocation score” (LAS) was used to determine which recipient was most in need (and would be predicted to derive the most benefit) from new lungs[68]; it has recently been updated by a “composite allocation score” (CAS). In the United States the CAS, and previously the LAS, replaced a previous system based on time on the waiting list which perversely incentivized clinicians to list patients early.[68] This is relevant to

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pediatrics as the CAS is calculated from 12 years of age.[67] Patients under 12 years in the United States are listed as "priority 1" or "priority 2" on the basis of disease severity.[69] Canada uses a "status" system[70] and the United Kingdom uses a tiered system (super urgent, urgent) followed by regional offers.[71] A detailed review of how these systems affect adult lung transplantation is beyond the scope of this review[72] but, inevitably, the way organs are allocated must benefit some individuals at the expense of others as no system can be perfect; and allocation systems are regularly reviewed and updated to adjust for discrepancies as they become apparent.[67,72,73]

7 | TECHNOLOGICAL APPROACHES TO ADDRESSING THE AVAILABILITY OF DONOR LUNGS

Disparities emerge in healthcare as new technologies emerge, as highlighted above when considering access to CFTR modulators. In lung transplantation, techniques in ex-vivo lung perfusion (EVLP) have developed to a point where lungs deemed unsuitable for transplant (due to aspirated secretions, ventilator-acquired infection) can be resuscitated and subsequently used, with outcomes comparable to those seen using lungs that satisfy usual criteria at up to 1-year posttransplantation.[74] Expanding the donor pool in this fashion should decrease waiting times for organs, and as regulators and funders in different countries move at different speeds, disparities can arise. The United States and Canada have a history of reciprocal organ sharing and the early development and adoption of EVLP in Canada has led to a disparity in access to these resuscitated lungs, with organs declined by US centers being subsequently transplanted into patients in Canada[75] with similar outcomes both short term and at up to 5 years. It therefore appears that US centres are declining organs that could be used for patients on their waiting list, putting them (and those behind them on the list) at a disadvantage.[76] Center volume again appears to be important with better outcomes in high-volume centers with greater EVLP experience.[77] Experimentally, EVLP can be used to support newer approaches such as prolonged organ preservation allowing for much longer travel times (up to 3 days[78]) and addressing blood groups A, B and O mismatch,[79] with the potential to dramatically reduce waitlist times if widely adopted, but as with many emerging health technologies there are significant cost implications for health systems willing to act as early adopters.

8 | SUMMARY AND CONCLUSIONS

Significant disparities are identified in pediatric solid organ transplantation,[3] and while data for pediatric lung transplantation are scarce it would be remiss of professionals active in the field to assume that this means that the factors affecting renal, liver, and heart recipients do not affect children with end-stage respiratory failure. Of the factors highlighted, geography (distance to center) is likely to be of the greatest importance with only 31/195 countries providing a transplant service[67] and little coverage for large populations in South East Asia and South America. Of the published data on outcomes, it does appear that centers performing higher numbers of pediatric transplants report improved survival, particularly in younger children,[26] and as overall numbers of lung transplants decrease in the CFTR modulator era, this finding may provide a driver for some centers to amalgamate their resources. This will have to be balanced against geographical factors as centralizing services resulting in greater journey distances to the transplant center for some families. If centers remain in the locality then efforts to share learning via digital hub and spoke models may support multidisciplinary teams in lower volume centers.

Additional bottlenecks are likely to be the number of surgeons who can perform superspecialist procedures such as lung trimming, and the availability of EVLP to increase the number of organs suitable for transplantation. The next decade should be a period of growth for pediatric lung transplantation if these challenges are met, and efforts to assess for potential disparities in the services we provide should run parallel to these endeavors.

AUTHOR CONTRIBUTIONS

Rossa Brugha: Writing—original draft (equal). **Diana Wu**: Writing—original draft (equal). **Helen Spencer**: Writing—review and editing (equal). **Lorna Marson**: Writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Perch M, Hayes D, Cherikh WS, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-ninth adult lung transplantation report-2022; focus on lung transplant recipients with chronic obstructive pulmonary disease. *J Heart Lung Transplant*. 2022;41(10):1335-1347.
2. Hayes Jr., D, Cherikh WS, Harhay MO, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-fifth pediatric lung transplantation report-2022; focus on pulmonary vascular diseases. *J Heart Lung Transplant*. 2022;41(10):1348-1356.
3. Rea KE, West KB, Dorste A, et al. A systematic review of social determinants of health in pediatric organ transplant outcomes. *Pediatr Tranplant*. 2023;27(1):e14418.
4. Mendeloff EN. The history of pediatric heart and lung transplantation. *Pediatr Tranplant*. 2002;6(4):270-279.
5. Avdimiretz N, Benden C. The changing landscape of pediatric lung transplantation. *Clin Transplant*. 2022;36(4):e14634.

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6. Rossa Brugha HS. Lung transplantation in children. In: Janes S, ed. *Encyclopedia of Respiratory Medicine*. 2nd Ed. Elsevier; 2021.
7. Gold A, Young JM, Solomon M, Grasemann H. Neuropsychological outcomes following pediatric lung transplantation. *Pediatr Pulmonol*. 2020;55(9):2427-2436. doi:10.1002/ppul.24915
8. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2021;40(11):1349-1379.
9. Cystic Fibrosis Canada. TRIKAFTA. Accessed December 27, 2022. https://www.cysticfibrosis.ca/our-programs/advocacy/access-to-medicines/trikafta
10. Stanojevic S, Vukovojac K, Sykes J, Ratjen F, Tullis E, Stephenson AL. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with cystic fibrosis. *J Cyst Fibros*. 2021;20(2):243-249.
11. Guo J, Wang J, Zhang J, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. *J Cyst Fibros*. 2022;21(5):866-872.
12. Hayes Jr., D, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric lung and heart-lung transplantation report-2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38(10):1015-1027.
13. Aurora P, Wade A, Whitmore P, Whitehead B. A model for predicting life expectancy of children with cystic fibrosis. *Eur Respir J*. 2000;16(6):1056-1060.
14. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. 2019;38(9):879-901.
15. Office for Health Improvement & Disparities. *Public health profiles*. Crown copyright. 2022. Accessed December 27, 2022. https://fingertips.phe.org.uk
16. Plumb LA, Sinha MD, Casula A, et al. Associations between deprivation, geographic location, and access to pediatric kidney care in the United Kingdom. *Clin J Am Soc Nephrol*. 2021;16(2):194-203.
17. Patzer RE, Sayed BA, Kutner N, McClellan WM, Amaral S. Racial and ethnic differences in pediatric access to preemptive kidney transplantation in the United States. *Am J Transplant*. 2013;13(7):1769-1781.
18. Pruthi R, Robb ML, Oniscu GC, et al. Inequity in access to transplantation in the United Kingdom. *Clin J Am Soc Nephrol*. 2020;15(6):830-842.
19. Ng DK, Moxey-Mims M, Warady BA, Furth SL, Muñoz A. Racial differences in renal replacement therapy initiation among children with a nonglomerular cause of chronic kidney disease. *Ann Epidemiol*. 2016;26(11):780-787.
20. Patzer RE, Mohan S, Kutner N, McClellan WM, Amaral S. Racial and ethnic disparities in pediatric renal allograft survival in the United States. *Kidney Int*. 2015;87(3):584-592.
21. Laster M, Soohoo M, Hall C, et al. Racial-ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients. *Pediatr Nephrol*. 2017;32(4):685-695.
22. Steinberg Christofferson E, Ruzicka EB, Bolt M, et al. Understanding disparities and barriers associated with pediatric transplant evaluation and time to listing: moving toward a more comprehensive picture. *Pediatr Tranplant*. 2022;26(2):e14182.
23. Amaral S, Patzer R. Disparities, race/ethnicity and access to pediatric kidney transplantation. *Curr Opin Nephrol Hypertens*. 2013;22(3):336-343.
24. NHSBT. *Annual Report on Cardiothoracic Organ Transplantation 2020/2021*. NHSBT; 2022.
25. Hayes Jr., D, Sweet SC, Benden C, et al. Transplant center volume and outcomes in lung transplantation for cystic fibrosis. *Transpl Int*. 2017;30(4):371-377.
26. Khan MS, Zhang W, Taylor RA, et al. Survival in pediatric lung transplantation: the effect of center volume and expertise. *J Heart Lung Transplant*. 2015;34(8):1073-1081.
27. Melk A, Babitsch B, Borchert-Mörlins B, et al. Equally interchangeable? how sex and gender affect transplantation. *Transplantation*. 2019;103(6):1094-1110.
28. Chambers DC, Yusen RD, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017; focus theme: allograft ischemic time. *J Heart Lung Transplant*. 2017;36(10):1047-1059.
29. Mangiameli G, Arame A, Boussaud V, et al. Lung transplantation in childhood and adolescence: unicentric 14-year experience with sex matching as the main prognosticator. *Eur J Cardiothorac Surg*. 2016;49(3):810-817.
30. Görler H, Strüber M, Ballmann M, et al. Lung and heart-lung transplantation in children and adolescents: a long-term single-center experience. *J Heart Lung Transplant*. 2009;28(3):243-248.
31. Grace BS, Kennedy SE, Clayton PA, McDonald SP. Racial disparities in paediatric kidney transplantation. *Pediatr Nephrol*. 2014;29(1):125-132.
32. Furth SL, Garg PP, Neu AM, Hwang W, Fivush BA, Powe NR. Racial differences in access to the kidney transplant waiting list for children and adolescents with end-stage renal disease. *Pediatrics*. 2000;106(4):756-761.
33. Samuel SM, Foster BJ, Tonelli MA, et al. Dialysis and transplantation among Aboriginal children with kidney failure. *Can Med Assoc J*. 2011;183(10):E665-E672.
34. Chaturvedi S, Ullah S, LePage AK, Hughes JT. Rising incidence of end-stage kidney disease and poorer access to kidney transplant among Australian aboriginal and torres strait islander children and young adults. *Kidney Int Rep*. 2021;6(6):1704-1710.
35. Schoenmaker NJ, Tromp WF, van der Lee JH, et al. Disparities in dialysis treatment and outcomes for Dutch and Belgian children with immigrant parents. *Pediatr Nephrol*. 2012;27(8):1369-1379.
36. Laster M, Soohoo M, Hall C, et al. Racial–ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients. *Pediatr Nephrol*. 2017;32(4):685-695.
37. Cao B, Adler JT, Bababekov YJ, Markmann JF, Chang DC, Yeh H. Pediatric kidney transplantation and mortality: distance to transplant center matters. *Pediatr Tranplant*. 2018;22(2):e13120.
38. Tjaden LA, Noordzij M, van Stralen KJ, et al. Racial Disparities in access to and outcomes of kidney transplantation in children, adolescents, and young adults: results from the ESPN/ERA-EDTA (European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association) registry. *Am J Kidney Dis*. 2016;67(2):293-301.
39. Anand A, Malik TH, Dunson J, et al. Factors associated with long-term graft survival in pediatric kidney transplant recipients. *Pediatr Tranplant*. 2021;25(4):e13999.
40. Gondos A, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. *Transplantation*. 2013;95(2):267-274.
41. Amdani S, Bhimani SA, Boyle G, et al. Racial and ethnic disparities persist in the current era of pediatric heart transplantation. *J Card Failure*. 2021;27(9):957-964.
42. Singh TP, Gauvreau K, Thiagarajan R, Blume ED, Piercey G, Almond CS. Racial and ethnic differences in mortality in children awaiting heart transplant in the United States. *Am J Transplant*. 2009;9(12):2808-2815.

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43. Green DJ, Brooks MM, Burckart GJ, et al. The influence of race and common genetic variations on outcomes after pediatric heart transplantation. *Am J Transplant*. 2017;17(6):1525-1539.
44. Chinnaratha MA, Chelvaratnam U, Stuart KA, et al. Liver transplantation outcomes for Australian aboriginal and torres strait islanders. *Liver Transpl*. 2014;20(7):798-806.
45. Mogul DB, Luo X, Chow EK, et al. Impact of race and ethnicity on outcomes for children waitlisted for pediatric liver transplantation. *J Pediatr Gastroenterol Nutr*. 2018;66(3):436-441.
46. Neff GW, Kemmer N, Kaiser T, Zacharias V, Majoras N, Safdar K. Outcomes in adult and pediatric liver transplantation among various ethnic groups. *Transplant Proc*. 2007;39(10):3204-3206.
47. Adler JT, Bababekov YJ, Markmann JF, Chang DC, Yeh H. Distance is associated with mortality on the waitlist in pediatric liver transplantation. *Pediatr Tranplant*. 2017;21(2):e12842.
48. NHS Blood and Transplant. Annual report on deceased donation and transplantation in paediatric patients. 2021-2022. 2022. Accessed June, 2022. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/28062/annual-report-on-donation-and-transplantation-in-paediatric-patients-1-april-2021-31-march-2022.pdf
49. Cossrow N, Falkner B. Race/ethnic issues in obesity and obesity-related comorbidities. *J Clin Endocrinol Metab*. 2004;89(6):2590-2594.
50. Wadhwani SI, Beck AF, Bucuvalas J, Gottlieb L, Kotagal U, Lai JC. Neighborhood socioeconomic deprivation is associated with worse patient and graft survival following pediatric liver transplantation. *Am J Transplant*. 2020;20(6):1597-1605.
51. Seikaly MG, Salhab N, Browne R. Patterns and time of initiation of dialysis in US children. *Pediatr Nephrol*. 2005;20(7):982-988.
52. Driollet B, Bayer F, Kwon T, et al. Social deprivation is associated with lower access to pre-emptive kidney transplantation and more urgent-start dialysis in the pediatric population. *Kidney Int Rep*. 2022;7(4):741-751.
53. Patzer RE, Amaral S, Klein M, et al. Racial disparities in pediatric access to kidney transplantation: does socioeconomic status play a role? *Am J Transplant*. 2012;12(2):369-378.
54. Thammana RV, Knechtle SJ, Romero R, Heffron TG, Daniels CT, Patzer RE. Racial and socioeconomic disparities in pediatric and young adult liver transplant outcomes. *Liver Transpl*. 2014;20(1):100-115.
55. Davies RR, Haldeman S, Pizarro C. Regional variation in survival before and after pediatric heart transplantation—an analysis of the UNOS database. *Am J Transplant*. 2013;13(7):1817-1829.
56. Mogul DB, Lee J, Purnell TS, et al. Barriers to access in pediatric living-donor liver transplantation. *Pediatr Tranplant*. 2019;23(6):e13513.
57. Dageforde LA, Petersen AW, Feurer ID, et al. Health literacy of living kidney donors and kidney transplant recipients. *Transplantation*. 2014;98(1):88-93.
58. Taylor DM, Bradley JA, Bradley C, et al. Limited health literacy is associated with reduced access to kidney transplantation. *Kidney Int*. 2019;95(5):1244-1252.
59. Austin M, Feurer I, Pinson C. Access to pediatric liver transplantation: does regional variation play a role? *J Gastrointest Surg*. 2006;10(3):387-394.
60. Francis A, Didsbury M, Lim WH, et al. The impact of socioeconomic status and geographic remoteness on access to pre-emptive kidney transplantation and transplant outcomes among children. *Pediatr Nephrol*. 2016;31(6):1011-1019.
61. Hogan J, Audry B, Harambat J, et al. Are there good reasons for inequalities in access to renal transplantation in children? *Nephrol Dial Transplant*. 2014;30(12):2080-2087.
62. Yoeli D, Goss M, Galván NTN, Desai MS, Miloh TA, Rana A. Trends in pediatric liver transplant donors and deceased donor circumstance of death in the United States, 2002-2015. *Pediatr Tranplant*. 2018;22(3):e13156.
63. Ahangari H, Atkinson-Palombo C, Garrick NW. Progress towards zero, an international comparison: improvements in traffic fatality from 1990 to 2010 for different age groups in the USA and 15 of its peers. *J Safety Res*. 2016;57:61-70.
64. Valapour M, Lehr CJ, Skeans MA, et al. OPTN/SRTR 2020 annual data report: lung. *Am J Transplant*. 2022;22(suppl 2):438-518.
65. Lancaster TS, Miller JR, Epstein DJ, DuPont NC, Sweet SC, Eghtesady P. Improved waitlist and transplant outcomes for pediatric lung transplantation after implementation of the lung allocation score. *J Heart Lung Transplant*. 2017;36(5):520-528.
66. Bourne B, Paraskeva M, Westall G, Snell G, Levvey B. Paediatric lung transplantation (PLTX) in Australia: small patients in a big country. *Transplantation*. 2020;104(S3):S556.
67. Avdimiretz N, Benden C. Worldwide organ allocation systems for pediatric lung transplantation. *Clin Transplant*. 2023;37(6):e15018.
68. Egan TM, Edwards LB. Effect of the lung allocation score on lung transplantation in the United States. *J Heart Lung Transplant*. 2016;35(4):433-439.
69. Colvin-Adams M, Valapour M, Hertz M, et al. Lung and heart allocation in the United States. *Am J Transplant*. 2012;12(12):3213-3234.
70. Hirji A, Zhao H, Ospina MB, et al. Clinical judgment versus lung allocation score in predicting lung transplant waitlist mortality. *Clin Transplant*. 2020;34(7):e13870.
71. Kourliouros A, Hogg R, Mehew J, et al. Patient outcomes from time of listing for lung transplantation in the UK: are there disease-specific differences? *Thorax*. 2019;74(1):60-68.
72. Benvenuto LJ, Arcasoy SM. The new allocation era and policy. *J Thorac Dis*. 2021;13(11):6504-6513.
73. Parker WF, Dussault NE, Jablonski R, Garrity ER, Churpek MM. Assessing the accuracy of the lung allocation score. *J Heart Lung Transplant*. 2022;41(2):217-225.
74. Tian D, Wang Y, Shiiya H, et al. Outcomes of marginal donors for lung transplantation after ex vivo lung perfusion: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2020;159(2):720-730.
75. Cypel M, Yeung J, Donahoe L, et al. Outcomes of lung transplantation at a Canadian center using donors declined in the United States. *J Thorac Cardiovasc Surg*. 2022;164(6):1661-1668.
76. Bowdish ME, Barr ML. Commentary: lungs across borders: American lungs in Canadian patients. *J Thorac Cardiovasc Surg*. 2022;164(6):1669-1670.
77. Chen Q, Malas J, Krishnan A, et al. Limited cumulative experience with ex vivo lung perfusion is associated with inferior outcomes after lung transplantation. *J Thorac Cardiovasc Surg*. 2024;167(1):371-379. doi:10.1016/j.jtcvs.2023.04.009
78. Ali A, Nykanen AI, Beroncal E, et al. Successful 3-day lung preservation using a cyclic normothermic ex vivo lung perfusion strategy. *EBioMedicine*. 2022;83:104210.
79. Wang A, Ribeiro RVP, Ali A, et al. Ex vivo enzymatic treatment converts blood type A donor lungs into universal blood type lungs. *Sci Transl Med*. 2022;14(632):eabm7190.

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