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Review

Surgery for patients with Alpha 1 Antitrypsin Deficiency: A review

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ABSTRACT

Background: Alpha 1 Antitrypsin Deficiency (AATD) is a genetic cause of emphysema/chronic obstructive pulmonary disease (COPD) and liver disease, making AATD patients a high-risk surgical group. Additionally, patients may eventually require lung and/or liver transplantation or lung volume reduction surgery (LVRS). This narrative review discusses perioperative considerations for elective procedures in AATD patients, and reviews patient outcomes in AATD-related transplantation and LVRS.
Data sources: PubMed search terms included: "pre-/peri-/post-operative management"; "COPD"; "AATD"; "lung/liver transplant"; "lung volume reduction."
Conclusions: Lung and liver transplantation in AATD patients are associated with very good long-term survival rates that are comparable to, and sometimes superior to, other transplant indications. Although not currently recommended in AATD, LVRS may have a role in a minority of patients. The value of Alpha 1 Antitrypsin (AAT) augmentation therapy following lung transplantation requires further study. Wherever possible, AAT therapy should be continued in the period around elective surgeries.

Introduction

Alpha 1 Antitrypsin Deficiency is an underdiagnosed genetic disorder that predisposes to lung and liver disease.[1] AATD is caused by mutations in the *SERPINA1* gene, and results in low circulating levels or reduced functionality of Alpha 1 Antitrypsin (AAT), an important serum protease inhibitor. Principally, AAT inhibits neutrophil elastase (NE) – reduced inhibition of NE in AATD causes proteolytic destruction of the lung architecture, and is the main pathological cause of early-onset emphysema related to AATD.[2] In addition, accumulation of abnormal AAT proteins in the liver can lead to liver disease in some patients.[3]

Emphysema/chronic obstructive pulmonary disease (COPD) related to AATD is progressive and irreversible; the most common causes of death in patients with severe deficiency are respiratory-related (~60% of AATD patients), with respiratory failure accounting for the majority of these (~70%).[4] Pharmacotherapy with intravenous purified human Alpha 1 Antitrypsin (AAT) therapy can slow progression of emphysema related to AATD,[5,6] but in some cases surgical intervention, i.e., lung volume reduction surgery (LVRS) or lung transplantation, may ultimately be required. In AATD patients with advanced liver disease, liver transplantation is the only treatment option.[3]

Here, we provide a review of the literature on general pre-, peri-, and post-operative surgical/anesthesiological considerations in AATD patients undergoing non-thoracic surgical procedures. We will also discuss pathologies related to AATD that may necessitate thoracic surgical intervention, patient outcomes vs. other disease settings, and recommendations for transplant candidate selection. Data on the role of AAT therapy following lung transplant in AATD will also be assessed.

Materials and methods

For this narrative review, literature was sourced via PubMed searches. Search terms included combinations of: AATD, COPD, pre-/peri-/post-operative management, lung volume reduction, lung transplantation, liver transplantation, outcomes, AAT OR Alpha 1 Proteinase Inhibitor OR A1PI.

General surgical considerations in AATD patients

The principal pathologies associated with AATD (i.e., lung and liver disease) may necessitate surgical intervention in some patients. Besides this, AATD patients will likely undergo elective procedures not related to these pathologies within their lifetimes and, depending on age and disease progression, individuals with AATD may fall into a high-risk category.

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Pre-existing lung disease poses a number of challenges to surgical intervention – COPD as a co-morbidity has been shown to significantly increase hospital stay.[7] Consequently, a thorough review of lung function parameters and risk-stratification should be performed prior to surgical intervention in AATD patients.[8] A blood gas assessment should form part of this – partial pressure of carbon dioxide ($PaCO_2$) >5.9 kPa and PaO_2 <7.9 kPa has been shown to predict worse outcomes in COPD patients.[9] To optimize patient outcomes, a number of pre- and post-operative measures should be undertaken, as outlined in Fig. 1. One recommendation specific to AATD is that, wherever possible, patients should continue to receive their scheduled doses of AAT augmentation therapy. Although, in all likelihood, it would not be harmful to omit a dose of AAT, all efforts should be made to prevent destabilization of the patient's condition. One argument for continuing therapy around surgical intervention is that patients with the Z mutation have a reduced acute-phase response (reduced up regulation of AAT levels) in response to surgical stress,[10] which may have broad implications for wound healing and susceptibility to infections. In particular, it is known that AAT levels increase minimally in the acute phase in patients with the PI*ZZ genotype (both alleles affected).[11] Therefore, there may be a role for the therapy in reducing post-operative inflammation and assisting in the healing process, although there is currently a lack of evidence for this. Other considerations include the use of post-operative antimicrobial prophylaxis, for which high-risk patients would be candidates.[12] Physiotherapy pre- and post-operatively is also advisable – this can reduce atelectasis (essential for the peri-operative phase) and can help prevent exacerbations and pneumonia post-operatively. Further, in patients with bronchiectasis, it is particularly important that sputum is managed by physiotherapy prior to surgical intervention – this can reduce risk of bronchial plugging and pneumonitis.[13] Due to possible induction of bronchospasm, mucolytics are not routinely recommended.

The pathophysiological consequences of COPD can result in significant complications during the perioperative phase.[14] For example, small airway collapse during surgery is more likely in COPD.[15] This is due to reduced alveolar elasticity and increased intrathoracic pressure caused by forced exhalation.[15] In addition, perhaps the most challenging perioperative aspect of surgery in patients with COPD is managing the 'deadspace' effect. In COPD, mismatch between airway ventilation and gas perfusion leads to areas in the lung that are ventilated but not perfused (deadspace), and areas that are perfused but not ventilated (shunts).[16] The deadspace effect is exacerbated by positive pressure ventilation (PPV) when exhalation is incomplete – an effect termed intrinsic positive end expiratory pressure (PEEPi).[15] The resultant increased intrathoracic pressure impedes venous blood return and can cause hypotension. This potential complication may be managed by ventilator adjustments including prolongation of the I:E ratio, utilizing a low tidal volume and respiratory rate even if it results in mild hypercapnia. An increase in extrinsic PEEP during ventilation, to keep airways patent and allow sufficient time for expiration, may also be required.[15] Overall, close monitoring and additional ventilator adjustments may be required to minimize the clinical consequences of PEEPi.[17]

An intervention that can be particularly complicated by COPD is laparoscopic surgery.[9,18] Due to difficulty in increasing ventilation in COPD patients, i.e., as a result of the deadspace effect and PEEPi, carbon dioxide resorbed during insufflation can result in hypercapnia, with possible progression to hypercapnic respiratory failure.[9,18] This can be compensated for by adjusting ventilation; however, this may not be possible in severe COPD.[18] To minimize risk of hypercapnia, the intraabdominal pressure (IAP) should be raised above the venous pressure.[9] However, raising the IAP causes the diaphragm to shift and can result in intraoperative atelectasis and ventilation-perfusion mismatch, with pulmonary shunting.[9] In addition, raising the IAP >15 mmHg can decrease venous return and reduce cardiac output, resulting in hypotension. Therefore, although laparoscopic surgery may be preferable owing to it being typically less invasive, benefits and risks of this intervention should be weighed, and it is essential to consider alternative surgical and anesthetic measures in patients with COPD/AATD, especially those with severe disease.

Surgical intervention for lung disease in AATD

Lung volume reduction

Lung volume reduction (LVR), both surgical (LVRS) and endobronchial (ELVR), are treatment options for advanced emphysema with good evidence for efficacy in terms of improving lung

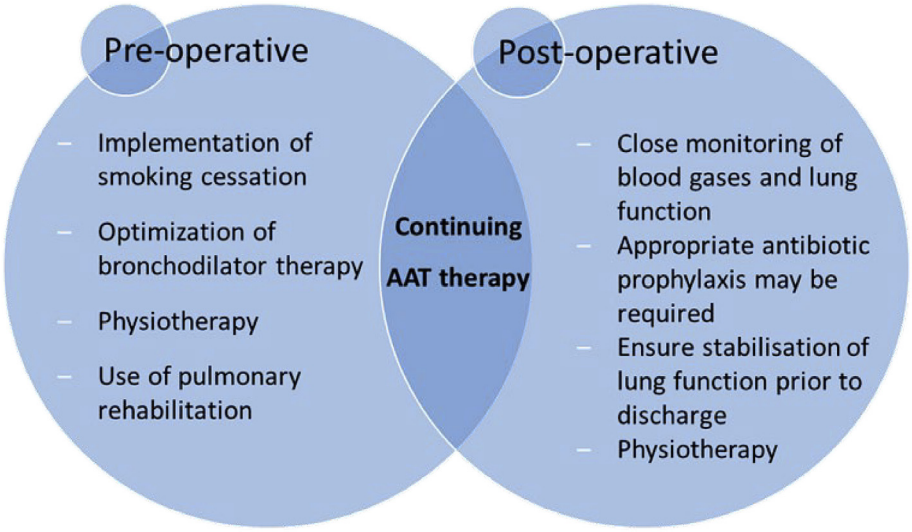

Fig. 1. Pre- and post-operative recommendations for AATD patients with lung disease. AATD, Alpha 1 Antitrypsin Deficiency.

function and walking distance.[19,20] LVR can be used as an alternative to lung transplantation, or potentially as a bridge to transplantation.[21] However, careful patient selection is crucial, with evidence of superior outcomes in patients with heterogeneous emphysema.[21,22] In addition, LVRS for non-upper lobe emphysema, has been associated with increased mortality.[23] At first glance, these data would suggest that LVR is generally less suitable for AATD patients as, contrary to smoking-related emphysema, which is typically centrilobular (involving the region of the acinus proximal to the bronchioles), AATD-related emphysema typically presents panlobularly (involving the entire acinus), with basal predominance.[24]

Several studies have assessed the use of LVR in AATD patients and have shown mixed results. One study in 21 patients with AATD-related emphysema noted short-term (3-month) improvements in lung function, including improvements in mean dyspnea score (from 3.7 ± 0.1 to 1.4 ± 0.2) and forced expiratory volume in one second (FEV1) % predicted (from $27 \pm 1.9\%$ to $38 \pm 3.3\%$).[25] Thereafter, improvements in the mean dyspnea score remained statistically significant for up to 3 years; however, increases in FEV1 were only maintained for 1 year.[25] A subgroup of patients showed sustained improvements in lung function for up to 3.5 years – these patients were found to have markedly heterogeneous emphysema and no radiologically identifiable signs of airway inflammation.[25] A further study assessed patient outcomes post-LVRS in 12 patients with AATD-related emphysema and 18 patients with smoker's emphysema. The groups were well-matched in terms of 6-min walking distance and dyspnea score but not FEV1% predicted, which was lower in the AATD group (24% vs. 31% predicted). Bilateral LVR surgery resulted in significant improvements in these parameters in both groups; however, the functional parameters, with exception of 6-min walking distance, returned to baseline after 6–12 months in the AATD group, with further deterioration at 2 years. In contrast, the functional parameters were significantly improved in the smoking-related emphysema group over this time. A sub-study of the National Emphysema Treatment Trial also supports these findings.[26] The analysis included 16 AATD patients (10 who underwent LVRS) – 2-year mortality was higher in AATD patients who underwent LVRS than those who were medically managed (20% vs. 0%), although the small sample size prevented statistical comparison.[26] Comparison of outcomes between the 10 AATD patients and the 554 AAT-replete individuals who underwent LVRS showed smaller improvements in 6-min walking distance and FEV1% predicted in the AATD group.[26]

The majority of the data on LVR in AATD are based on LVRS; however, as a less invasive procedure, ELVR is beginning to supersede LVRS in general COPD.[20] One recent case series, involving the implantation of endobronchial valves in 15 AATD patients, reported positive results. Twelve of the patients were followed up for at least 1 year, with a 54% mean increase in FEV1 and improvements in quality of life reported.[20] No significant deterioration in lung function was observed over the total 4-year follow-up and one patient was able to discontinue oxygen therapy.[20] The authors concluded that ELVR should be considered a treatment option in carefully selected AATD patients.[20]

These findings would appear to confirm that LVR is generally less suitable for AATD-related emphysema, given its typical presentation. As a result, LVR is not recommended by the recent Alpha-1 Foundation guidelines for the management of AATD.[27] Nevertheless, individual emphysema morphology should be taken into account before dismissing LVR as a treatment option, as AATD patients with markedly heterogeneous emphysema may benefit more than others. In particular, ELVR is a measure that warrants further exploration in AATD.

Lung transplantation

A minority of AATD patients (around 7%) undergo lung transplantation.[28] A 1994 report by the St. Louis International Lung Transplant Registry recorded as many as 13% of lung transplants to be as a result of AATD.[29] Since the implementation of the lung allocation score (LAS), this number has declined in recent years, with the proportion recently assessed as under 5% (Fig. 2) – nonetheless, AATD remains the fourth most common indication for lung transplantation worldwide.[30]

Although lung transplantation due to AATD can feasibly be grouped with COPD-related transplant, there are important differences in patient demographics, disease pathophysiology, and other transplant considerations (Table 1). As compared with general COPD, lung transplantation is usually required at a younger age, and patients generally have had less exposure to tobacco smoke.[31,32] A recent Spanish study comparing characteristics of lung transplant recipients (217 with COPD and 19 patients with AATD) found that patients with AATD were on average 10 years younger (43.0 ± 7.7 vs. 53.6 ± 6.1 years old, $p < 0.001$) and had around 14 fewer pack-years (23.9 ± 15.0 vs. 50.0 ± 29, $p < 0.002$), in addition to a lower PCO_2 (41.7 ± 7.6 vs. 47.9 ± 9.7 mmHg, $p < 0.004$).[31] These findings align with the known natural history of AATD, i.e., respiratory symptoms usually present at a younger age than with smoking-related COPD.[1]

The extent of lung tissue destruction typically observed in AATD (i.e., panlobular emphysema) is likely a contributing factor toward the younger age and higher frequency of lung transplantation in AATD vs. smoking-related COPD. In addition, AATD-related emphysema has been shown to be more frequently associated with bilateral sequential lung transplantation than smoking-related COPD.[29] Furthermore, the pathophysiology of AATD-related emphysema can result in surgical complications specific to AATD. For example, as a result of the panacinar nature of emphysema typically seen in AATD, the emphysematous regions often merge, resulting in increased lung compliance that can lead to acute native lung hyperinflation (Fig. 3), which may be more common following AATD-related than COPD-related single lung transplantation.[33] This consideration, combined with the generally younger age of AATD lung transplant recipients, may account for the higher rates of bilateral sequential lung transplantation.

In all lung transplant cases, careful candidate selection is essential to optimize post-transplant survival.[34,35] This is reflected by the LAS system used in the United States, which prioritizes lung transplantation based on urgency and chance of survival rather

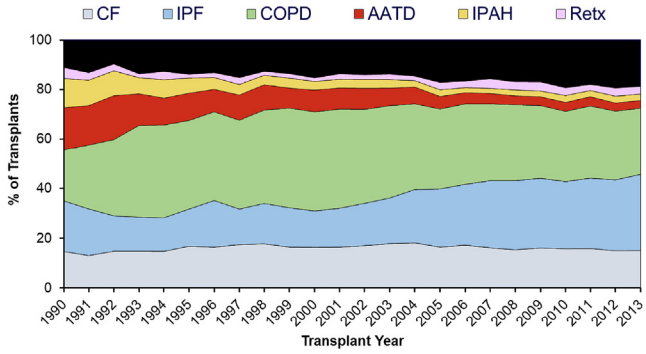

Fig. 2. The International Society for Heart and Lung Transplantation (ISHLT) statistics for adult lung transplants by indication and year.[30] AATD, Alpha 1 Antitrypsin Deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; Retx, retransplant.

Table 1
Lung transplant considerations: AATD vs. COPD.[24,29,31,33,38]

Demographics	Pathophysiology	Other transplant considerations
- Younger age (up to 10 years younger) - Significantly fewer pack years (up to 14 fewer) - Lower PCO_2	- Generally more widespread lung tissue destruction - Higher frequency of panacinar emphysematous regions, increasing lung compliance - Emphysema is typically basally-predominant, with lower rates of apically-predominant emphysema that is commonly associated with smoker's COPD	- More frequently associated with bilateral lung transplantation - Possibly worse lung function decline following bilateral lung transplantation than COPD - Native lung hyperinflation possibly a more common complication following single lung transplant

AATD, Alpha 1 Antitrypsin Deficiency; COPD, chronic obstructive pulmonary disease; PCO_2, partial pressure of carbon dioxide.

than waiting list time. A recent consensus document for patient selection in lung transplant by the Pulmonary Council of the International Society for Heart and Lung Transplantation gives detailed criteria for candidate selection that are applicable to transplant in AATD (Table 2).[35] One of the absolute contraindications (significant organ dysfunction) is a particularly important consideration in AATD patients due to the potential presence of AATD-related liver disease. One survey of AATD patients reported that around 8% of patients had established liver disease, with around 5% reporting concurrent symptoms of obstructive lung disease.[28] Lung transplant in these patients would be contraindicated unless they were also candidates for liver transplant or combined lung and liver transplant – these topics will be discussed later in the review.[35]

In terms of the overall value of lung transplantation in AATD, there are conflicting reports. A recent prospective study of the Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) registry in the United Kingdom compared clinical parameters, quality of life, and survival between 32 AATD transplant patients and 48 matched non-transplant patients.[36] Post-transplantation, quality of life (St. George's Respiratory Questionnaire; SGRQ) scores improved significantly ($p < 0.002$) compared with a non-transplant group matched for FEV1. Post-transplantation survival rates were 81.3% at 90 days, 74.2% at 1 year, 52.9% at 5 years, and 45.2% at 10 years. However, survival was reported to be no better than a second group of non-transplant patients matched for gas transfer and a third group matched for SGRQ.

Despite these data raising questions regarding the overall value of lung transplant in AATD, data from Sweden suggest that lung transplant recipients with AATD have a superior long-term chance of survival compared with those without AATD (Fig. 4).[37] In this study, no difference in survival was found at 1 year; however, survival was significantly higher in the AATD group at 3 years and 5 years, with a marked difference observed at 10 years: median (95% confidence interval) survival was 59% (49–69) vs. 31% (22–40) ($p < 0.001$) for AATD vs. non-AATD recipients at 10 years post-transplantation, respectively.[37] Interestingly, 10-year survival in AATD recipients was noticeably higher in the Swedish study than in the UK study (59.0% vs. 45.2%, receptively), which may be a result of the larger sample size in the Swedish study or differences in aftercare between healthcare systems.

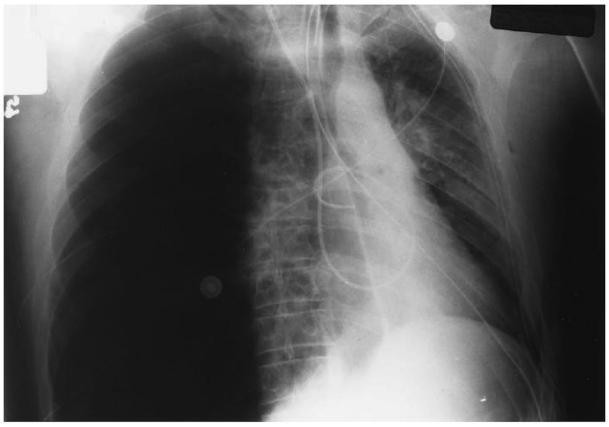

Fig. 3. Chest X-ray showing acute native hyperinflation following a single left lung transplantation. Reused with permission from Weill et al., *J Heart Lung Transplant* 1999.[33]

In terms of a specific comparison with COPD, recent data from The Cleveland Clinic from 276 lung transplant procedures (45 related to AATD and 231 related to COPD) found there to be no difference in early or late mortality (up to 15 years), although FEV1 decline in bilateral transplants was noted to be more rapid in AATD patients than in AAT-replete patients.[38] Older data from the St. Louis International Lung Transplant Registry comparing AATD with general COPD transplant recipients are supportive of superior survival in AATD recipients. Although survival after the first 2 years post-bilateral lung transplantation was slightly better for COPD recipients, later survival was superior for AATD recipients; however, no statistical comparisons were presented.[29] Other data support a similar short-term survival in general emphysema/COPD and AATD.[32,39]

In contrast, data reported by Perrot et al. regarding 521 lung transplantations between 1983 and 2003 at a single Canadian center showed significantly worse survival ($p = 0.04$) in AATD patients ($n = 63$) than in COPD patients ($n = 97$).[40] In particular, deaths in the AATD group were more often attributed to sepsis than in the COPD group: 18 for AATD vs. 5 for COPD.[40] The influence of sepsis on survival in AATD patients was more apparent after 6 months than other indications: rates of late sepsis-related death were 21% (10/47) for AATD patients vs. 6% (21/365) for all other transplant recipients ($p = 0.0001$).[40]

Overall, there are conflicting data surrounding post-lung transplant survival in AATD vs. other transplant indications, which may be attributed to differences between healthcare systems and/or the age of the data. However, it is known that survival among AATD patients is generally very good, as shown by the most recent data.[37,38] Nonetheless, the reported higher rates of sepsis-related death in AATD lung transplant recipients are notable. This may be related to the inflammatory component of AATD, which is discussed later in this review.

Liver disease

The overall proportion of AATD patients who will develop liver disease is not fully understood.[41] As previously mentioned, one survey of AATD patients recorded a minority (around 8%) of adult patients as having established liver disease.[28] A recent systematic review of 35 studies found that 7% of children with AATD and 10.5% of AATD patients who survived to adulthood developed liver

Table 2
Recommendations for lung transplant candidate selection.[35]

General criteria for lung transplant	Absolute contraindications	Relative contraindications
- >50% risk of death from lung disease in 2 years without transplant - >80% likelihood of surviving past 90 days after transplantation - >80% chance of 5-year post-transplantation survival provided there is adequate graft function	- Current cigarette smoking - Recent malignancy – 5-year disease-free period is usually required - Chronic infection with highly virulent/resistant microorganisms - Active *Mycobacterium tuberculosis* infection - [a]Class II or III obesity (BMI ≥35.0 kg/m^2) - Atherosclerosis with end-organ ischemia - Untreated significant organ dysfunction - Acute medical instability (e.g., sepsis, MI) - Uncorrectable bleeding diathesis - Current or significant history of non-adherence to medical therapy - Psychiatric/psychological conditions that would preclude cooperation with medical team or significantly impact adherence - Lack of adequate social support structures - Substance abuse/dependence	- Age >65 years with limited physiological reserve: age cannot be an absolute contraindication, although patients >75 years are unlikely to be candidates - Class I obesity (BMI 30.0–34.9 kg/m^2) - Malnutrition (progressive or severe) - Hepatitis B/C – however; transplantation can be considered in patients without signs of cirrhosis - HIV infection – transplantation can be performed in patients with stable disease and no current AIDS-defining illnesses - *Burkholderia cenocepacia*, *Burkholderia gladioli*, or multi-drug–resistant *Mycobacterium abscessus* infection – transplantation can be considered in successfully managed patients - Other conditions that can cause but have not resulted in end-organ damage (e.g., diabetes) should be optimally medically managed - Disease burden level of atherosclerosis that would increase risk of post-transplant end-organ damage

[a] Note: with rising levels of obesity, many now consider class II or III obesity to be relative contraindications; AIDS, acquired immunodeficiency syndrome; BMI, body-mass index; HIV, human immunodeficiency virus; MI, myocardial infarction.

cirrhosis.[42] It remains an under-appreciated aspect of AATD, and has been found to account for around 12% of deaths associated with the condition.[4] Liver disease primarily affects patients with the 'Z' AAT phenotype – other variants implicated include the 'S' phenotype (to a lesser degree) and the rare M_{Malton} variant.[1] The 'Z' variant and others exhibit polymerization behavior, which results in accumulation at the site of biosynthesis (the endoplasmic reticulum of hepatocytes), and is the primary mechanism leading to AAT deficiency in blood and liver injury.[43] This accumulation leads to caspase activation and apoptotic cell death, which can ultimately lead to fibrosis, cirrhosis and hepatocellular carcinoma.[3,44]

Typically, clinically significant liver disease presents later in life, and is a more common cause of death in non-smoking patients.[1,4] Nevertheless, liver disease can also present in children and particularly in neonates as 'neonatal hepatitis syndrome,' which is commonly associated with severe, prolonged jaundice. There is also some evidence suggesting that heterozygosity for AATD variants can exacerbate existing liver disease, e.g., biliary atresia, in children.[45]

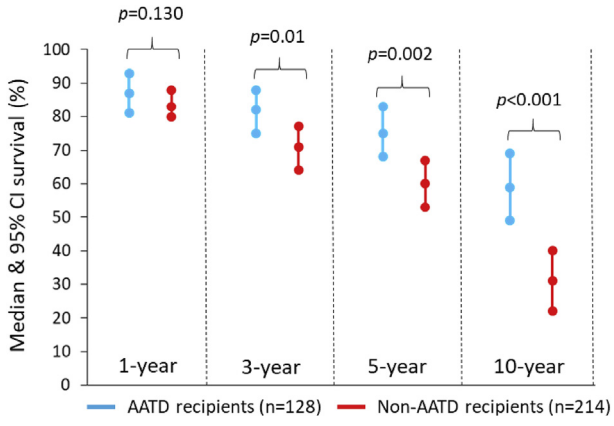

Fig. 4. Long-term survival post-lung transplantation in recipients with or without AATD.[37] AATD, Alpha 1 Antitrypsin Deficiency; CI, confidence interval.

In patients with genotypes more strongly associated with liver disease (e.g., PI*ZZ, PI*SZ, and PI*ZM_{Malton}), monitoring of liver function should be conducted. Given their lower risk, it is less clear whether PI*MZ individuals should be monitored for liver disease, although this risk may increase with advanced age (i.e., >70 years).[46] Diagnostic tests for liver disease can include liver ultrasound, a Fibroscan® (used to measure the degree of fibrosis), and laboratory analysis of standard liver biomarkers, albumin, international normalized ratio, and platelets.[27,47] However, it should be noted that liver biomarkers (alanine aminotransferase in particular) have been shown to lack sensitivity in detecting liver dysfunction in AATD patients,[48] and it is therefore important to consider a range of liver monitoring methods. In particular, liver ultrasound has been shown to be effective in detecting fatty liver disease in AATD patients.[48]

In terms of treatment of liver disease, supportive care and treatment of symptoms is warranted; however, liver transplantation is the only curative measure.

Liver transplantation

Pediatric

AATD-related liver dysfunction can necessitate transplantation in children or adults, and in general, is associated with excellent outcomes.[49] Children presenting with significant jaundice secondary to AATD can rapidly deteriorate into liver failure precipitating liver transplantation, and consequently, there are added challenges relating to rapidly sourcing a donor organ.[50]

Nonetheless, it is striking that AATD is the second most common indication for liver transplantation in children after biliary atresia.[51]

Studies assessing outcomes post-liver transplantation in children with AATD have shown very good outcomes in terms of long-term survival, quality of life, and growth performance.[52–55] A French study from 1994 assessed post-transplant characteristics in 16 PI*ZZ children who underwent liver transplantation. Median age at AATD diagnosis was 6 months (range: 1–48 months), and there was a significant duration between age at diagnosis and assessment for transplantation: age range at transplant assessment was 1–15 years. One death was reported at 6 months due to graft necrosis; however, the majority (94%) of recipients were alive after 22 months of follow-up and had excellent quality of life and normal circulating AAT levels. A more recent study reported outcomes of AATD-related liver transplantation (n = 35) compared with biliary atresia-related liver transplantation (n = 116) in a single center since the mid-1960s.[53] Overall, 1-, 5-, and 10-year survival was 82.7%, 75.5% and 76.5%, respectively in the AATD group, and was superior at all time points to the group who underwent biliary atresia-related transplantation.[53] The authors concluded that the difference in survival was likely due to the AATD patients being significantly older than the biliary atresia patients at the time of transplantation: 6.0 years (range: 1.0–9.0) vs. 1.0 year (range: 0.0–3.0), respectively ($p < 0.001$).[53]

Adult

Despite AATD being a common indication for childhood liver transplantation, the highest burden of advanced liver disease associated with AATD is later in life.[49] A Medicare study from 1993 identified 116 liver transplant cases to be related to AATD – the average age of recipients was 38 years, with most patients aged between 38 and 54 years, and only 12 (10%) under the age of 13. This study also found the mean 5-year survival rate to be high post-AATD-related transplant: 72.9 ± 5.3%.[56] A recent study by Carey et al. specific to AATD-related liver transplantation assessed patient outcomes in 3 major transplant centers in the US between 1987 and 2012.[57] Seventy-three patients were identified with severe deficiency (50 PI*ZZ and 23 PI*SZ), and were compared with 50 heterozygous normal (PI*MZ) transplant cases.[57] PI*MZ patients were the oldest on average (57.7 ± 7.3 years), followed by PI*SZ patients (53.0 ± 11.2) and PI*ZZ patients (47.8 ± 15.7); $p < 0.01$ for PI*MZ vs. PI*SZ and $p = 0.09$ for PI*SZ vs. PI*ZZ.[57] Significantly, only 4% of PI*ZZ patients had co-existing liver disease, compared with 43.5% of PI*SZ patients and 90% of PI*MZ patients ($p < 0.001$ for all comparisons). This finding plainly illustrates the differences in risk conferred by different *SERPINA1* genotypes, with homozygosity representing a far greater contributing factor toward eventual liver transplantation than heterozygosity. Interestingly, although not statistically significant, survival at nearly all time points (1, 3, 5, and 10 years) was higher for PI*MZ cases despite the younger age of PI*ZZ and PI*SZ patients at baseline.[57] In particular, 10-year survival was 86% for PI*MZ cases vs. 79% and 72% for PI*SZ and PI*ZZ cases, respectively.[57]

Carey et al. also assessed lung function parameters pre- and post-lung transplantation in 17 PI*ZZ patients.[57] Lung function was found to be similar overall between pre-transplant and post-transplant periods, although the FEV1 and forced vital capacity ratio was slightly lower post-transplant.[57] A further study by Jain et al. assessed lung function for up to 3 years post-liver transplantation in seven AATD patients and showed similar results. After the mean follow-up time of 2.7 ± 1.2 years, pulmonary function was found to be unchanged, leading the authors to conclude that liver transplantation, and subsequent normal secretion of AAT, may halt progression of emphysema related to AATD.[58]

Combined lung and liver transplantation

Some patients with AATD develop advanced lung and liver disease concurrently.[28] In patients with end-stage emphysema (LAS <50%) complicated by cirrhosis who would not be expected to survive lung transplantation alone, combined lung-liver transplant (CLLT) may be the only treatment option.[59] A recent study from a single transplant center reported 8 cases of CLLT, one of which was a patient with AATD.[59] The patient was a 52-year old female who was followed up for over 3.5 years.[59] In this time, one post-operative complication was reported (bile duct ischemia); however, there was no acute cellular rejection and the patient survived.[59] Notably, overall survival in the study was only 50%, and the AATD patient was also followed up for the longest period. Although it is difficult to draw conclusions regarding the value of CLLT in AATD based on these data alone, as the procedure both resolves the emphysema component of AATD and should normalize serum AAT levels, it would seem logical that CLLT in AATD would be associated with positive outcomes. In addition, as compared with conditions such as cystic fibrosis, there would be minimal extra-pulmonary and extra-hepatic disease complications post-transplantation. Furthermore, patients would generally be younger and have fewer comorbidities than, for example, COPD patients. This is provided that the liver used for the transplantation was not from a PI*ZZ donor – at least one case of acquired AATD post-liver transplantation from a deficient donor has been reported.[60] Interestingly, one study found accumulation of Z AAT in 0.8% of donor livers among 789 transplant cases.[61]

AAT therapy and transplant

The primary pharmacological treatment for patients with emphysema secondary to AATD is AAT therapy, typically dosed weekly at 60 mg/kg intravenously. It is the only pharmacological treatment that has been shown to significantly slow progression of emphysema related to AATD, as assessed by computed tomography (CT) lung densitometry.[5,6] Registry data also suggest that AAT therapy in AATD confers a survival advantage vs. no treatment,[62] and this is corroborated by an extrapolation analysis of lung densitometry data from the largest clinical trial of AAT therapy in AATD completed to date (the RAPID clinical trial program).[5,6]

The role of AAT augmentation therapy following AATD-related lung transplantation is less clear. Given the lower utility of LVR in AATD vs. general COPD, and the decline in COPD-related transplant in recent years, AAT therapy may have an increasingly important role in postponing transplantation, due to its ability to preserve lung tissue. However, a recent research letter in the *European Respiratory Journal* by Conrad et al. raises questions surrounding the utility of AAT augmentation therapy following lung transplant.[63] The study assessed 1-, 3-, 5-, and 10-year post-lung transplant survival between AATD patients who received AAT therapy prior to transplantation (n = 58), AATD patients who received no AAT therapy prior to transplantation (n = 47), and COPD patients (n = 246).[63] There was no significant difference in age between the prior AAT therapy and no AAT therapy groups, although COPD patients were significantly older. Unexpectedly, 3-, 5-, and 10-year survival was significantly worse in the prior AAT therapy group than the no AAT therapy AATD group and the COPD group.[63] In particular, 10-year survival was 26% vs. 69% in the prior AAT therapy vs. the no AAT therapy groups, respectively ($p < 0.001$). The authors have no definitive explanation for these findings, as age and clinical parameters were similar between these two groups at the time of transplantation.[63] One possible explanation is that the prior AAT therapy patients had significantly more advanced disease than the no prior AAT therapy patients. Alternatively, given the significant immunomodulatory functions of AAT, withdrawal of therapy in the

early peri-transplant period could have a rebound proinflammatory effect.[63]

Despite there being uncertainty regarding the relationship between AAT therapy and long-term survival post-lung transplantation, there are arguments for continuing therapy immediately before and after transplantation. One such argument, as discussed earlier, is the lower acute phase response by AAT in patients with the Z mutation.[10,11] Further, it has been shown that excessive inflammation and neutrophil activity – with a concurrent increase in uninhibited NE – occur in the post-lung transplant period in AATD patients, with further increases during periods of infection and rejection/chronic rejection.[64] High levels of inflammation post-transplant may help to explain the higher rate of sepsis-related deaths reported in AATD patients,[40] as neutrophil build-up is known to be a key mechanism of organ injury in sepsis.[65] Therefore, in the period around lung transplantation, AAT therapy may help to stabilize inflammatory responses and protect the allograft from neutrophil infiltration and damage by NE. Further, there are limited data suggesting that re-introduction of AAT therapy in the period immediately after lung transplantation has a stabilizing effect on FEV1.[66]

It should be noted that lung transplantation in AATD does not solve the underlying deficiency; consequently, recurrence of emphysema has been observed after 11 years post-transplantation in an AATD patient.[67] Therefore, there is an added rationale to re-introduce AAT therapy if a decline in lung function is detected. Nonetheless, more data are required on the utility of AAT augmentation therapy following lung transplantation. Conversely, liver transplantation in AATD (from a non-deficient donor) results in normal biosynthesis and secretion of endogenous AAT.[27] For this reason, AAT therapy is not recommended post-liver transplantation in AATD.[27]

Future horizons for AAT therapy in transplant

The known immunological functions of AAT are numerous. AAT is known to modulate/inhibit proliferation of a number of immune cell types, including natural killer cells, T-cells, B-cells, monocytes, neutrophils, and eosinophils.[68] In addition, AAT down-regulates histamine release from mast cells and inhibits cytokine release, particularly tumor necrosis factor alpha.[68] Consequently, AAT therapy is being investigated for its utility in a number of immune-mediated and transplant-related indications.[69]

For example, there has been interest in the potential of AAT therapy for reducing complications, ischemia-reperfusion injury (IRI) in particular,[70] associated with lung transplantation in AAT-replete subjects. In preclinical studies, AAT has been shown to reduce IRI and improve tissue oxygenation and lung mechanics after lung transplantation in rats[71] and pigs.[72] Furthermore, in steroid refractory graft vs. host disease (GVHD), a condition associated with extremely high morbidity and mortality, AAT therapy has shown promising results in Phase 2 clinical trials.[73,74] Marcondes et al. reported AAT therapy to be well tolerated and 8 of the 12 patients showed improvements in GVHD manifestations, with 4 patients showing complete responses to treatment.[73] In addition, recently published data by Magenau et al. indicate that AAT therapy significantly reduces the need for additional, excessively toxic, immunosuppressive therapies.[74] Consequently, a low rate of infectious mortality (10%) was reported at 6 months.[74] AAT therapy has also been investigated for its utility in pancreatic islet cell transplantation to treat recent-onset type-1 diabetes. In a preclinical clinical study, AAT therapy was shown to protect transplanted pancreatic islet cells from immune-mediated destruction in mice.[75] This was thought to be due to significant cytokine down-regulation.[75] Administration of AAT therapy to children with recent-onset diabetes has shown promising results in terms of improving glucose control.[76]

The significant interest in AAT therapy for transplant and other indications is partly driven by its low toxicity in comparison to current immunosuppressing therapies – few serious treatment-related adverse events have been reported in over three decades of experience with AAT therapy.[77]

Conclusions

Lung and liver transplantation can be necessitated in AATD patients and both procedures are associated with very good long-term survival rates that are comparable to, and sometimes superior to, other transplant indications. Nonetheless, there are several clinical considerations unique to AATD-related transplantation, and when any surgical intervention is undertaken in AATD patients, the clinical profile of the patient should be considered carefully, as many will constitute high-risk subjects. Although not currently recommended in AATD, LVR may have a role in a minority of carefully selected AATD patients with markedly heterogeneous, non-basal emphysema. The role that AAT therapy plays in transplant in AATD remains unclear – one absolute recommendation is that it should not be utilized in AATD patients who have received a successful liver transplant. There is a strong rationale for continuing AAT therapy immediately before and after lung transplantation due to higher levels of inflammation and elastase activity. In addition, wherever possible, AAT therapy should be continued in the period around elective surgeries. Furthermore, due to its significant immunomodulatory and anti-inflammatory properties, AAT therapy may be of use in other transplant settings.

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Appendix A. Supplementary data

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