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Update on cystic fibrosis: selected aspects related to lung transplantation

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Summary

Survival after lung transplantation for cystic fibrosis has improved substantially. To date, 1-year survival is as much as 80–90% and 5-year survival 60–70%. Experience of surgical techniques, peri- and postoperative management and long-term follow-up care has grown. High risk patients for whom transplantation was contraindicated ten years ago are today being transplanted.

Prerequisites for a successful outcome are appropriate timing of referral, careful consideration of medical issues in other organs, and psychosocial support systems. Panresistant organisms are a special problem in candidates with cystic fibrosis, and advances in microbiological testing and characterisation of these organisms are warranted. Living donor lobar transplantation has become an option in rapidly deteriorating children and young adults. Selected aspects of the evolving field of lung transplantation are discussed.

Key words: lung transplantation; cystic fibrosis; Burkholderia cepacia complex; Pseudomonas aeruginosa; aspergillus

Introduction

Over the last decade there has been a considerable increase in the lifespan of patients with cystic fibrosis to over 30 years. In the majority of patients death is still due to respiratory failure. In patients with advanced pulmonary disease lung transplantation is the only effective therapeutic option, not only to prolong survival but also to enhance quality of life. Cystic fibrosis is the major indication for lung transplantation in Switzerland, and over 33% of all lung transplants are performed in patients with cystic fibrosis. With increasing experience of lung transplantation worldwide and in this country, evidence is accumulating which will guide practice in patient selection and timing of transplant, as well as postoperative management and long-term follow-up. Exclusion criteria operative in the early days, such as infection by multiresistant pathogens or previous thoracic procedures (pleurodesis), are no longer in themselves considered contraindications today, though they may still complicate the peri- and postoperative course in these patients. This article discusses recent developments in this rapidly evolving field.

Referral criteria and timing of lung transplant

In 1998 an international consensus committee developed guidelines for the selection of lung transplant candidates with cystic fibrosis (table 1) [1]. Generally, it is thought that patients should be referred when their expected 2-year survival is less than 50%. For cystic fibrosis, parameters include FEV_1 <30%, the presence of hypoxia and/or hypercapnia, and rapidly progressive clinical deterioration with increasing hospital stays or major haemoptysis. These parameters are based in part on the results of Kerem et al. [2], who analysed risk factors for survival in a large cystic fibrosis centre. Recently, Liu et al. created a survivorship model to predict 5-year survival using the following 9 parameters: age, gender, FEV_1%, weight, pancreatic sufficiency, diabetes mellitus, *Staph. aureus* infection, *B. cepacia* infection, and the number of acute exacerbations within the last year [3]. In a retrospective cohort study the same authors compared patients with cystic fibrosis undergoing lung transplant with those who did not [4]. They found that patients with a predicted 5-year survival of <30%

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Table 1

Guidelines for referral of lung transplant candidates with cystic fibrosis.

FEV_1 predicted <30%
Rapidly progressive respiratory deterioration:
increasing numbers of hospitalisations
massive haemoptysis
recurrent pneumothorax
PaO_2 <7.3 kPa (55 mm Hg)
$PaCO_2$ >6.7 kPa (50 mm Hg)
Multi-resistant organisms
Increasing cachexia
Young female patients: particularly poor prognosis: early referral

according to 9-parameter modelling did benefit from lung transplantation. If FEV_1 <30% was chosen as the single criterion for selection for lung transplant, survival with and without transplant was similar, indicating that FEV_1 alone does not sufficiently select patients for whom lung transplantation will be beneficial.

In addition, further studies point out that shorter distances in the six-minute walk, the presence of pulmonary hypertension [5] or side differences in perfusion scanning [6] are indicative of poorer survival in cystic fibrosis patients on the waiting list for transplantation.

Colonisation with resistant pathogens

Burkholderia cepacia complex

Burkholderia cepacia (*B. cepacia*) emerged as a respiratory pathogen in cystic fibrosis patients 20 years ago [7]. Pulmonary infection is usually chronic and refractory to antimicrobial therapy (due to decreased cell permeability [8], inducible chromosomal beta-lactamases [9], altered penicillin-binding proteins [10] and the presence of antibiotic efflux pump [11]). After acquisition, patients often show a steady decline in lung function. Some present with a sepsis-like syndrome ("cepacia syndrome") involving necrotising pneumonia with bacteraemia with an excessive immune response and large amounts of circulating pro-inflammatory cytokines such as TNF-alpha and IL-8. Virulence factors of *B. cepacia* include different classes of pili which mediate adherence to respiratory epithelial cells [12]. The so-called "cable pilus" is a cable-like pilus expressed in the ET12 strain of *B. cepacia*, a strain which has been transmitted among cystic fibrosis patients in North America and the United Kingdom [13].

In the early era of lung transplantation, mortality due to bacterial infections was high and so at that time many centres excluded patients with multiresistant organisms from their waiting lists. One of the first reports of *B. cepacia*-positive patients undergoing lung transplantation came from Toronto [14]: of 22 CF patients transplanted between 1988 and 1991, 15 cultured positive for *B. cepacia* and 7 of these died. In contrast, only 5 of 27 patients transplanted between 1990 and 1993 at the University of North Carolina were *B. cepacia*-positive, and only one died [15]. Postoperative *B. cepacia*-associated complications included pneumonia, empyema, subdural empyema, and bronchiolitis obliterans due to *B. cepacia*.

Recent advances in the taxonomy of *B. cepacia* have resulted in epidemiological differentiation and new insights into its virulence in the setting of lung transplantation. In 1992, detailed genetic analysis led to the creation of the genus *B. cepacia* (previously known as *Pseudomonas cepacia*). Then, in 1997, Vandamme et al. in Belgium [16] determined several distinct bacterial species within *B. cepacia*, the so-called "genomovars". Together, the

Table 2

Burkholderia cepacia complex or phenotypically similar isolates from cystic fibrosis patients.

Species / Genomovar	binomial designation	frequency	characteristics	epithelial cell invasion
Genomovar I	*B. cepacia*	1%		+
Genomovar II	*B. multivorans*	10–38%		++
Genomovar III		50–80%	poor prognosis patient-to-patient spread (+ in agricultural soil)	++
Genomovar IV	*B. stabilis*	1–4%		+
Genomovar V	*B. vietnamiensis*	2–5%		+
Genomovar VI		2%		
Genomovar VII	*B. ambifaria*	<1%		
Genomovar VIII	*B. antina*	<1%		
Genomovar IX		<1%		
Genomovar X	*B. ubonensis*	<1%		
B. fungorum		<1%		
B. gladioli		<1%		
Ralstonia pickettii		<1%		
Pandoraea spp.		<1%		

genomovars were integrated into the "*B. cepacia* complex". At present 10 different genomovars are distinguished, some of them already carrying a binomial designation (table 2).

In lung transplantation, certain genomovars are associated with higher mortality than others. In a recent analysis [17] of 121 patients transplanted for CF, 21 were *B. cepacia*-positive, 1 with genomovar I, 7 with genomovar II, and 12 with genomovar III. The 5 cepacia-related deaths occurred exclusively in patients carrying genomovar III, indicating that genomovar III predisposes to early mortality after lung transplantation. ET12, an epidemic strain which is highly transmissible and responsible for most of the deaths in Toronto and Manchester [18], also belongs to genomovar III. Similarly, De Soyza et al. from Newcastle, England [19], demonstrated that in their series of 84 lung transplant recipients with cystic fibrosis (of which 11 were positive for *B. cepacia*: 3 with genomovar II, 2 with genomovar V, and 5 with genomovar III) only patients with genomovar III died of cepacia-related complications, whereas patients carrying other genomovars had a better outcome.

To date, studies are under way to investigate the effects of synergistic antibacterial testing and specific multiple antibiotic regimens in reducing mortality in this patient population. The Toronto group has already reported increased survival in presumed genomovar III recipients with a triple antibiotic regimen and a reduction in immunosuppression in the early post-transplantation period [20].

B. cepacia complex in cystic fibrosis patients appears to be acquired both from the environment and from other patients. The evidence of patient-to-patient spread of bacteria from the *B. cepacia* complex and the adverse prognosis in those who are infected demands strenuous efforts to prevent fresh acquisition.

Reliable genotypic assays using polymerase chain reaction in conjunction with phenotypic methods have been developed for identification of species within the *B. cepacia* complex. However, misidentification rates are still high. Reanalysis of 1000 isolates which had been identified as *B. cepacia* complex by the referring laboratories could not confirm the diagnosis in 11% of cases, and, conversely, members of the *B. cepacia* complex were diagnosed in 36% of isolates not identified by the referring laboratory [21]. Given the impact of such identification for a patient, all efforts should be undertaken to diagnose correctly organisms of the *B. cepacia* complex.

In Switzerland the rate of infection with pathogens of the *B. cepacia* complex in cystic fibrosis patients has thus far been low compared with the US or the UK. In the Zurich Lung Transplant Programme only 2 of 45 patients transplanted for cystic fibrosis were *B. cepacia*-positive (genomovar unknown), and both are alive 11 and 21 months after transplantation.

If patients are referred for lung transplantation in our centre, careful specific *B. cepacia* testing is performed using a combination of phenotypic and genotypic microbiologic assays with international collaboration.

Multiresistant *Pseudomonas aeruginosa* and other Gram-negative bacilli

When patients are referred for lung transplantation they are often colonised by multi- or panresistant organisms such as *P. aeruginosa*. In the early days this was considered a contraindication. More recently it has been demonstrated that cystic fibrosis patients infected with panresistant *P. aeruginosa* have similar post-transplant outcomes to patients with sensitive bacteria, and so they should not be ruled out for transplantation [22]. However, many centres recommend that these patients should be identified early before transplantation, and that antibiotic susceptibility and synergy testing should be performed. These tests should be repeated at regular intervals while the patients are on the waiting list, to ensure that recently tested effective antibiotic drug combinations are available at the time of transplant surgery [23]. Other emergent Gram-negative strains such as *Stenotrophomonas maltophilia* or *Alcalygenes xylosoxidans* are treated similarly.

Aspergillus

In our experience up to 50% of patients with cystic fibrosis referred for transplantation are colonised with *Aspergillus sp*., and invasive aspergillosis is a serious complication after lung transplantation. However, in a retrospective analysis Paradowski et al. found no correlation between pre-transplant colonisation with *Aspergillus* and post-transplant invasive disease, and *Aspergillus* is not considered a contraindication [24]. Fortunately, fewer patients suffer today from invasive aspergillosis after transplantation. This may be due to consequent prophylaxis with itraconazole or amphotericin B inhalation, as has been advocated by some centres after transplantation [25]. Also, it may be related to the fact that modern immunosuppressive therapy contains fewer steroids than previously.

Non-tuberculous mycobacteria

Cystic fibrosis is a risk factor for the development of non-tuberculous mycobacteria (NTM) infection [26]. Prevalence in this population varies between 4% and 20% [27–30]. The most frequently isolated pathogens are *M. avium* complex, *M. abscessus*, *M. kansasii*, and *M. fortuitum*. NTM are difficult to culture in the sputum of cystic fibrosis patients because of overgrowth of cultures by other pathogens, in particular *Pseudomonas* species. Hence if the clinical index of suspicion is high, multiple sputum specimens should be analysed to increase recovery of the organism.

On the other hand, recovery of NTM in sputum may pose a dilemma, since the question

whether the pathogen indicates active infection or airway colonisation is often difficult to answer. Diagnostic criteria for NTM infection include multiple positive airway cultures, respiratory symptoms or a decline in FEV_1 not responsive to conventional antibiotic treatment, and CT findings such as small peripheral nodules, "tree in bud" appearance or cavitary disease.

Since immunosuppression is a known risk factor for NTM infection, these pathogens arouse concern in the setting of lung transplantation. If on referral for transplantation the patient shows repetitive NTM-positive sputa, NTM should be treated. After transplantation, NTM may be more often present than anticipated. Malouf et al. demonstrated mycobacterial infections in 10% of lung transplant recipients, most of the infections being due to *M. avium* complex [31]. The authors feel that NTM infections after lung transplantation may be underestimated and may be an unrecognised cause of graft dysfunction.

Liver disease

25% of cystic fibrosis patients show hepatic dysfunction due to underlying disease. 3% present with severe liver disease and portal hypertension. Hepatic fibrosis with portal hypertension (including hypersplenism and oesophageal varices) and synthesis dysfunction is a contraindication for isolated lung transplantation, and combined lung/liver transplantation may be considered. The combination of endstage lung and liver disease in these patients is particularly challenging for both surgical and postoperative management. These patients are often in a poor nutritional condition related to severe intestinal malabsorption and chronic infection. Despite these increased perioperative risk factors [32], recent results from the combined registry of the United Network of Organ Sharing and the International Society of Heart and Lung Transplantation show that overall survival in combined lung/liver transplantation is 64% and 56% after 1 year and 5 years respectively [33]. Whereas early survival is dependent on lung and liver transplant surgery, long-term survival chiefly depends on follow-up after lung transplant.

The question of timing is more difficult to answer in combined transplantation. Patients with severe liver but mild pulmonary disease qualify for isolated liver transplantation. However, in patients with moderate lung disease and colonisation of the bronchial tree by *Pseudomonas* and *Aspergillus*, the risk of perioperative mortality due to infectious complications in isolated liver transplantation increases [34, 35].

Nutrition

Despite forced high caloric intake (including gastrostomy or tube feeding), cystic fibrosis patients with endstage lung disease are usually malnourished. The reasons for this include pancreatic insufficiency, high energy expenditure, and frequent exacerbations. It has been shown that patients with a low body mass index (<18 kg/m^2) are at increased risk of death on the waiting list [36]. Every effort should therefore be made to prevent further weight loss when patients are listed for transplantation.

Osteoporosis

The prevalence of osteoporosis in cystic fibrosis is higher than in the general population [37, 38]. The risk factors include malabsorption of vitamin D and calcium deficiency, hypogonadism, low body weight [39] and corticosteroid therapy. After transplantation, bone loss is increased due to immunosuppressive therapy with calcineurin inhibitors and corticosteroids. Patients considered for transplantation should undergo aggressive therapy with calcium and vitamin D supplements as well as bisphosphonates, to prevent further bone loss before and after transplantation. The favourable effects of this treatment on bone density have already been demonstrated in several groups [40].

Pre-transplant thoracic procedures

Pleural adhesions due to repeated infection, pleurodesis for pneumothorax or other thoracic procedures are often seen in patients with cystic fibrosis. They are not considered a contraindication but may complicate and prolong the transplantation procedure. In patients with pneumothorax, thoracoscopic pleurectomy is in general preferred to chemical pleurodesis. However, in individual cases the best course may be to decide on the choice of procedure in consultation with the lung transplant centre.

Mechanical ventilation

While mechanical ventilation was long considered a contraindication, stable, ventilator-dependent patients are now undergoing successful transplantation in experienced centres. Meyers et al. have shown that patients with varying underlying diseases who became ventilator-dependent after listing for transplantation may achieve acceptable 1-year survival after transplantation if they are in stable single organ failure without inflammation at the time of transplant. In contrast, transplantation invariably fails in unstable ventilated patients [41]. Patients with cystic fibrosis who need intubation for haemoptysis or pneumothorax generally have favourable outcomes. Non-invasive positive pressure ventilation has been shown to improve gas exchange, to decrease minute ventilation and to reduce the work of breathing in patients with cystic fibrosis and respiratory failure [42], making this ventilation strategy an important tool for waiting list patients requiring assisted ventilation.

Psychosocial issues

Today, the connection between emotional well-being and reliable medication compliance and adherence to treatment is well known [43]. If the lung transplant recipient's environment is dysfunctional with lack of dedicated support personnel, transplantation is less likely to be successful. In adolescent transplant recipients in particular, care should be taken to ensure a positive outlook on life with strong emphasis on sought-after goals as well as interpersonal relationships. By anticipating the emotional needs of this population the health care team can improve the overall success of transplantation. At the time of referral, close attention should be focused on the psychosocial situation and, if necessary, intensive psychosocial counselling and therapy should be instituted.

Living donor lobar transplantation

The discrepancy between the steadily increasing demand for donor lungs and their availability has led to the development of living donor lobar donation. The procedure involves the removal of a lower lobe from each of two donors and subsequent transplantation into a child or small adult [44]. In experienced centres [45], short- and intermediate-term results are comparable with cadaveric transplantation. However, this procedure simultaneously involves three patients and the potential morbidity (and mortality) must be taken into account. Thus far there have been no donor deaths, but minor donor complications such as pleural effusion, air leaks, pneumonia etc. are common [46]. As opposed to the liver, the lung is a non-regenerating organ and the procedure is obviously more risky for the donor compared to kidney transplantation. In addition, the psychological pressure on the parents of a child with cystic fibrosis can be enormous, given the fact that they are often members of a cystic fibrosis association or community where the "good action" of potential donors will be encouraged [47, 48].

Bearing these ethical considerations in mind, living donor lobar transplantation has a role in children and small adults who are rapidly deteriorating and who have no chance of receiving a cadaveric organ in time.

Results after lung transplantation

Compared to the early days, survival after transplantation has improved substantially. In experienced centres, 1-year survival of more than 80% and 5-year survival of more than 60% are now achieved. On the one hand, experience of surgical and anaesthesiological technique, peri- and postoperative management and long-term follow-up care has grown. On the other hand, the indications for transplant have widened and high-risk patients for whom, due to mechanical ventilation, multiresistant organisms, other organ involvement etc., transplantation was contraindicated ten years ago are transplanted today.

For well selected patients with cystic fibrosis, lung transplantation results in a survival benefit [49]. Charman et al. have recently shown that as early as 60 days after transplantation the risk of death is lower post-transplantation compared to longer time on the waiting list. Most importantly, quality of life is significantly better after transplantation compared to the time on the waiting list [50–52].

The transplant team's growing experience, coupled with meticulous monitoring of graft function and consequent prophylaxis and treatment of infections and acute rejections, has produced stable early and intermediate post-transplant courses in many recipients.

Later in the follow-up, bronchiolitis obliterans is the biggest obstacle to better long-term survival. Whether earlier detection and consequent treatment of potential risk factors will reduce the incidence of this complication remains to be seen.

In some respects patients with cystic fibrosis are ideal candidates for transplantation, in that they are used to frequent medical consultations and intensive drug therapy, and are also vigilant in the matter of infections.

Conclusion

Today, lung transplantation can improve survival in cystic fibrosis patients with advanced lung disease. Appropriate timing of transplantation, careful consideration of medical issues in other organs, and psychosocial support systems are prerequisites for a successful outcome. Living donor lobar transplantation has become an option in rapidly deteriorating children and small adults.

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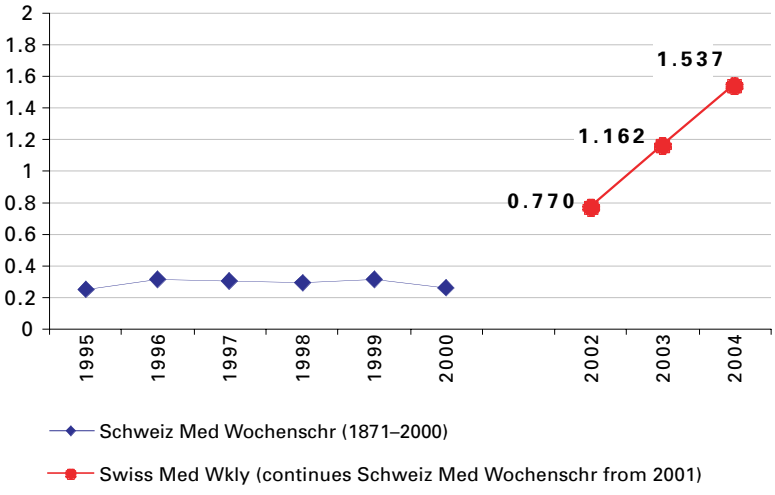

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