

MINI-SYMPOSIUM : CYSTIC FIBROSIS

# Lung transplantation and end of life issues in cystic fibrosis

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## KEYWORDS

cystic fibrosis,  
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**Summary** Lung transplantation has been available as a therapeutic option for patients with end-stage cystic fibrosis lung disease for over 15 years, but the outcome following transplantation remains poor, and the supply of organs limited. For this reason some children opt to continue with medical treatment followed by terminal care rather than undergo transplantation. This article summarizes the current status of lung transplantation, including current referral guidelines and contraindications and also addresses current practice in terminal care.

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## INTRODUCTION

Three decades ago only a quarter of children born with cystic fibrosis (CF) were expected to reach their 16th birthday. Since then, life expectancy of children diagnosed with CF has improved dramatically, with UK data suggesting median survival of over 30 years.<sup>1</sup> Despite this improvement, a substantial number of patients with CF do not survive into adulthood, with lung disease being the commonest cause of death.

Lung transplantation has been available as a therapeutic option for these patients for over 15 years, but the initial enthusiasm for transplantation has been tempered as outcome has remained poor, and the supply of organs limited. For these reasons some children opt not to undergo transplantation, but continue with medical treatment followed by terminal care. Paediatricians caring for children with end-stage CF lung disease have the difficult task of assisting the child and family in making informed choices regarding these options, at a time when distress and anxiety are likely to be high. The aim of this review is to update the reader on the current status of lung transplantation, and to clarify some of these issues.

## LUNG OR HEART-LUNG TRANSPLANTATION

Transplantation has been employed as therapy for end-stage lung disease since the early 1980s, and by 1999 almost 1000 children had received lung or heart-lung transplants worldwide.<sup>2</sup> The majority have been children with CF. Early transplants were almost exclusively heart-lung transplants, where both heart and lung are transplanted whilst the recipient is on cardiopulmonary bypass. As a CF lung transplant recipient will normally have normal cardiac anatomy and good cardiac function, the explanted heart can then be transplanted into another patient with terminal cardiac disease (the domino procedure). Over the last 5 years there has been a worldwide shift away from heart-lung transplantation in favour of double or bilateral lung transplantation. This procedure either involves removal of both diseased lungs and transplant of both donor lungs during cardiopulmonary bypass (double lung transplantation), or removal and transplant of one lung followed by removal and transplant of the second lung (bilateral sequential lung transplantation). This latter procedure is increasingly favoured, as it does not normally require cardiopulmonary bypass. Both double and bilateral lung transplantation allow the donor heart to be transplanted to another recipient.

Living donor bilateral lobar transplantation was first described in 1994 and involves the removal of a left and

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right lower lobe from two volunteer donors and sequential transplant into the recipient. This technique overcomes problems of donor shortage. However, there are difficult ethical issues involved, as the procedure is not without risk to the donors, and true informed consent in such emotionally charged situations may be difficult to establish.

## PROBLEMS OF DONOR SHORTAGE

As the potential benefits of lung or heart lung transplantation have become better understood, the number of potential recipients has increased. This has not been matched by an increase in the number of donor organs available, and the resultant mismatch is one of the most pressing issues facing lung transplant programmes at present.

The procedure for allocating organs differs between countries. In North America organs are allocated on waiting list seniority basis, with patients waiting the longest having priority for organs. In the paediatric service in the UK, organs are allocated by turn to the three paediatric transplant centres, whilst in the adult service organs are allocated on a regional basis. Centres can then allocate them to patients as they see fit, and the majority then attempt to prioritize patients with the poorest clinical status and the shortest life expectancy. Both approaches have their drawbacks. In the USA the current mean waiting time for heart–lung transplantation is approximately 2 years. This situation obliges centres to list patients for transplantation when they have at least 2 years' predicted life expectancy. UK centres can wait longer to list patients, but with the knowledge that many of these patients may never receive a transplant. A recent report showed that less than half the paediatric CF patients listed at their centre between 1989 and 1999 had received transplants, the remaining children having died on the waiting list.<sup>3</sup>

## OUTCOME FOLLOWING TRANSPLANTATION

Choice between lung or heart–lung transplantation is dependent on surgical and logistic considerations, and some centres believe that the latter procedure results in fewer problems in younger children. The results for the two procedures are similar, and are markedly poorer than for other solid organ transplants. The International Registry reports survival of 70–80% at 1 year and 30–45% at 5 years for both procedures.<sup>4</sup>

The poor long-term outcome (Fig. 1) is related to the susceptibility of the transplanted lung to graft rejection, with the majority of the early deaths related to acute rejection or to overwhelming infection as the patient is heavily immunosuppressed. Those patients who survive the early post-transplant period are still at high risk of

developing bronchiolitis obliterans syndrome (BOS, Figures 1–4). This condition is sometimes referred to as chronic lung rejection, but appears to be related to episodes of acute rejection and lower respiratory infection in the early post-transplant period.<sup>5,6</sup> Once developed, it is irreversible, and is the major contributor to morbidity and mortality in patients surviving the first 3 months. At least 50% of early survivors of early survivors will develop BOS by 3 years post-transplant.<sup>6</sup>

Given the irreversible nature of BOS, improvements in post-transplant outcome are more likely to come from improvements in immunosuppression. At present, the majority of centres use very similar regimens, with methylprednisolone and antilymphocyte globulin in the early post-operative period, and then long-term immunosuppression using a combination of three drugs: either cyclosporin or tacrolimus; azathioprine; and prednisolone. Side effects from these drug combinations are considerable, and some patients still have problems with breakthrough rejection. Although development of new immunosuppressive agents is continuing there have been no recent major advances in this area.

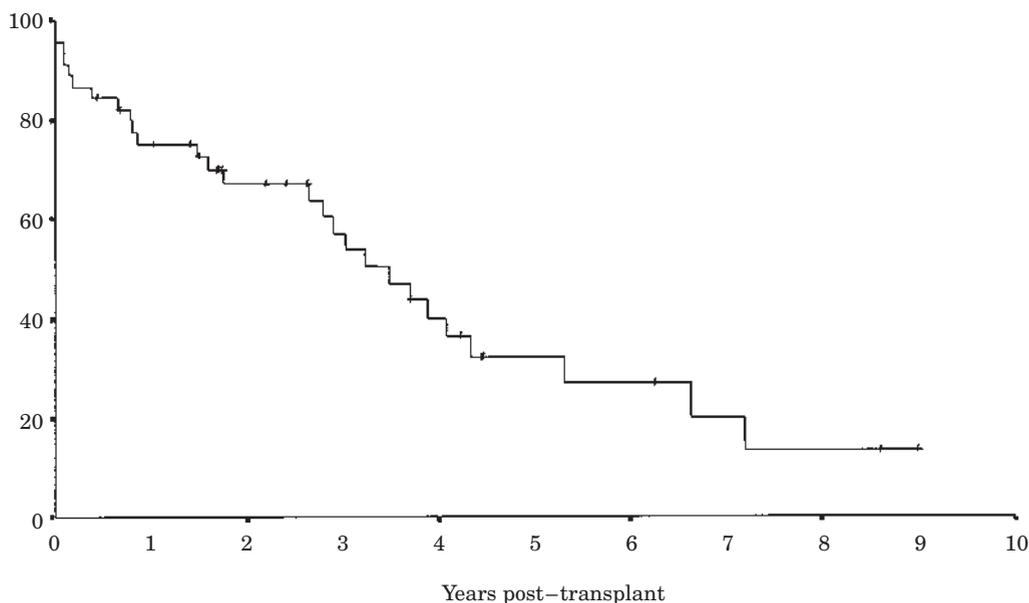
Other than BOS, long-term complications of transplant are generally related to immunosuppression, and include opportunistic infection, malignancy, and drug-related organ damage. In particular, cyclosporin and tacrolimus can cause renal failure. Other specific side effects include hypertension, gum hypertrophy, and hirsutism (cyclosporin), induction of diabetes (tacrolimus), neurotoxicity (cyclosporin and tacrolimus) and bone marrow suppression (azathioprine). However, the attrition caused by BOS is so dramatic that these complications are seen less commonly in lung transplant recipients than in recipients of other solid organ transplants.

## SELECTING PATIENTS FOR TRANSPLANTATION

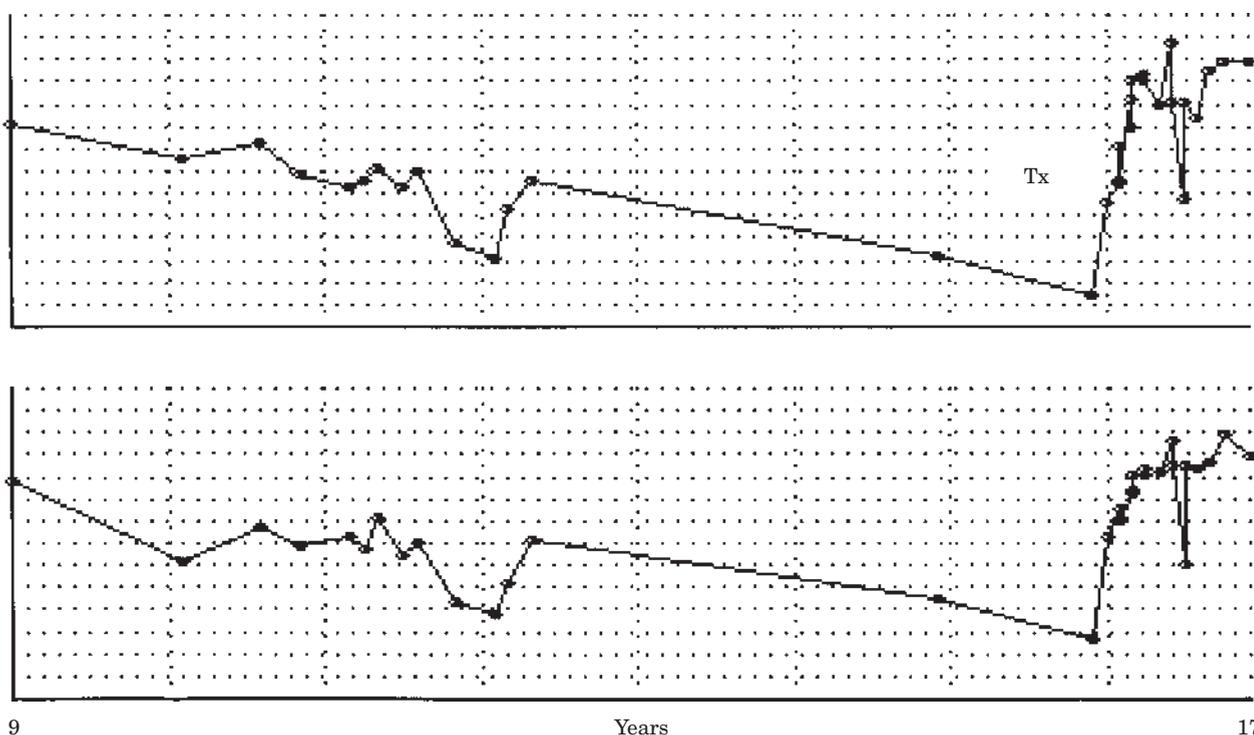
With such limited post-transplant survival, the timing of transplantation has become an important clinical decision. The decision to recommend transplantation in children with CF depends on three factors: life expectancy of 2 years or less; poor quality of life; and no contraindications to transplantation. Assessment of these three factors together determines whether lung transplantation is an acceptable risk for the child.

## PREDICTION OF LIFE EXPECTANCY

Determining life expectancy in children with CF referred for transplantation assessment is a difficult procedure, and review of a variety of clinical and physiological measurements is preferable to prediction based on lung function measurement alone. Although a number of clinical



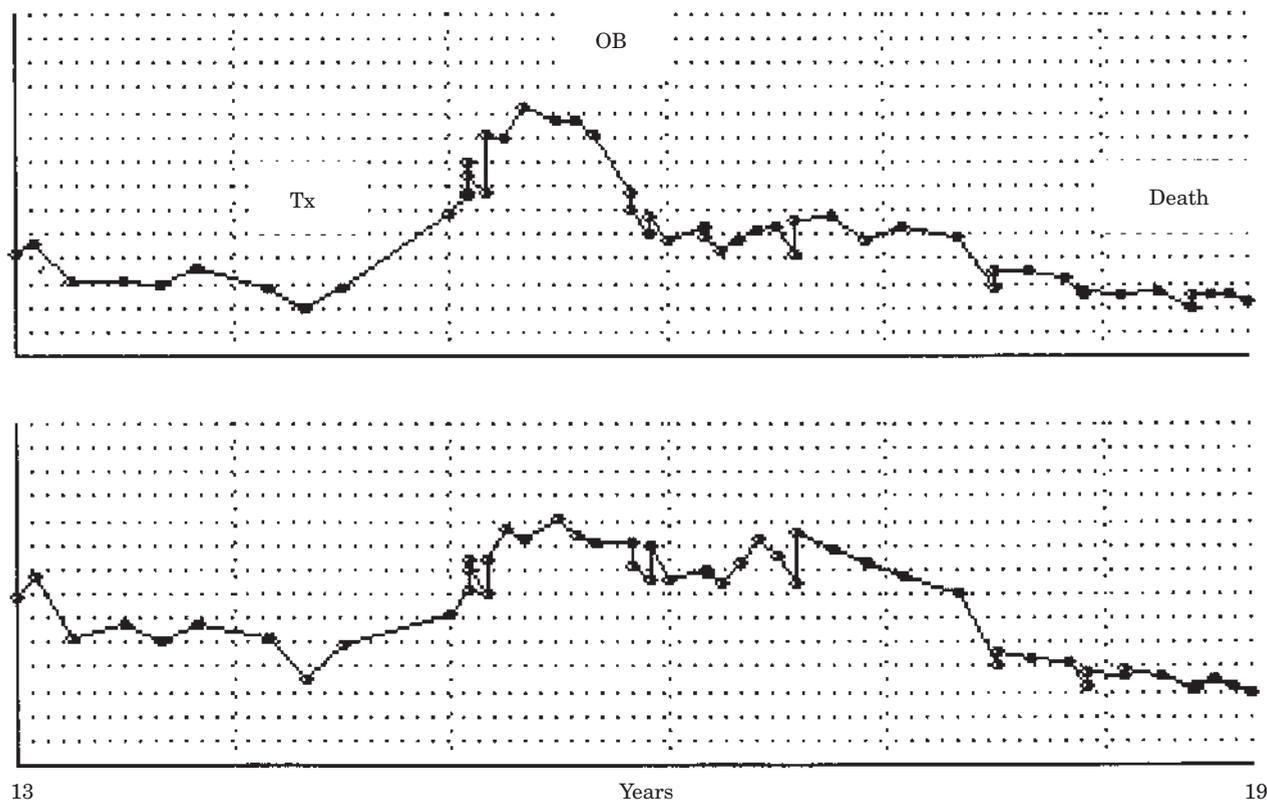
**Figure 1** Kaplan-Meier survival curve for paediatric CF patients receiving lung or heart lung transplants at Great Ormond Street Hospital between 1989 and 1999.



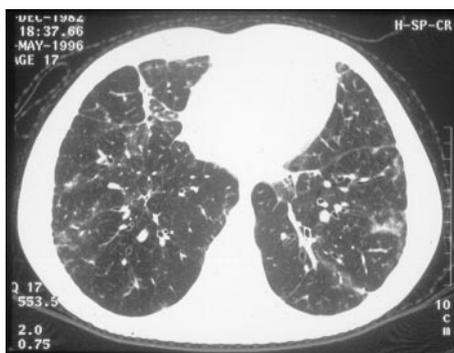
**Figure 2** Longitudinal lung function for a child with CF undergoing lung transplantation. Upper graph shows change in FEV<sub>1</sub>, lower graph shows change in FVC. Sudden deterioration and recovery in the post transplant period coincided with a successfully treated acute rejection episode.

scoring systems for CF are in regular usage, these are of limited use in determining life expectancy. There have been previous studies that have employed proportional hazards modelling in order to identify measurements that are of prognostic value in these patients, with particular

emphasis on the use of lung function measurements to determine life expectancy. Kerem *et al.* studied the survival of 673 patients (children and adults) from the Hospital for Sick Children, Toronto, over a 13-year period (1977–1989).<sup>7</sup> They identified a forced expiratory



**Figure 3** Longitudinal lung function for a child with CF undergoing lung transplantation and then developing bronchiolitis obliterans syndrome. Upper graph shows change in  $FEV_1$ , lower graph shows change in FVC.



**Figure 4** Computed tomogram showing typical features of post lung transplant obliterative bronchiolitis, with bronchial dilatation, bronchial wall thickening, and reduced pulmonary vascular markings. A 'signet ring' sign is seen in the left lung.

volume in 1 second ( $FEV_1$ ) of less than 30% predicted, young age, and female gender as risk factors for death within 2 years. The authors also studied the value of percentage ideal weight as a predictor, but found it of little value, particularly in younger patients. Hayllar *et al.* studied 403 patients, predominantly adults, between 1969 and 1989.<sup>8</sup> This analysis identified low  $FEV_1$ , low forced vital capacity (FVC), short stature, high leukocyte count, clinically detected hepatomegaly, and low plasma albumin

and high alkaline phosphatase concentrations as the best predictors of survival. A more recent study of 181 children with severe CF lung disease referred for transplant assessment identified young age, female sex, low  $FEV_1$ , low arterial oxygen saturation during 12 min walk test, high age-adjusted resting heart rate, low plasma albumin concentration, and low blood haemoglobin concentration as the best predictors of survival.<sup>9</sup> The results from this study are in line with previous recommendations that children should be referred for transplantation assessment when their  $FEV_1$  falls to 30% or lower, but that younger children, girls, and patients deteriorating rapidly should be considered for referral sooner. There is now evidence that children under 10 years of age<sup>10</sup> and children with very advanced lung disease (authors' own data) have acceptable post-transplant outcome, and referral should not be denied for these reasons.

## QUALITY OF LIFE

Assessment of quality of life is even less exact than estimation of life expectancy, as there are no widely accepted measures of quality of life in childhood. Assessment is therefore made by the clinician in combination with other members of the transplant team, and takes account of ability to partake in daily activities such as schooling or

social activity, exercise tolerance, time spent in hospital, and requirement for oxygen and intravenous antibiotic therapy. As far as practicable this assessment is taken from the child's perspective rather than from the parent's, and detailed information from the referring centre is of great value. Although inexact, assessment of quality of life is an essential component of the risk assessment. A child with an FEV<sub>1</sub> of 30% is unlikely to be accepted for transplantation if they still maintain a quality of life acceptable to that child.

## ABSOLUTE AND RELATIVE CONTRAINDICATIONS

Contraindications to lung transplantation have yet to be fully determined. Although a number of consensus statements have been published recently,<sup>11</sup> some of the recommendations in these statements are still being debated. Accordingly, there is some variation between transplant centres regarding contraindications to transplantation, and a patient who is refused by one centre may well be accepted by another. This section therefore expresses the views of the authors, and to a large extent reflects the guidelines of Great Ormond Street Hospital for Children Thoracic Transplant Unit, where both authors have previously worked.

It is best to consider these factors as absolute contraindications, relative contraindications, and conditions that require pre-transplant assessment so that treatment can be modified. It is important to note that previous thoracic surgery, including pleurectomy and pleurodesis, is no longer considered an absolute contraindication.

### Absolute contraindications

*Severe irreversible damage to other organs* — particularly with regard to renal dysfunction, as immunosuppressive agents are unlikely to be tolerated in these patients. Patients with hepatic disease are assessed individually — severe disease is an absolute contraindication or an indication for liver and lung transplant;

*Malignancy* — 5 years disease free is required before transplantation can be considered;

*HIV infection*;

*Hepatitis B antigen positivity, or hepatitis C seropositivity with evidence of ongoing disease*;

*Active mycobacterium tuberculosis infection*;

*Major psychiatric illness* — this would impair adherence to the post-transplant medical regimen;

*Ventilator dependent respiratory failure* — this is considered an absolute contraindication at most centres, not only because of the poor post-transplant survival of such patients,<sup>4</sup> but also because of the improbability of them receiving organs in time. We believe that transplantation should never compromise appropriate terminal care and

suggest that patients should be removed from waiting lists when they enter the terminal phase.

### Relative contraindications

*Burkholderia cepacia chronic infection* — there have been reports of cepacia syndrome occurring in the immediate post-transplant period, and some units, particularly in the USA, consider this an absolute contraindication. This is not the case in most UK or European centres;

*Pan-resistant Pseudomonas aeruginosa chronic infection*.

### Pre-transplant factors requiring intervention

*Psychosocial concerns* — some centres consider these to be an absolute contraindication to transplantation, but whilst poor compliance with medication post-transplant is potentially disastrous, there is no evidence that poor compliers can be adequately identified in the pre-transplant period. Furthermore, there is no evidence that family dysfunction or social class have any impact on post-transplant survival;

*Systemic corticosteroid therapy* — dosage is reduced wherever possible to aid anastomotic healing;

*Diabetes mellitus* — good control is important;

*Poor nutritional state* — there is still uncertainty over the impact of a poor nutritional state on post-transplant outcome but a patient with <70% of ideal weight will require intervention. Improvement in nutrition may in some cases improve the overall health of the child such that transplantation is no longer considered necessary;

*Atypical mycobacteria infection*;

*Methicillin-resistant Staphylococcus aureus colonization*;

*Aspergillus colonization*;

*Seronegativity for measles* — vaccination is recommended.

## BENEFITS OF TRANSPLANTATION

There is increasing evidence that lung or heart–lung transplantation can increase life expectancy in appropriately selected patients. Testing this hypothesis has not been straightforward, as randomized controlled trials would not be acceptable in this situation. However, hazard modelling techniques can be employed to calculate the survival benefit from transplantation. There have now been a few published studies that have employed these methods and obtained similar results. One of these calculated a hazard ratio for transplantation of 0.31, equating to a reduction in risk of death of 69% (95% confidence intervals 28–87%) for children with CF transplanted at their centre.<sup>3</sup>

Assessing the impact of transplantation on health-related quality of life is even more difficult, but there is some evidence that quality of life is enhanced in early

survivors of lung transplantation. There are no published data from children, largely because of the difficulty in measuring quality of life in childhood. However, it is known that over 90% of children still surviving 3 years post lung transplantation have no limitation to their activity.<sup>2</sup> Staff working within transplant programmes would insist that the majority of patients do have a substantial improvement in quality of life in the early post-transplant period, and it is this benefit, more than increase in longevity, that justifies the procedure.

## NON-INVASIVE POSITIVE PRESSURE VENTILATION

Non-invasive positive pressure ventilation (NIPPV) delivered via a nasal or face mask has been employed in patients with CF who are awaiting lung transplantation. Initial reports suggest that the majority of patients selected for NIPPV tolerate it well and achieve improvements in clinical status, arterial blood gases and reduction in O<sub>2</sub> requirement.<sup>12</sup> As yet this intervention is rarely offered to children, even those who are awaiting lung transplantation, as there are concerns that this prevents delivery of optimal terminal care. Adult centres in the UK and paediatric centres in the USA often take a more aggressive approach with their patients, and this is likely to be an area of controversy in the future.

## TERMINAL CARE

Lung transplantation is not a cure for CF lung disease. At best it is a palliative procedure, which can provide a child extra years of life, with improved pulmonary function allowing them to undertake previously impossible activities. At worst it can shorten life, or provide false hope as children await a transplant that will never occur. Few families have this understanding of transplantation from lay sources, and it is the responsibility of the referring paediatrician together with the transplant team to ensure that no child is listed for transplantation with an unrealistic expectation of what the procedure can provide. Following this education process, some children will prefer not to be referred for transplant assessment, whilst others will go through the assessment process to gain more information, but will then decline. It is important to understand that terminal care is still a valid option for patients with end stage CF lung disease.<sup>13</sup>

Although there is a wealth of literature on terminal care in childhood cancer, surprisingly little has been written about care of children dying from CF. The usual approach to children dying of cancer has been to provide palliative care in a home or hospice setting, with minimal therapeutic intervention. In contrast, a higher proportion of CF patients die in hospital, and the majority of them continue to receive therapy (such as intravenous anti-

otics), in addition to opiates and benzodiazepines.<sup>14</sup> One explanation for this difference in approach is that respiratory failure in late stage CF lung disease follows a fluctuating course, with occasional reports of children seemingly in terminal respiratory failure who subsequently improve. Other explanations are that children with CF have spent so much time in hospital that they do not find a side room on “their” ward to be threatening, and may draw comfort from the continuation of their usual therapy. Indeed, the ward nursing staff may have become so involved with the child and family that their support during the final illness becomes invaluable.

There is undoubtedly variation between centres in how they approach terminal care, but the primary rule for most centres is that terminal care should be actively managed to provide as comfortable and dignified a death as possible. There may be some conflict here when patients are listed for transplantation, but are clearly entering a terminal phase. The usual practice is for children to be removed from the transplant list at this time, in order for them to receive terminal care in the appropriate way.

### KEY POINTS

- Lung or heart–lung transplantation is a valid therapeutic option for patients with severe CF lung disease, with the potential to prolong survival and improve quality of life.
- In order to receive maximum benefit from the procedure, patients must be referred early enough for timing of transplantation to be optimized. Current recommendations are that patients with an FEV1 of 30% predicted or less should be referred for transplantation, though girls, younger children, and patients deteriorating rapidly may need to be referred sooner.
- There are very few absolute contraindications to transplantation, and if there is any uncertainty over whether referral is appropriate the concerns should be discussed with the transplant centre.
- The risks of lung or heart–lung transplantation are such that some patients may prefer not to consider this option, and in these cases the patients’ wishes should be respected.
- The possibility of lung transplantation should never be allowed to compromise appropriate terminal care.

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