Review

Cystic fibrosis and the thoracic surgeon

Matilde Rolla a, Antonio D’Andrilli b,*, Erino A. Rendina b, Daniele Diso c,1, Federico Venuta c

a Department of Cystic Fibrosis, University of Rome ‘La Sapienza’, Policlinico ‘Umberto I’, Rome, Italy
b Department of Thoracic Surgery, University of Rome ‘La Sapienza’, ‘Sant’Andrea’ Hospital, Via di Grottarossa 1035, 00189 Rome, Italy
c Department of Thoracic Surgery, University of Rome ‘La Sapienza’, Policlinico ‘Umberto I’, Rome, Italy

Received 1 June 2010; received in revised form 19 July 2010; accepted 21 July 2010; Available online 6 September 2010

Summary

Indications for thoracic surgery in patients with cystic fibrosis (CF) are principally represented by pleural diseases including pneumothorax, pleural effusion, and empyema and by parenchymal lung diseases including bronchiectasis, hemoptysis, and pulmonary abscess. Moreover, lung transplantation has proved a viable therapeutic option for progressive respiratory failure due to end-stage CF. Main surgical experiences in this setting are reviewed and discussed.

Keywords: Cystic fibrosis; Thoracic surgery; Lung transplantation

1. Introduction

Pleuro-pulmonary complications are the main cause of morbidity and mortality in patients with cystic fibrosis (CF) [1,2]. Although there have been significant advances in medical therapy [3], conservative management may not be sufficient to control the sequelae of the disease in some cases, and thoracic surgical intervention may become a mandatory therapeutic option for a number of patients with CF.

Thoracic surgery in CF patients gave rise to some concern about critical mortality rates, reportedly as high as 30% in the 1960s. This has been partially overcome with improvements in anesthetic and surgical techniques, as also in perioperative management, thus reducing the surgical mortality to significantly lower rates (up to 0.5%) in recent years [4–7].

Indications for thoracic surgery in patients with CF are principally manifested by pleural diseases including pneumothorax, pleural effusion and empyema and by parenchymal lung diseases including bronchiectasis, hemoptysis (related or not to bronchiectasis), and pulmonary abscess. Moreover, lung transplantation (LT) has proved to be a viable therapeutic option for progressive respiratory failure due to end-stage CF.

2. Pleural diseases

2.1. Pneumothorax

Spontaneous pneumothorax is a relatively common complication in patients with CF. In a retrospective observational study of the National Cystic Fibrosis Patient Registry published in 2005 [8] the incidence has been reported to be as high as 3.4% with an annual rate of 0.64%, although higher rates have been reported in other studies. Previous reviews have reported incidence rates ranging between 6.4% [9] and 18.9% [10,11].

The increased risk of pneumothorax in the CF population is principally related to a check-valve phenomenon due to mucus retention that increases air pressure differences favoring rupture of the blebs or bullae into the pleural space [12]. In addition, cases of iatrogenic pneumothorax due to lung injury during procedures such as venous line placement or thoracentesis should be considered as well.

The occurrence of spontaneous pneumothorax increases the risk of death in patients with CF. According to the Cystic Fibrosis Foundation Registry data [13], during the years ranging from 1990 to 1999 the mortality of CF patients experiencing pneumothorax was 48.6% compared to 12.2% of patients without pneumothorax. The reported median age at the time of the first pneumothorax is 21 years [8]. The incidence increases proportionally with age and severity of the disease. In a large retrospective study [8], about 75% of CF patients who developed pneumothorax showed a forced expiratory volume in 1 s (FEV1) < 40% of the predicted value.
The presence of infectious organisms such as *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, and *Aspergillus*, an FEV1 <30% of the predicted value, enteral feeding, pancreatic insufficiency and massive hemoptysis were found to be significant risk factors for the occurrence of pneumothorax in this series [8].

Basic therapeutic indications for the treatment of spontaneous pneumothorax are common to non-CF patients. There has been a general agreement among the medical fraternity [14] that a small (generally less than 20% of the volume of the hemithorax) asymptomatic pneumothorax can be managed by observation alone. A symptomatic pneumothorax or one that is occupying more than 20% of the pleural space should be treated initially with tube thoracostomy and application of negative pressure. For patients with recurrent pneumothorax or persisting air leaks (over 5–7 days), further treatment to prevent future recurrences is indicated.

Non-surgical or surgical options have been proposed and employed in this setting.

Non-surgical treatment consists of chemical pleurodesis using agents such as quinacrine, silver nitrate, tetracycline or talc, administered via a chest tube.

Surgical therapy includes resection or ablation (electrocautery or laser) of blebs or bullae, associated with chemical or surgical pleurodesis or pleurectomy. The main options for surgical pleurodesis include mechanical, electrocautery or laser abrasion of the parietal pleura. Video-assisted thoracic surgery (VATS) is actually the approach of choice for such operations and indications for thoracotomy have become occasional in the recent years.

Although current data in the literature have shown that a surgical approach is more effective in preventing pneumothorax relapses, concern about perioperative complications directly related to the procedure or due to underlying multi-organ disease have aided in limiting the indications for surgical interventions in patients with CF.

Non-surgical therapies are often preferred because of the reduced invasiveness and the theoretical tendency to produce more limited pleuropulmonary sequelae in potential candidates to future interventions including LT. The main limitations to these 'blind' procedures are the need for prolonged pleural drainage and the unequal deposition of chemical agents resulting in incomplete pleurodesis [15,16].

Looking at the data in the literature, there is a lack of randomized controlled trials comparing the efficacy and safety of the different techniques employed for the treatment of pneumothorax in CF patients [13]. Moreover, the number of scientific contributions on this topic has been decreasing in recent years; most studies refer to experiences that have occurred a few decades ago; very few papers have been published in the last 10 years. But this does not mean a consensus has been reached.

Several studies appearing in the 1980s and 1990s have indicated that higher success rates are achieved by surgical procedures despite an increase in treatment-related morbidity.

A study by Spector and Stern [10], reporting a 26-year experience with 99 CF patients, has compared conservative treatments including tube thoracostomy alone or tube thoracostomy with instillation of quinacrine, tetracycline, silver nitrate or talc, with surgical therapy including partial pleurectomy through limited thoracotomy. The surgical group in this series presented a significantly higher resolution rate (95%) if compared with the conservative treatment group (44.4%) and a lower recurrence rate (11% vs 17%).

Among patients undergoing conservative treatments (tube thoracostomy or non-surgical pleurodesis), only those receiving talc slurry achieved complete resolution of pneumothorax (100% rate) with no recurrence. However, due to the small number of patients, no significant conclusion can be acquired by these results. Although complications were minimal in each group, interestingly, morbidity was higher in the tube thoracostomy group (5.1%) than in the surgical group (3.5%). The authors concluded that pleurectomy should be recommended as the treatment of choice, reserve non-surgical talc pleurodesis for patients with respiratory failure and a compromised clinical status, or for the occasional patients in whom surgical intervention fails.

Another study [17] including 65 pediatric and adult patients has investigated the role of non-surgical treatment in this setting in comparison with surgical treatment. All the management techniques analyzed, with the exception of needle aspiration, resulted in a satisfactory rate of resolution (70–100%). Conservative therapies, which were the most frequently used options, reported high recurrence rates reaching 79% after thoracentesis, 63% after trochar thoracocentesis, 86% after tetracycline pleurodesis, and 43% after silver nitrate pleurodesis. The only non-surgical pleurodesis technique which yielded an acceptable recurrence rate (12.5%) was the one with the use of quinacrine, whereas surgical treatment with partial pleurectomy via limited thoracotomy reported no recurrence.

In another experience published in the early 1980s [11], thoracotomic surgical treatment performed in a series of 20 episodes of pneumothorax in 17 adult patients with CF reported an 11.7% recurrence rate. Surgical therapy consisted of abrasion pleurodesis or pleurectomy; it was performed in seven cases as first-line treatment and in 13 cases after previous failed conservative treatments. Perioperative mortality was 17.6%. In the same study, recurrence rates observed after conservative management with chemical pleurodesis or intercostal drainage were as high as 50% and 55.2%, respectively.

A similar study by Seddon and Hodson [18] on 27 adults with CF has compared surgical pleurodesis with pleurectomy for the management of pneumothorax. There were no significant differences in postoperative respiratory function, incidence of recurrence (50% vs 36.8%) and incidence of major postoperative complications (12.5% vs 15.7%) between the two groups.

Given the tendency toward minimally invasive approaches over time, the efficacy of pleurodesis with talc or mechanical abrasion using a VATS technique has been investigated in more recent studies [19,20]. Ozcan and colleagues [19] reported in 2003 a series of 22 children (8 with CF) receiving 32 surgical procedures. Talc pleurodesis was employed in the large majority of cases [28], with only four patients undergoing pleural abrasion. Blebectomy was performed as an associated procedure in four patients only. Although the resolution rate after initial surgical treatment of pneumothorax was 100%, the only three patients presenting persisting air leaks (over 7 days) belonged to the CF group.
Recurrences at 4-year follow-up were 2 (6.2%), one after talc pleurodesis and one after pleural abrasion. Both were treated by repeated VATS with talc insufflation. There was one perioperative death. In seven patients with severe respiratory failure, regional anesthesia was used. Because the occurrence of pneumothorax increases morbidity and mortality of CF patients whose respiratory function is already compromised by the underlying lung disease, the authors suggest that early VATS at first episode of pneumothorax is justified to provide immediate effective relief of symptoms and prevention of recurrence.

In the early era of VATS, other previous studies investigated the role of minimally invasive techniques in this setting. In a very limited series [21] of five patients with CF, thoracoscopic talc poudrage of the entire pleural surface, either under regional or general anesthesia, has been reported as an effective method to treat secondary pneumothorax, yielding 100% success rate with no recurrence or complication.

Subsequently, the possibility of successful management of recurrent pneumothorax secondary to CF by thoracoscopic localized apical talc poudrage [22] has been reported as an effective alternative to complete pleurodesis in order to avoid extensive adhesions that could limit the possibility of a future LT.

More recently, the possibility of an effective treatment with the application of a biological glue via mini-thoracotomy has been reported [23].

Conclusively, based on a systematic review of the literature (Table 1), it is still not possible to draw definitive conclusions regarding the safety and efficacy of the various treatment modalities for the management of recurrent or persistent pneumothorax in patients with CF. Although higher efficacy of the interventional procedures has been shown for non-CF patients, the increased risk for postoperative complications in the CF population suggests the need for further comparative evaluation of the different treatment options by means of large prospective randomized studies. In recent years, the encouraging results and limited morbidity obtained with the thoracoscopic techniques [24], frequently performed under loco-regional anesthesia, indicate that this minimally invasive approach could represent the best compromise between the need of minimizing surgical trauma and the need for effective control of the disease.

Among patients undergoing LT following pleurodesis for pneumothorax, increased perioperative morbidity and mortality resulting from hemorrhage due to pleural adhesions have been reported in the early years of heart and LT [25]. This has led to suggestions of a more conservative approach to pneumothorax management in patients with CF, in order to limit the pleural and pulmonary sequelae. However, in a more recent study [26], patients undergoing LT with previous pneumothorax, with or without pleurodesis, showed no significant differences with regard to intraoperative blood products, duration of procedure, and morbidity. These data

| Table 1. Surgical and non-surgical management of pneumothorax in CF. |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Author ('yr) CF patients | Management | Postop. success rate | Recurrence rate | Postop. mortality |
| McLaughlin ('82) 65/65 | Observation | Chemical pleurodesis 87.5% | Thoracostomy 63% | — |
| | Trocar thoracostomy | Chemical pleurodesis 12.5—86% | Pleurectomy 100% | — |
| | Chemical pleurodesis | Chemical pleurodesis 0% | Pleurectomy 0 | — |
| | (different options) | | | |
| Pleurectomy | | | | |
| Penketh ('82) 46/46 (surgery 17) | Observation | Observation 83.8% | Observation 50% | | |
| | Drain | Drain 67.4% | Drain 55.2% | Persistent drain 50% | Pleurectomy 17.6% |
| | Non-surgical pleurodesis | Non-surgical pleurodesis — | Non-surgical pleurodesis 100% | Pleurectomy 11.7% | |
| Surgery (pleurectomy) | | | | |
| Pleurectomy | Pleurectomy 100% | Pleurectomy 11.7% | Pleurectomy 1.7% | |
| | | | | |
| Tribble ('86) 5/5 (surgery 5) | Thoracoscopic talc | Thoracoscopic talc 100% | Thoracoscopic Talc 0 | 0 |
| Seddon ('88) 27/27 | Thoracotomic pleurectomy | — | Pleurectomy 36.8% | Pleurectomy 5.2% | Pleurectomy 12.5% |
| | Thoracotomic pleurodesis | — | Pleurectomy 50% | Pleurectomy 100% | — |
| Spector ('89) 99/99 | Observation | Observation 50% | Observation 70% | Observation 0 | Tube 0 | Chemical pleurodesis 0 |
| | Tube thoracostomy | Tube thoracostomy 31% | Tube thoracostomy 17% | — | — | — |
| | Non-surgical chemical pleurodesis | Chemical pleurodesis 45% | Chemical pleurodesis 15% | | | |
| | Talc pleurodesis (n. 5) | — | — | | | |
| Pleurectomy | Talc pleurodesis 100% | Talc pleurodesis 0% | Talc 20% | Pleurectomy 1.7% | |
| Noppen ('94) 1/1 | Thoracoscopic apical talc | 100% | 0 | 0 | 0 |
| | Biological glue (mini-thoracotomy) | 100% | 0 | 0 | 0 |
| Garske ('02) 1/1 | — | — | — | — | — |
| Ozcan ('03) 8/22 | Thoracoscopic talc or abrasion + blebectomy | 100% | 6.2% (CF 12.5%) | Overall 4.5% | |
| Hafen ('06) 11/11 | Tube/needle aspiration (first-line) | — | Tube/needle aspiration 50% | Overall 9% | |
| | Thoracoscopic blebectomy and/or pleurodesis | | | | |
may suggest that previous pleural procedures for pneumothorax should not be considered a contraindication for LT any more.

Pleurectomy for the treatment of pneumothorax precludes the possibility of using the expleural plane in case of further surgery and therefore can be considered a strong limitation for future operative procedures including transplantation. Chemical pleurodesis, if very localized, could offer some advantages in this setting avoiding mediastinal dense adhesions that may damage the phrenic nerve and compromise the diaphragmatic function.

2.2. Pleural effusion and empyema

Despite the elevated incidence of lung infections in patients with CF, massive pleural effusions requiring drainage are not frequent. General rules of treatment for abundant parapneumonic effusions are the same as for patients without CF, including drainage with thoracentesis or tube thoracostomy if fluids reaccumulate [27]. If colonized parapneumonic effusion becomes an empyema, drainage of the pleural cavity is always indicated. A multi-loculated empyema always requires a surgical procedure, usually by VATS, to evacuate and debride the pleural space. Thoracotomy with decortication of the underlying pulmonary parenchyma may be indicated in case of chronic empyema with fibrotic lung entrapment.

3. Parenchymal lung disease

The main pulmonary complications secondary to CF include bronchiectasis, acute or chronic atelectasis, abscess formation, and hemoptysis, with or without bronchiectasis. Conservative therapies include physiotherapy and systemic or inhaled antibiotics for infective disease and local application or systemic infusion of procoagulant agents for hemoptysis, and have shown increasing efficacy over time but are not sufficient in some cases. CF patients generally develop a diffuse parenchymal disease not amenable to surgical treatment, and only a small proportion of them presents with localized lesions for whom a resective surgical treatment may be indicated.

Resection of the damaged part of the lung has been proposed with the aim of removing the destroyed non-functioning parenchyma in order to prevent bacterial spreading and eliminate the source of recurrent hemoptysis refractory to conservative treatment. Localized bronchiectasis represents the most frequent indication for pulmonary surgery in patients with CF. Surgical approach may be required for diseases with either lobar or segmental extension.

Success in surgical management of bronchiectasis reported in patients without CF [28,29] has suggested that resective lung surgery should be considered as a valid option for patients with CF as well. Interestingly, experiences of surgical approaches for the management of CF pulmonary complications have been reported since the early 1970s [30,31]. Mearns and colleagues [30] reported the results of surgery on a series of 23 pediatric CF patients undergoing lobectomy or segmentectomy. Twelve of these presented single localized parenchymal lesions and underwent surgery with radical intent, whereas 11 showed multiple or extended lung lesions and received pulmonary resection for palliation or as a life-saving procedure. Immediate favorable postoperative outcome was observed in 13 patients (56%). There was one operative death (4.3%) and only one patient did not report benefit from surgery (4.5%). The remaining 21 patients showed some benefit from surgery at 1 year. Improvement in symptoms in terms of sputum production, chronic cough, and development of new bronchiectasis lesion was registered in 50% of patients with single lesion and 36% of patients with multiple lesions.

Marmon and colleagues [31] performed 11 pulmonary resections including nine lobectomies, one pneumonectomy, and one segmentectomy in 10 pediatric CF patients. They reported a follow-up ranging from 7 months to 13 years. Indications for surgery were: abscess and bronchiectasis in nine cases and atelectasis and life-threatening hemoptysis respectively in one each. There were no perioperative complications and all patients experienced subjective and objective improvement (decreased cough, sputum production, and incidence of exacerbations). Tracheostomy was never required in this group of patients.

Other smaller series by Steinkamp and colleagues [32] and Lucas and colleagues [33] with a shorter follow-up have subsequently confirmed the improvement in terms of overall clinical status, respiratory symptoms, and physical activity after pulmonary resection for localized disease. Detailed preoperative imaging is recommended [33,34] in order to ensure that the parenchymal disease is confined to the lobe or segment to be resected.

Reassessment of the results by the same author after long-term follow-up has confirmed the improvement of symptoms and lung function in the majority of patients, but has showed a tendency toward occurrence of new abnormalities in the parenchymal areas adjacent to those resected.

Another interesting experience published in the early 1990s by Smith and colleagues [5] includes 14 pediatric and adult CF patients undergoing 17 major lung resections (13 lobectomies and four pneumonectomies). Indications for surgery were atelectasis and bronchiectasis in most patients. However, in four cases, the operation was performed because of bronchopleural fistula (two cases) or hemoptysis not responding to medical therapy or selective embolization (two cases). Preoperative pulmonary function tests showed a wide heterogeneity with an FEV1 ranging between 11% and 88% of the predicted value. As a result, in the 12 surviving patients at a minimum follow-up of 1 year, not only was there a significant decrease in the postoperative FEV1 but also a significant reduction in the number of hospitalizations for pulmonary exacerbations (from 2.2 admissions/year to 1.1 admissions/year). The mean postoperative hospitalization was 8.5 days. The presence of a preoperative FEV1 less than 30% of the predicted value was uniformly associated with a poor outcome in this series.

The possibility to consider extended resections, and even pneumonectomy as a worthwhile therapeutic option in this setting, has been underlined by other authors [35,36]. Otgun and colleagues [35], in a large retrospective study including 54 children treated with major lung resection for
bronchiectasis of various etiologies, including CF, have reported an 18.5% incidence of pneumonectomies. Twenty-four percent of patients in this series received incomplete resection. Improvement of the clinical status was registered in 85% of patients with a mortality and morbidity of 5.6% and 14.8%, respectively. The rate of success was clearly higher in children receiving complete resection. Pneumonectomies were well tolerated without increase in morbidity and mortality, suggesting that this type of operation may be preferred instead of leaving residual disease when bronchiectasis is unilateral.

Häusler and colleagues [36] have described two cases of emergency right pneumonectomy in children with complete lung atelectasis and abscess formation. Preoperative FEV1 in the two children was 36% and 14% of the predicted value, respectively. Despite the severe underlying disease, these two patients experienced a remarkable improvement in quality of life.

More recently, Camargos and colleagues [37] have published the results of a series of 21 pediatric patients (mean age: 8 years) with severe chronic atelectasis and/or bronchiectasis secondary to CF surgically treated at two different institutions over a 16-year period. Lobectomy or bilobectomy was the most frequently performed operation (90.4%; associated with segmentectomy in three cases). Single segmentectomy was performed only in three cases. There were no significant differences when comparing parameters related to nutritional and colonization status before and after surgical treatment. Similarly, there was no statistically significant difference when comparing preoperative FEV1 with the one registered 1 and 2 years after surgery. However, results in terms of improvement in quality of life and reduction of number of exacerbations were more consistent than those showed by functional parameters. Moreover, results on pulmonary function, in this pediatric population before and after resection, are difficult to compare and therefore less accurate, as young age at the time of surgery hampers the ability to perform spirometry. The estimated survival probability was 93.8% 11 years after resection. Although in the literature there are no other studies assessing long-term survival in patients with CF undergoing lung resection, when comparing the results of this study with those of recent survival analysis [38,39] performed on patients not receiving lung surgery, there are no significant differences in survival. This could indicate that lung resection seemingly does not influence the final outcome.

Despite the lack of standardized indications for surgery in patients with pulmonary disease secondary to CF, the evidence resulting from published experiences [30–37,40] (Table 2) allows to draw some conclusions. There is wide consensus on the indication that lobectomy or segmentectomy should be considered in every case of unilateral severe parenchymal localized disease refractory to medical therapy

<table>
<thead>
<tr>
<th>Author ('yr)</th>
<th>CF patients</th>
<th>Indication for surgery</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Postop. mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mearns ('72)</td>
<td>23/23</td>
<td>Localized bronchiectasis</td>
<td>Lobectomy</td>
<td>Overall benefit (1 year) 91.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>Segmentectomy</td>
<td>Immediate benefit 56%</td>
<td></td>
</tr>
<tr>
<td>Marmon ('83)</td>
<td>10/10</td>
<td>Atelectasis</td>
<td>Lobectomy</td>
<td>Subjective and objective improvement</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abscess</td>
<td>Pneumonectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemoptysis</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinkamp ('88)</td>
<td>3/3</td>
<td>Bronchiectasis</td>
<td>Lobectomy</td>
<td>Clinical improvement 100%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atelectasis</td>
<td>Pneumonectomy</td>
<td>Decrease of mean postoperative FEV1</td>
<td>14.2%</td>
</tr>
<tr>
<td>Smith ('91)</td>
<td>14/14</td>
<td>Bronchiectasis</td>
<td>Lobectomy</td>
<td>Decrease of mean number of hospitalizations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atelectasis</td>
<td>Pneumonectomy</td>
<td>Decreased symptoms 71%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchopleural fistula</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucas ('96)</td>
<td>6/6</td>
<td>Bronchiectasis</td>
<td>Lobectomy</td>
<td>Improvement in general and respiratory status and physical activity 100%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atelectasis</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bragonier ('98)</td>
<td>3/3</td>
<td>Bronchiectasis</td>
<td>Lobectomy</td>
<td>Clinical benefit 100%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atelectasis</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hausler ('99)</td>
<td>2/2</td>
<td>Abscess</td>
<td>Pneumonectomy</td>
<td>Clinical improvement 100%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atelectasis</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otgun ('04)</td>
<td>2/54</td>
<td>Bronchiectasis</td>
<td>Lobectomy</td>
<td>Clinical improvement 85%</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonectomy</td>
<td>Segmentectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camargos ('08)</td>
<td>21/21</td>
<td>Atelectasis</td>
<td>Lobectomy</td>
<td>No significant improvement in FEV1 and nutritional status</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchiectasis</td>
<td>Bilobectomy</td>
<td>Improvement in quality of life and no. of exacerbations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Segmentectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and intensive physiotherapy, including a prolonged postural drainage program.

Additional criteria for surgery include an anatomic location of the disease to be resected that would not compromise the integrity of the adjacent healthy parenchyma and a preoperative FEV1 or FVC over 30% of predicted. Pneumonectomy has been reported as a feasible operation in some emergency situations with irreversible damage of one entire lung, or in some very selected patients in whom lesser resection would severely affect the adjacent parenchyma.

Further special considerations are needed when considering surgical resection for hemoptysis or lung abscess because the spectrum of clinical alternatives to surgery is broader.

3.1. Hemoptysis

Hemoptysis is a relatively common complication of CF occurring with an average annual incidence of 0.87% and overall in 4.1% of patients. Its incidence is, reportedly, higher in adults (up to four times with respect to children) with an increased 2-year mortality [41].

Primary treatment of this complication is conservative and consists of bed rest, topical cooling, and intravenous infusion, or local bronchoscopic application of tranexamic acid [42].

The second-line approach, in case of failure of conservative management, is generally represented by bronchial artery embolization (BAE). Controversial results have been reported with the use of this technique.

Resolution within 24 h of major or persistent hemoptysis has been obtained in 96.6% of patients by Vidal and colleagues [43] in a group of 30 adults with CF undergoing 42 embolization procedures, with no major complications. However, a considerable recurrence rate was registered with only 62% of patients free from hemoptysis 5 years after treatment. The number of collateral arteries was the only factor associated with risk of death and recurrent hemoptysis. Moreover, patients undergoing BAE showed higher risk of respiratory function deterioration, death and need for LT if compared with a control group of patients who did not receive embo- 

Another study [44] comparing the long-term results (mean follow-up of 54 months) of BAE with those of conservative treatment, reported a 46% recurrence and need for re-embolization rate in the BAE group, without significant differences between the two treatment options.

Although several studies report similar recurrence rates [45–47], better results have been obtained in some experiences.

An Italian group [48] has registered a 21% recurrence rate although the mean follow-up time was limited (15 months).

A study by Antonelli and colleagues [49] has compared the efficacy of early BAE and medical therapy with medical therapy alone in CF patients presenting non-massive hemoptysis. After 3 years, patients who underwent embo- 

lization had significantly fewer bleeding episodes and pulmonary exacerbations, and a better quality of life without experiencing adverse effects related to the procedure.

Surgery may have a role in a minimal number of patients experiencing massive hemoptysis from cavitary lung disease, which is usually the most difficult to control with BAE [45,50,51]. Accurate preoperative localization of the bleeding site is crucial before surgery. Angiography, CT scan with contrast medium, and bronchoscopy are the most useful tools in this regard.

When the lobe to be resected is extensively destroyed, its removal may be further justified and it is not likely to affect the patients’ lung function. However, in other cases showing persisting bronchial hemorrhage with an intact lung parenchyma, an alternative surgical approach has been proposed by some authors [27]: it consists of surgical interruption of all the systemic vessels that supply the bleeding lobe. This technique that is likely to be more tedious and demanding, appears reasonable, particularly in patients with minimal pulmonary reserve, although its systematic use has not been reported in any published experience. In order to avoid parenchymal resection and minimize pleural adhesions for further surgery, an extrapleural bronchial artery ligation has been proposed. In a small series of four patients with persistent or recurrent massive hemoptysis after BAE, immediate success was achieved in all cases with this technique [52]. However, death occurred due to severe chest infection in one patient who was asphyxiated with hemoptysis, requiring ventilation preoperatively. Recurrent bleeding from contralateral bronchial arteries occurred in two patients, 12 and 36 months after surgery, respectively.

Considering the data in the literature, many of the surgical experiences in patients with CF include cases of lobectomy for the treatment of severe recurrent or persisting hemoptysis confirming that major pulmonary resection must be considered as an effective final therapeutic option in this setting. These procedures can be performed with low morbidity in patients with relatively healthy adjacent lung parenchyma.

3.2. Lung abscess

Systemic antibiotic therapy proves effective in resolving most of the infectious complications occurring in CF patients, but may not be sufficient in case of abscess formation due to the difficulties of the antimicrobial agents to reach these partially destroyed, not vascularized, areas of the lung. Thoracotomic surgical treatment in these patients may represent the final therapeutic option in severe persistently refractory cases.

Less invasive approaches have been proposed in non-CF patients, and the encouraging results may lead to their employment in patients with CF too.

Herth and colleagues [53] have recently reported the successful treatment of 38 patients with lung abscess using drains placed broncoscopically. After a mean time of about 1 month of antibiotic therapy, the endoscopic drainage were placed achieving resolution of the abscess in a mean time of 6.2 days.

In another study [54], five out of six patients with pulmonary abscess refractory to medical therapy were effectively treated by fluoroscopically placed percutaneous drains.

These less traumatic approaches may provide a viable alternative to surgery, especially among the high rate of CF
patients presenting increased surgical risk. For patients with acceptable operative risk, lung resection has been performed in several cases included in main published series and have proved safe and effective, suggesting that these should be considered adequate procedures in appropriately selected groups.

4. Lung transplantation

Cystic fibrosis is the most common indication for LT in children and for bilateral LT in adults [55,56]. Overall, it is the third most common indication for which LT is performed.

The first heart transplantation and LT for CF were performed in 1983 but the recipient survived only for 6 months. Subsequently, in 1985, two other CF patients were transplanted in the United Kingdom and they were alive and well 3 years later [57].

Actually, the combined heart transplantation and LT undertaken in the early era of this surgical treatment for CF is rarely performed now [55,56] and the popular approach is the bilateral sequential LT [58]. This technique allows to save the recipient heart, the replacement of which is unnecessary in almost all cases, and may be accomplished without the use of cardiopulmonary bypass. The operation is most frequently performed through a bilateral thoracotomy without sternal splitting, therefore improving postoperative functional recovery and preventing postoperative sternal complications [59–61].

LT is indicated for patients with end-stage lung disease secondary to CF, whose lung function and quality of life are declining despite maximal medical therapy. In particular, referral criteria include [62]:

- Progressive respiratory impairment manifested by an FEV1 <30% of the predicted, severe hypoxemia and hypercapnia.
- Increasing frequency and duration of hospital treatments for pulmonary exacerbations.
- Major life-threatening pulmonary complications, such as recurrent massive hemoptysis.
- Increasing antibiotic resistance of bacteria infecting the lung.

According to the International Society of Heart and Lung Transplantation Registry data reporting overall 1-year, 5-year, and 10-year survival rates of 78%, 51%, and 28%, respectively, for all types of recipients, the CF patients show a year, and 10-year survival rates of 78%, 51%, and 28%.

Transplantation Registry data reporting overall 1-year, 5-years, and 10-years survival rates of 80.6% at 1 year, 53.8% at 5 years, and 32.1% at 10 years [63]. Further improvement was observed in the recent years since 2000 (5-year survival 72.7 ± 7.3%).

Another study analyzing the data from the US Cystic Fibrosis Foundation Patient Registry [72] has achieved a different conclusion. This study included 514 children in the waiting list, 248 of whom underwent LT. The interaction of LT with other clinically relevant covariates was analyzed in order to estimate the effect of transplantation on survival. As a result, the authors found that only one patient over 248 who underwent LT derived a significant estimated survival benefit.

This article has been criticized by many clinicians [65] for its methodology. Moreover, many authors have underlined that excellent results with 10-year survival rates reaching 60% taking into account the pediatric population in the most experienced centers are clearly in contrast with the conclusions in this study.

Complications of LT in CF patients are generally similar to those observed in other recipients with different diagnosis. Primary graft dysfunction occurs in the early postoperative period in about 10% of patients presenting with diffuse parenchymal infiltrates and compromised oxygenation, and is associated with a poor early and late outcome [73].

Acute rejection occurs principally within the first 6 months following transplantation and has been reported with an incidence of up to 70% [74]. Chronic rejection is more common after the first year reaching a 65% incidence among 5-year survivors in some series [73]. It is characterized by obliterative bronchiolitis that leads to decreased pulmonary function.
CF patients are at increased risk for infectious complications that, in many cases, may be caused by the pretransplant colonizing microorganisms. Aspergillus and other saprophytic fungi may be responsible for parenchymal and anastomotic infections \[73,75\], while viral infections, especially with cytomegalovirus, may also present with systemic symptoms. Renal failure is a well-known problem after LT and is common to all transplantation procedures.

Other complications occurring with increased frequency include malignancies and gastroesophageal reflux (GER). Lymphoma is the most common malignancy occurring in CF patients with an incidence of 5%, that increases up to 20% in Epstein–Barr virus (EBV) seronegative patients who receive EBV-positive organs \[63,76,77\] CF recipients, because of their younger age, are more frequently EBV-seronegative and have therefore a higher risk for this complication.

GER may develop or worsen after LT and its presence can be associated with allograft dysfunction and chronic rejection. The pathophysiology of GER in CF patients is thought to be related to multiple factors including postural drainage and transient lower esophageal sphincter relaxation \[78\].

Results from principal experiences of LT for CF report the achievement of normal pulmonary function after transplantation in most patients. The improvement generally continues during the first year, but respiratory function declines as chronic rejection starts. CF patients also show a significant improvement in exercise tolerance, New York Heart Association (NYHA) class, and 6-min walking distances shortly after transplantation. However, maximum exercise capacity tends to be reduced, likely due to skeletal muscle dysfunction \[79\].

Although limited information is present in the literature assessing the quality of life in these patients, recent reports have shown significant improvement early after transplantation with some deterioration after the development of chronic rejection \[80\]. In a review of the United Network for Organ Sharing (UNOS) data on 1637 LT recipients with CF, older age was associated with decreased early postoperative infections, hospitalization, and treatment for rejection. There were no age-related differences with respect to 30-day and 1-year survival \[81\].

LT in patients previously undergoing pulmonary resection, although rare, may be a technical challenge principally due to the anatomical changes including chest wall asymmetry and mediastinal shift. Previous pneumonectomy represents a significant risk factor for posttransplantation morbidity and mortality. In particular, mediastinal shift has been reported to be responsible for some lethal bronchovascular complications occurring perioperatively \[82\]. Moreover, the bigger volume of the recipient’s pleural cavity after contralateral pneumonectomy must be considered and a careful evaluation of the donor’s organ size \[82\] done. Similarly, previous lobectomy, except when performed in early infancy, induces an asymmetric thorax which the transplant surgeon has to deal with. Lobar transplantation or completion pneumonectomy of the residual previously operated lung may be a viable strategy. The possibility of synchronous LT and contralateral pneumonectomy has been reported for the treatment of end-stage respiratory insufficiency secondary to bronchiectasis and extensive destruction and retraction of one lung determining a markedly asymmetric chest \[83\]. In other CF patients with asymmetric thorax due to previous lobectomy, bilateral transplantation and lung volume reduction with lobectomy have been performed with good results \[84\].

Re-transplantation still remains a controversial procedure with different guidelines across the centers. However, recently published data from the United States \[85,86\] have proved that outcomes may be similar to those of unilateral transplant if adjusted for potentially influencing variables. In the extensive experience of Egan and colleagues \[70\], five CF patients have been re-transplanted due to BOS, with one operative death and 1-year survival of 60%. Renal disease and poor functional status are the most significant risk factors predicting an unfavorable outcome.

The shortage of donor organs has led to a significant number of deaths on the waiting list for lung transplantation. Alternative approaches have been therefore undertaken in order to circumvent this problem.

Living donor lung transplantation (LDLT) is a procedure in which two lobes (usually the lower lobes) are taken from healthy donors and transplanted in a small, usually pediatric, recipient. As of today, this operation has been performed successfully in hundreds of patients worldwide \[87–93\]. According to the International Society for Heart and Lung Transplantation Registry data, the survival appears to be similar to that obtained with cadaveric donors. In particular, data from the 2004 US Organ Procurement and Transplantation Network (OPTN) reported similar 1-year and 3-year survival, while 5-year survival for LDLT recipients was better in the pediatric population (especially within 11 years) and worse in the adult population with respect to cadaveric donor LT recipients \[92\]. In the series from the University of North Carolina, lobar transplant was associated with a poorer survival (37.5% at 1 and 5 years) with respect to bilateral lung transplantation from cadaveric donors (survival: 81% at 1 year and 59% at 5 years) \[70\].

Somatic growth and the growth of the transplanted lung are an important issue in LDLT. It has been proven that FEV1 and FVC can increase in relation with posttransplantation growth in infants \[94\] and older children \[95\], but this phenomenon can affect only the increased volume of each alveolar unit rather than alveolar growth or increased surface area for gas exchange. In a single-center study of pediatric recipients \[96\] no significant improvement in Diffusion Lung Capacity for Carbon Monoxide (DLCO) was seen in the first year following transplantation, suggesting lack of alveolar growth. No donor’s death has been reported, but there have been serious complications \[93\]. Careful patient selection has to be done, based on physiological and social factors, as this is an operation that puts three patients at risk.

Overall, it is clear that a multidisciplinary approach is essential when dealing with CF patients. They are cured at birth by CF experts who are not pediatricians only. Prenatal diagnosis has led to a better prognosis of the complications typical of this disease and CF patients can now reach adulthood in excellent clinical conditions. However, this does not mean that CF patients do not present major problems. For this reason, a strict cooperation with an experienced thoracic surgery team is mandatory.
Acknowledgment

We wish to thank Elisabetta Grigioni for data management and editorial revision.

References


Hadjiliadis D. Special considerations for patients with cystic fibrosis.


