

Pneumothorax in cystic fibrosis

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Abstract: Pneumothorax is recognized as a common and life-threatening complication in cystic fibrosis (CF) patients, especially in those who are infected with *P. aeruginosa*, *B. cepacia* or *Aspergillus*, need enteral feeding, are diagnosed as suffering from allergic bronchopulmonary aspergillosis (ABPA), developed massive hemoptysis, and their respiratory function is seriously compromised. Structural impairment and altered airflow dynamics in the lungs of CF patients are considered as the main predisposing factors, but also inhaled medications and non-invasive positive pressure ventilation (NIPPV) could increase the risk of pneumothorax. Clinical presentation could range from dramatic to very mild. Management of spontaneous pneumothorax occurring to patients with CF is essentially similar to that for non-CF patients. Therapeutic options include intercostal tube drainage, video-assisted thoracoscopic surgery (VATS), and medical or surgical pleurodesis. Pneumothorax increases both short- and long-term morbidity and mortality in CF patients and causes significant deterioration of their quality of life.

Keywords: Cystic fibrosis (CF); pneumothorax; antibiotics, macrolides

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Introduction

Cystic fibrosis (CF) is an autosomal genetic disease affecting a variety of organs, but especially involving respiratory tract and pancreas. The lungs undergo gradual destruction, as an effect of persistent microbial colonization, chronic inflammation and recurrent infections caused by highly pathogenic bacteria, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Several constituents of the innate immunity are also affected by the disease (1). As a consequence, despite the amazing progress in treating CF-related lung disease, it still accounts for nearly 85% of the mortality (2).

The spectrum of the clinical manifestations of the

disease is explained by the presence of mutations of the gene for cystic fibrosis transmembrane conductance regulator (CFTR), inherited from each parent (3). CFTR regulates a c-AMP anion channel on the apical surfaces of epithelial cells, and reduced or abolished activity of this protein results to defected transport of chloride, HCO₃ and sodium ions across membranes, and the accumulation of thick mucus (4). The airways of the affected lungs are clogged by purulent secretions and deformed due to the development of bronchiectatic lesions, while in the parenchyma the formation of multiple cavitations or cysts, areas of bronchiolar consolidation, fibrosis and air-trapping compromise respiratory adequacy (5).

Epidemiology

Pneumothorax is a known serious complication in CF patients (6). In a retrospective observational cohort study, Flume *et al.* reviewed the data of 28,858 patients with CF who had been followed up over 10 years at CF centers across the United States. Pneumothorax occurred with an average annual incidence of 0.64% and 3.4% of the patients overall. The same study was able to recognize a number of risk factors associated with an increased occurrence of pneumothorax, including the presence of *P. aeruginosa*, *Burkholderia cepacia* or *Aspergillus* in sputum cultures, FEV₁ <30% of predicted, enteral feeding, pancreatic insufficiency, allergic bronchopulmonary aspergillosis (ABPA) and massive hemoptysis. There was no increased occurrence by sex, but pneumothorax was more prevalent in older patients (median age 21 years) with more severe pulmonary impairment and was not only a cause of increased morbidity, but was responsible for increased 2-year mortality (7). Actually much older studies have concluded that the incidence of pneumothorax in CF patients has increased as improved treatment has resulted in prolonged survival (8-10). A review covering 26 years of experience from a single center reported 99 patients with at least one episode of pneumothorax out of 1,268 patients with CF who were followed between 1959 and 1987 (11). Another, though smaller retrospective study reported 17 episodes of pneumothorax in 11 patients from a cohort of approximately 500 children with CF living in the area of Victoria, Australia, over a 15-year period. The authors found only a slight higher than the predicted decline in lung function (6% *vs.* 4%) over the 2-year period around pneumothorax. Nevertheless, they suggested that increased rate was more likely attributed to *P. aeruginosa* and *B. cepacia* colonization than to pneumothorax per se (12).

It is evident that the estimation of the incidence of pneumothorax in CF patients varies, depending not only on the age of the patients (e.g., children *vs.* adults) and the severity of the lung impairment in the included cohort of patients, but also on the efficacy of the overall management of the respiratory component of the disease, a fact that is reflected on the year of publication (old *vs.* recent).

Etiology

Both structural impairment and altered airflow dynamics in the lungs could be considered as predisposing factors for the occurrence of spontaneous pneumothorax in CF

patients. Rupture of subpleural blebs and bullae in the visceral pleura apparently represent a common underlying mechanism. Nevertheless, there is a poor correlation between the presence of blebs or cysts and pneumothorax in CF patients (13). In addition, endobronchial obstruction and inflammation due to accumulation of viscous secretions and inflammatory cells, especially macrophages, cause air-trapping and induce overpressure in the alveolar tissue, resulting in rupture of pulmonary parenchyma (14). It is reported that shear forces generated during abrupt acceleration/deceleration of a CF patient, increased mechanical stress on the pleura, causing bilateral pneumothorax (15).

Although a substantial percentage (8-21%) of CF patients are smokers and smoking is a well-known factor related to spontaneous pneumothorax, there is a lapse of reported cases of such etiology (16-19). It has been shown that inhaled medications (e.g., dornase- α , tobramycin) could increase the risk of pneumothorax, probably due to the acute decrease in FEV1 following inhalation (20). Also, transplant listed CF patients requiring non-invasive positive pressure ventilation (NIPPV), are in increased risk for pneumothorax. In such challenging clinical situation, pneumothorax may cause significant deterioration of the respiratory status necessitating the withdrawal of NIPPV (21).

ABPA is prevalent (7.8%) in cystic fibrosis and is clearly related to respiratory complications, including pneumothorax (22).

Thoracic endometriosis is a rare condition characterized by catamenial hemoptysis and pneumothorax. This condition is observed, albeit extremely rarely, in CF patients, for which could present a life threatening event (23).

Clinical presentation

In one pioneering publication including 49 patients who have attended the Brompton Hospital between 1964 and 1969 it was spotted that spontaneous pneumothorax could be either a terminal event or an incidental finding which required no specific treatment (24). The majority of the patients experience pain, and shortness of breath, while some of them die acutely (7). Development of acute respiratory failure requiring ventilatory support is possible. Sood *et al.* reported that 3 (2%) out of 136 admissions of CF patients in the ICU during a 9-year period were due to pneumothorax. One patient required intubation and all three improved and were discharged after an average ICU stay of 1.6 days (25). However, a more recent retrospective

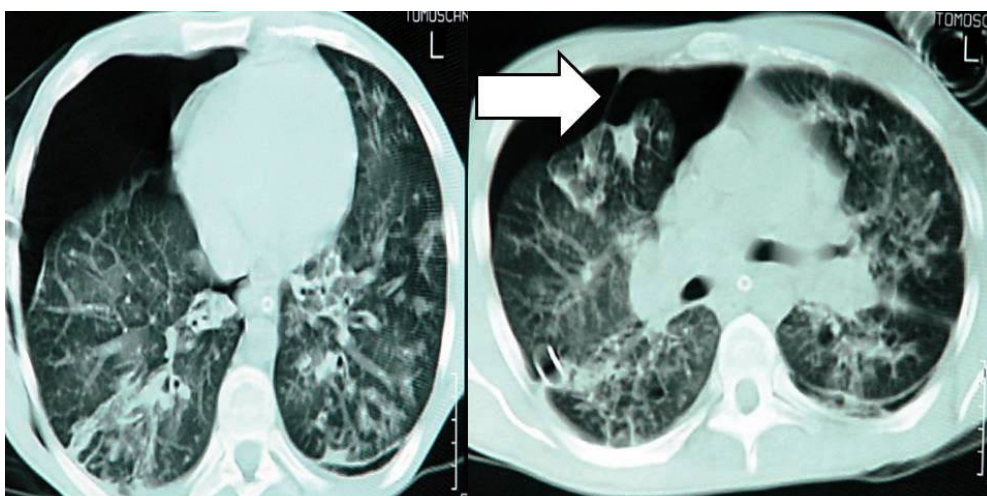


Figure 1 Pneumothorax in CF patient: pleural adhesions prevent further collapse of the lung (arrow). Personal data. CF, cystic fibrosis.

analysis from a single center provided data showing that only 59% of 22 patients intubated for pneumothorax and/or hemoptysis survived to hospital discharge (26).

Diagnosis

When clinically suspected, pneumothorax should be diagnosed by the proper imaging technique. Performing a chest radiograph is the simplest method to diagnose pneumothorax (27). Diagnosis may be difficult in CF patients when relying on plain radiography alone, due to the presence of cysts and bullae. CT scanning of the chest facilitates not only diagnosis but also the selection of appropriate management (28,29) (*Figure 1*).

The use of MRI in the clinical management of complications of advanced CF, such as pneumothorax, is of limited value (30).

Management

The aim of treatment in CF patients is the safe and effective resolution of pneumothorax with prevention of recurrence (31). Historically, a variety of therapeutic interventions were employed, including sclerosant agents (quinacrine, silver nitrate, iodine, talc, etc.), pleural abrasion, intercostal drainage, pleurectomy and Heimlich flutter valve (32-37). Most of these methods were quite successful, but there were significant differences in the recurrence rates. Quinacrine sclerosis and, particularly, parietal pleurectomy appeared to be among the most

effective methods of management (38,39). Pleural suction drainage was reported to have the lowest long-term success rate (33).

However, according to the British Thoracic Society (BTS) guidelines for the management of spontaneous pneumothorax [2003], the treatment of pneumothorax for patients with CF is similar to that for non-CF patients, giving emphasis to early and aggressive treatment and suggesting that surgical intervention should be considered after the first episode, provided that the patient is fit for the procedure (40). BTS guidelines state that a small pneumothorax without symptoms can be observed or aspirated, while large pneumothoraces require treatment with intercostal tube drainage. It is stressed that the air-leak is usually from the upper lobes making important the siting of the tube in the correct place (*Figure 2*). The authors consider that patients with recurrent pneumothoraces should undergo partial pleurectomy, which has a success rate of 95%. On the contrary, patients that are too ill for surgical intervention, intubation and suction present the best option, having in mind that it can take 2-3 weeks for the lung to re-expand. The 2003 guidelines accepted the conclusions of Noyes and Orenstein [1992] that administration of sclerosant agents present, at least partial, contraindication for subsequent lung transplantation, as they make lung removal more difficult, prolong the ischemic time for the donor lungs and can cause excessive bleeding (41). Notably, others suggested the avoidance of therapeutic pleurectomy due to the same reasons (42). Although BTS guidelines were updated in 2010 (43) without major differences from the



Figure 2 Apical pneumothorax in cystic fibrosis (CF) patient: intercostal tube drainage. Personal data.

previous edition, they highlighted that pleural procedures (including pleurodesis), do not have a significant adverse effect on the outcome of subsequent lung transplantation, adopting thus, the relevant conclusions of a more recent comparative study (44). Despite that optimism, a more conservative approach suggests that each patient should be considered individually when evaluating the impact of the previous pleural procedure on the candidacy for lung transplantation (45). Especially pleurectomy is considered by thoracic surgeons as a major obstacle to future operative procedures, including transplantation (46).

These treatment suggestions were somewhat challenged by certain experts arguing the superiority of video-assisted thoracoscopic surgery (VATS) (47). Their major arguments are focused on better safety, shorter postoperative period and less pain medication required, despite the marginally higher recurrence rates observed with VATS. These arguments are also supported by previous studies including small series of CF patients, reporting excellent results with VATS, without complications or subsequent recurrences of the pneumothorax (48,49).

Concurrently to BTS 2010 guidelines, an ad hoc American committee published clinical practice guidelines for cystic fibrosis pulmonary therapies. According to their statement, all CF patients with a large pneumothorax should be admitted to the hospital and have a chest tube placed. In case of recurrent large pneumothorax the patient should undergo,

preferably surgical, pleurodesis. As for the pneumothorax cases being under ventilatory support with BiPAP, the panel felt that discontinuation of non-invasive ventilation is the preferred option. Finally, the panel suggested that CF patients with pneumothorax should neither fly on a plane, nor perform spirometry or lift weights for 2 weeks after the pneumothorax has resolved (50).

Autologous “blood patching” pleurodesis has been used successfully for the treatment of persistent air-leak in patients with spontaneous pneumothorax but there is very limited experience with cystic fibrosis patients. A case report of a young CF patient underlines the possibility for development of tension pneumothorax during the procedure, secondary to blood clot (51). Also, biological glue has been tried successfully (52).

The debate of chemical versus surgical pleurodesis (53) was reviewed by the Cochrane Collaboration which confirmed the lack of randomized controlled studies in this population (54).

Lung transplantation is considered as the ultimate solution to the problem of refractory and/or recurrent pneumothorax (55).

Continuation or withholding of physiotherapy during or immediately after the management of pneumothorax is an issue. According to the above mentioned American guidelines, some airway clearance techniques such as positive expiratory pressure and intrapulmonary percussive ventilation should not be used. Alternative airway clearance therapies include high-frequency chest compression, active cycle breathing and autogenic drainage (56). Nevertheless, once the therapeutic intervention has been undertaken, physiotherapy should focus on maintaining effective sputum clearance to prevent atelectasis and lobar collapse due to obstructive secretions. In addition, inspired oxygen should be adequately humidified and effective analgesia should be administered to relieve aggravation of pain caused by the chest tube during airway clearance techniques, leading to sputum retention (57,58).

Prognosis

Pneumothorax is a cause of significant short- and long-term morbidity and mortality in CF patients. It is reported that 50-90% of the patients will suffer a recurrence (defined as a pneumothorax that develops on the ipsilateral side more than 7 days after the resolution of the first event) and 46% will experience a subsequent contralateral pneumothorax (7,35). According to Flume *et al.* attributable mortality is estimated at 6.3-14.3%, while the 2-year mortality rate in

patients following a pneumothorax is 48.6% (59). An analysis of data from the European Epidemiologic Registry of Cystic Fibrosis (ERCF) including more than 7,000 patients, was able to demonstrate that pneumothorax was among the factors associated with poor pulmonary function, as reflected by $FEV_1 > 10\%$ of predicted values (60). It should be noted that as it was previously showed, FEV_1 is the strongest predictor of survival and one of the major indicators for lung transplantation (61,62). Moreover, ERCF data covering the decade 1990-1999 estimate the mortality of CF patients experiencing pneumothorax at 48.6%, compared to 12.2% of patients without pneumothorax (54). As reported by Spector and Stern (11), the median survival after the first pneumothorax is 29.9 months and a more recent study confirmed that patients who had suffered a pneumothorax prior to referral to the adult clinic were less likely to become long-term survivors (i.e., aged > 40 years) (63). An Australian study focused on CF patients requiring surgical intervention, reported 50% mortality in children with pneumothorax (64). Finally, according to a study in German CF patients, recent pneumothorax precipitates symptoms of anxiety (65-79), deteriorating their quality of life (80-93).

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