

Pulmonary Complications of Cystic Fibrosis

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Summary

Earlier diagnosis, treatment of exacerbations, and the use of long-term therapies have all improved the lifespan of patients with cystic fibrosis (CF). However, the natural history of CF airways disease remains one of worsening bronchiectasis and obstructive airways impairment. The progression of airways disease leads to eventual respiratory failure, but some will suffer other acute respiratory complications that require intervention, including pneumothorax, massive hemoptysis, and respiratory failure. Here I discuss the pathophysiology of these complications and the patient-related and treatment-related factors associated with their occurrence. Knowledge of these associations may play great importance in treatment decisions regarding the care of the patient and the respiratory therapist should be aware of the implications. Since disease severity is associated with all 3 conditions, aggressive treatment of the underlying condition is imperative, which includes the performance of airway-clearance therapies. Though some might argue that airway-clearance therapies might aggravate or even precipitate complications such as hemoptysis and pneumothorax, others will defend that there are airway-clearance therapies that might be safely performed. Aerosolized medications such as dornase alfa and tobramycin have been associated with a lower incidence of massive hemoptysis and are recommended therapies for patients with advanced airways disease, yet they are also associated with a higher incidence of pneumothorax, which suggests careful assessment of their potential bronchospastic effect in patients with advanced airways disease. The respiratory therapist also plays a key role in the care of the patient with respiratory failure. Here is also discussed the role of ventilatory support and airway-clearance therapies in the patient with advanced stage disease. Now, more than ever, the patient needs caregivers with the knowledge and sensitivity to provide appropriate palliative care. *Key words: cystic fibrosis, respiratory complications, pneumothorax, hemoptysis, respiratory failure.* [Respir Care 2009;54(5):618–625. © 2009 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) is a genetic disease with clinical manifestations including sinusitis, chronic lower airways infection, and pancreatic insufficiency, among others (Table 1). Some problems occur in patients at an early age (eg, chronic airways infection, pancreatic insufficiency), whereas others more commonly occur in older patients (eg, CF-related diabetes). Lung disease is one of the most challenging problems and accounts for more than 90% of deaths in CF patients.¹ The natural history of the lung disease consists of early and persistent infection,² an exaggerated inflammatory response,^{3,4} structural airway changes (ie, bronchiectasis), and progressive airways obstruction, ultimately resulting in respiratory failure. There may be intermittent pulmonary exacerbations, or acute worsening of infection and obstruction, which require more intensive therapies. As airways disease worsens, there is an increased likelihood of respiratory complications that may be serious, including pneumothorax, hemoptysis, and respiratory failure. Respiratory therapists (RTs) should have knowledge of these complications, as they will play a key role in the care of these patients.

Pneumothorax

Pneumothorax is defined as the presence of air within the pleural space. It is a well-known complication of CF, first reported in 1966.⁵ Our knowledge of spontaneous pneumothorax in patients with CF is similar to that of patients with spontaneous pneumothorax in other lung diseases.

Epidemiology

Spontaneous pneumothorax in CF has an average annual incidence of 0.64%, or 1 in 167 patients per year.⁶ Approximately 3.4% of all patients will suffer this complication during their lifetimes. In a recent analysis, the median age for pneumothorax was 21 years, and 72.4% occurred in patients greater than 18 years of age.⁶ The

Table 1. Complications of Cystic Fibrosis

Respiratory
Sinusitis
Chronic pulmonary infection
Airway obstruction
Bronchiectasis
Hemoptysis
Pneumothorax
Respiratory failure
Pancreatic
Pancreatic insufficiency (exocrine)
Chronic pancreatitis
Hepatobiliary
Focal biliary cirrhosis
Steatosis
Cholelithiasis
Gastrointestinal
Meconium ileus
Distal intestinal obstruction syndrome
Malabsorption
Gastroesophageal reflux
Rectal prolapse
Renal
Nephrolithiasis
Endocrine
Diabetes mellitus
Osteoporosis
Delayed sexual development
Hypogonadism
Genitourinary
Obstructive azoospermia (males)

principal risk factor for pneumothorax is severe obstructive airways impairment, and 75% of pneumothoraces occur in patients with a forced expiratory volume in the first second (FEV₁) less than 40% of predicted.⁶ Other factors associated with pneumothorax are listed in Table 2. These are derived from analysis of the CF Patient Registry and do not necessarily imply a cause and effect. Some are clearly an association and cannot be assumed to be part of the pathophysiology (eg, Medicaid insurance). Those that may be part of the pathophysiology are addressed later.

Many patients (estimated 50–90%) may suffer a recurrence,⁷ defined as a pneumothorax that develops on the ipsilateral side more than 7 days after the resolution of the initial pneumothorax, and there is a high rate (46%) of subsequent contralateral pneumothorax.⁸ There is high morbidity, with pain, shortness of breath, and an adverse effect on overall lung function, but it is also associated with high health-care costs, with increased visits, hospitalizations, and hospital days.⁶ Some patients will die acutely as a result of pneumothorax, with an attributable mortality estimated at 6.3–14.3%, and it also may be a prognostic factor, as the 2-year mortality rate in patients following a pneumothorax is high (48.6%).⁶

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Table 2. Clinical Factors Associated With Pneumothorax

<i>Pseudomonas aeruginosa</i>
<i>Burkholderia cepacia</i>
Aspergillus
FEV ₁ < 30% predicted
Gastrostomy tube feeding
Pancreatic insufficiency
Medicaid insurance
Allergic bronchopulmonary aspergillosis
Massive hemoptysis
Dornase alfa
Inhaled tobramycin

FEV₁ = forced expiratory volume in the first second
(Adapted from Reference 6.)

Pathophysiology

The pathophysiology of pneumothorax in CF patients is thought to be similar to that of other diseases with spontaneous pneumothorax. Patients typically have severe obstructive airways disease, so plugging of the distal airways with thick secretions may result in trapping of air within the alveoli. When the alveolar pressure exceeds interstitial pressure, air moves into the interstitium, with passage into the hilum (pneumomediastinum), followed by rupture of the mediastinal parietal pleura, causing pneumothorax. Less commonly there may be rupture of subpleural blebs on the visceral pleura, but there is a poor correlation between the presence of blebs or cysts and pneumothorax in the CF population.⁹

Lung function (eg, FEV₁) declines with age as a result of the chronic airways infection and inflammation. High-resolution computed tomography of the chest has demonstrated air-trapping at end-expiration in non-CF patients with spontaneous pneumothorax, consistent with the notion that air trapping is part of the pathogenesis of this complication.¹⁰ Air-trapping has also been reported in CF patients with pneumothorax, as demonstrated by an increase in residual volume.^{11,12}

There are other factors known to be associated with spontaneous pneumothorax, such as smoking tobacco.^{13,14} The estimated prevalence of smoking in CF patients is 8–21%,^{15,16} but there are no reported cases of pneumothorax in a CF patient who is also a smoker.

Other factors identified to be associated with pneumothorax in CF are shown in Table 2. They include the presence of the airway pathogens *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and aspergillus.⁶ *P. aeruginosa* and *B. cepacia* are well-known to be associated with progressive decline in lung function, and the association with pneumothorax may be related to the more severe disease, with increased inflammation and airway secre-

tions obstructing the distal airways. However, aspergillus is typically considered a colonizer of the CF airways and not necessarily a pathogen.¹⁷ There is a greater prevalence of allergic bronchopulmonary aspergillosis (ABPA) in patients with CF.¹⁸ ABPA is an asthma-like complication that may result in increased air-trapping as a possible reason for its association with pneumothorax. The presence of aspergillus in sputum cultures alone is not sufficient to make the diagnosis of ABPA, and far more CF patients have aspergillus in the sputum than have ABPA. Therefore, there may be other factors associated with aspergillus that suggest it is a true pathogen and not merely a colonizer.¹⁹

There is an association between inhaled medications (eg, dornase alfa, tobramycin) and pneumothorax. The risk of the inhaled agents may be related to the finding that some patients experience an acute decrease in FEV₁ following inhalation of medications.²⁰

Diagnosis

Patients will present with acute onset of chest pain and breathlessness, and the diagnosis is confirmed via chest radiograph. In unusual cases there may be pleural adhesions that prevent collapse of the lung away from the chest wall, such that the pneumothorax will not be apparent on chest radiograph and computed chest tomography may be needed to make the diagnosis (Fig. 1).

Management

Patients who have small pneumothoraces may be managed with either observation or small catheter aspiration, but this approach is often met with failure in the patient with CF.^{21,22} Placement of a chest tube for evacuation of the pleural space is the recommended initial treatment. There is a high rate (estimated 37%) of treatment failure with chest tube drainage alone.⁷ Given the high rate of recurrence, it is estimated that 70% of patients may ultimately require more definitive treatment (ie, pleurodesis).⁷ Surgical pleurodesis appears to be the most effective, but if the patient is unable to tolerate surgery, chemical pleurodesis (eg, talc) should be performed. Although contralateral pneumothorax is common, prophylactic pleurodesis on the opposite side is not considered standard therapy. For those patients who may be referred for lung transplantation, previous pleurodesis is not an absolute contraindication to lung transplantation.²³

The knowledge of factors associated with pneumothorax should influence therapies. Since there is an association with ABPA, all patients should be evaluated for this diagnosis, as this may lead to treatment with steroids or other therapies.²⁴ Inhaled or systemic corticosteroids are not recommended as a routine therapy for CF patients, but

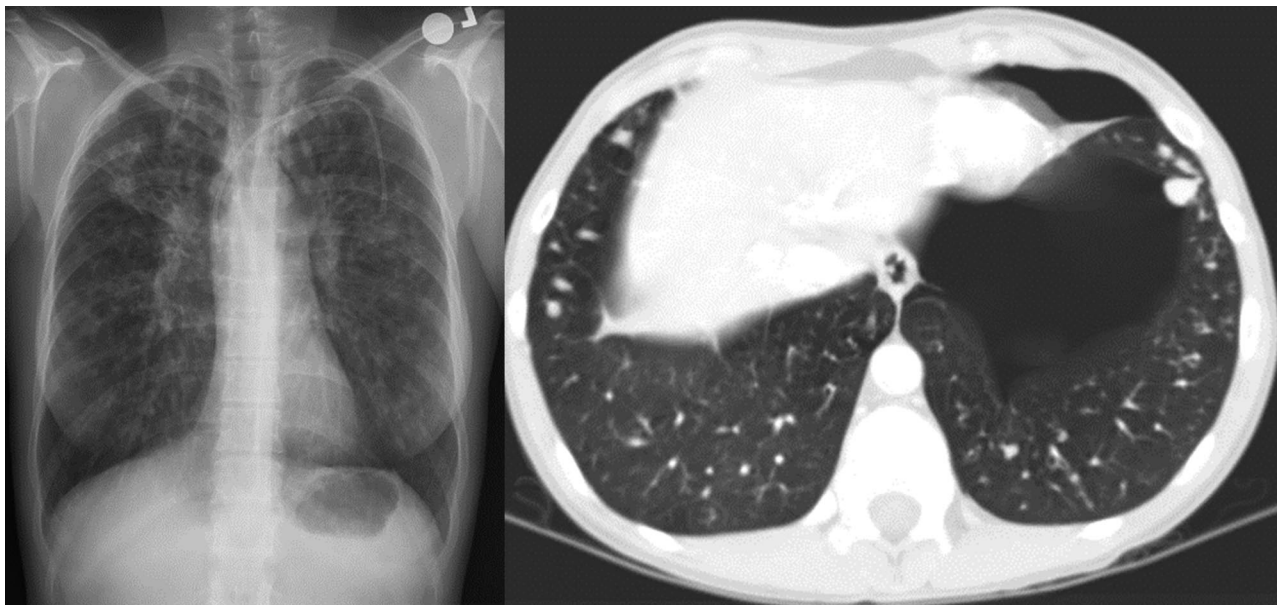


Fig. 1. Chest radiograph (left) of a patient with cystic fibrosis and acute left-side chest pain demonstrates chronic changes of cystic fibrosis, but there is no visible pneumothorax. A lateral radiograph also did not reveal a pneumothorax. Computed tomogram (right) shows a loculated pneumothorax in the left chest. Pain was resolved with placement of a chest tube.

this recommendation excludes those patients with concomitant ABPA.²⁵ It may also be prudent to evaluate the acute effects of inhaled medications on airway reactivity in patients with more severe lung impairment (eg, FEV₁ < 50% of predicted).

The RT will play a key role in the care of patients at risk for or who have a pneumothorax. The RT should be aware of the potential risk of aerosolized medications in patients with advanced-stage disease and recommend spirometry following inhalation, to assess for bronchospasm. Airway clearance is challenging in the patient with a pneumothorax, for a variety of reasons. First, there may be fears that some therapies that provide positive pressure to the airways could cause or exacerbate a pneumothorax. Although this is exceedingly uncommon, it may be prudent to recommend alternative airway clearance therapies such as high-frequency chest compression, active cycle breathing, or autogenic drainage, rather than positive expiratory pressure or intrapulmonary percussive ventilation. Second, the patient who has a chest tube may experience pain and will want to resist taking a deep inspiration, which may disallow performance of airway clearance, but both of these may worsen their underlying disease and health status. The RT should work with the patient to find a comfortable yet effective method of clearing secretions.

Massive Hemoptysis

Patients with CF commonly cough up blood; in a retrospective review over 5 years, 9.1% of patients had he-

moptysis.²⁶ For most of those patients the bleeding was infrequent, but 20% had hemoptysis more than once per month. The bleeding is most commonly scant to moderate, but massive, life-threatening bleeding can occur. Massive hemoptysis is defined as acute bleeding greater than 240 mL in a 24-hour period or recurrent bleeding greater than 100 mL/d over several days.⁶

Epidemiology

The average annual incidence of massive hemoptysis is 0.87%, or 1 in 115 patients per year, and approximately 4.1% of all patients with CF will suffer this complication during their lifetime.²⁷ As in the case of pneumothorax, massive hemoptysis occurs more commonly in older patients with more advanced disease; however, 22% of patients will have either normal lung function or only mild obstructive airways impairment. The median age for massive hemoptysis is 23 years, and 75% of cases occur in patients > 18 years of age.²⁷ The major factors that have been associated with massive hemoptysis in the CF population include *Staphylococcus aureus*, pancreatic insufficiency, and diabetes.²⁷

Like pneumothorax, massive hemoptysis is associated with high health-care costs, with increased visits, hospitalizations, and hospital days, and there is also an adverse effect on overall lung function.²⁷ Mortality attributable to massive hemoptysis has been estimated at 5.8–16.1%,²⁷ and such patients may warrant earlier consideration for lung transplantation.

Pathogenesis

Massive hemoptysis occurs when there is rupture of a bronchial artery, with passage of blood into the airways. Chronic inflammation in the airways stimulates bronchial artery hypertrophy and angiogenesis.²⁸ In a mouse model, changes of angiogenesis and microvascular remodeling appear soon after initial infection and appear to be genetically controlled.²⁹ Vascular endothelial growth factor is known to promote angiogenesis and is elevated in the serum during a CF pulmonary exacerbation.³⁰

S. aureus is the one bacterium that has been identified to be associated with an increased likelihood of massive hemoptysis. Bacterial products may lead to alterations in the pulmonary epithelium and vascular endothelium and stimulate bronchial artery proliferation,^{27,28,31} resulting in a system of enlarged, dilated, and tortuous vessels with collaterals and bronchopulmonary anastomoses.²⁸ Although *Aspergillus fumigatus* has been associated with massive hemoptysis in non-CF patients (eg, mycetomas),³²⁻³⁴ the presence of aspergillus in sputum cultures has not been associated with a risk of massive hemoptysis in CF patients.²⁷ Alternative causes of massive hemoptysis include bronchial artery aneurysms and catamenial bleeding related to endometrial tissue in the airways, but these are infrequent.^{35,36}

Diagnosis

It is presumed that massive hemoptysis is coming from a pulmonary source, but pseudohemoptysis (eg, from the nose, sinuses, or gastrointestinal tract) should be considered as well. A chest radiograph may help localize the bleeding site, although often the site cannot be determined.³⁷ Coagulation abnormalities may cause worse bleeding and should be evaluated; patients with CF may have a vitamin K deficiency related to fat malabsorption and antibiotic usage. It is also important to recognize that some patients with CF have substantial liver disease; this may be severe enough to cause esophageal varices, which may be the actual source of the bleeding, but may also be the cause of a coagulation defect and thrombocytopenia that can worsen bleeding from the lung. Bronchoscopy may help to identify the source of bleeding, but some have suggested that bronchoscopy is not indicated because it may not alter management of the patient.

Management

Although frightening, most episodes of major bleeding will stop spontaneously, and no intervention to stop the bleeding is required.³⁸ Most patients will be treated as if this is a manifestation of pulmonary exacerbation. Such a strategy typically includes antibiotic therapy and more ag-

gressive airway clearance. However, it is not clear whether to continue airway clearance therapies, for fear that a clot may be dislodged and make the bleeding persist or even worsen. Some have suggested that certain methods of airway clearance may be less likely to have such an effect and will yet lead to clearance of purulent secretions. Inhaled dornase alfa is used to enhance clearance of airway secretions.³⁹ A study in mice found that instillation of sputum from CF patients into the airways caused bleeding if pretreated with bovine dornase alfa, but this effect was not seen with dornase alfa alone.⁴⁰ It is likely that release of neutrophil elastase activity was the cause of lung injury. Some patients who are using dornase alfa may attribute their hemoptysis to the medication, but this is probably coincidental. A review of registry data found a reduced likelihood of massive hemoptysis in patients using dornase alfa.²⁷

Antibiotics are typically used to treat pulmonary exacerbation, and the choice of antibiotics is often based on prior experience and the results of sputum bacterial cultures. Given the association of *S. aureus* with massive hemoptysis, it may be prudent to include antibiotics that are effective against *S. aureus* until sputum culture results are available. Also, inhaled tobramycin has been associated with a reduced likelihood of massive hemoptysis,²⁷ which suggests that suppression of *P. aeruginosa* may be beneficial for the prevention of future events.

If the bleeding persists, intervention is warranted. Patients with hemodynamic instability or the possibility of airway compromise should be observed in an intensive care unit. Bronchial artery embolization can stop the bleeding and should be performed only by those with considerable experience. Although the primary goal is to embolize the culprit vessel, many advocate that all large and suspicious bronchial arteries should be embolized.⁴¹ Despite bronchial artery embolization, there is a high recurrence rate (> 50% within 4 months),^{27,41,42} and patients may require repeat embolization. One might ponder the long-term effects of bronchial artery embolization, but these are not known; we do know that these patients are at a much higher risk for a decline in lung function, death, and an accelerated need for lung transplantation.⁴¹ If bronchial artery embolization is not successful or cannot be performed, lung resection (eg, lobectomy) is a final option, but all measures should be taken to preserve lung function. There are reports of alternative successful therapies, including intravenous premarin,⁴³ desmopressin and vasopressin,⁴⁴ and tranexamic acid.^{45,46}

The role of the RT is also key in the care of patients with massive hemoptysis. The RT should know of the benefit of certain aerosolized medications and their association with a reduced incidence of massive hemoptysis. The RT can encourage the patients to use their long-term medications meant to maintain their health and prevent

complications. Airway clearance is again important for the patient with massive hemoptysis. Although there may be fear that airway clearance therapies may dislodge a clot and exacerbate bleeding, this is unlikely to occur, and if the hemorrhage is related to the underlying infection and inflammation, clearance of airway phlegm is an important component of care. Again, the RT has multiple methods of airway clearance from which to choose for such a patient. Some therapies may seem less rigorous and less likely than others to induce bleeding, although there are no studies that have demonstrated such a finding. However, therapies such as active cycle breathing or autogenic drainage might be preferable to high-frequency chest compression or intrapulmonary percussive ventilation.

Respiratory Failure

As stated earlier, the natural history of CF airways disease is one of progressive injury and worsening obstruction, ultimately resulting in respiratory failure.¹ There is eventual need for supplemental oxygen, and patients may develop hypercapnia with pulmonary hypertension. These patients are potential candidates for lung transplantation, and this is the time to have that discussion with the patient and their family.⁴⁷

Pathogenesis

The cause of respiratory failure is multifactorial; obstructed airways cause ventilation-perfusion mismatch, increased dead-space ventilation, inflammatory infiltration, and exudation of fluid into the air space, which causes shunt physiology.^{48,49} The likelihood of hypoxemia and a need for supplemental oxygen is greater when FEV₁ is < 40% of predicted.^{50,51} Acid-base status is further complicated by loss of salt through sweat with a metabolic alkalosis.⁵² In addition, nutritional status and lung health are closely related, and patients with severe airways disease are frequently malnourished,⁵³ and there may be respiratory muscle weakness.

Management

Most important is to relieve the patient's symptoms (eg, dyspnea, pain). Therapies for pulmonary exacerbation are also considered palliative.^{54,55} These may include bronchodilators, antibiotics, and airway clearance measures. In rare cases a therapeutic bronchoscopy may be performed to remove secretions occluding the central airways, but this is a risky procedure, given the severity of the lung disease, and is not indicated for small-airways impaction. As stated earlier, the patient is often malnourished and will require nutritional intervention; supplemental calories are indicated and the clinician must balance the risks of tube

feeding (eg, aspiration) and parenteral nutrition (eg, infection).

Noninvasive ventilatory support is increasingly used to treat respiratory failure in patients with CF.⁵⁶ Assisted ventilation increases tidal breathing and rests the respiratory muscles,⁵⁷ and has been shown to improve quality of life by reducing exertional dyspnea, decreasing chest pain, and improving exercise tolerance.⁵⁶ It may also improve clearance of airways secretions because of aeration of air space distal to the secretions.⁵⁸

Intubation and mechanical ventilation are discouraged for patients with respiratory failure in the setting of severe airways obstruction, because it typically results in a dismal outcome.⁵⁹ However, for patients with milder disease who suffer acute respiratory failure, the prognosis is much better, and intubation should not be withheld. Also, some patients with severe disease may be awaiting lung transplantation, which could be performed soon and while the patient remains on the ventilator.⁶⁰ All patients with severe lung disease should have a plan for how respiratory failure will be managed. If the patient is listed for lung transplantation, the transplant center should be involved in the decision regarding intubation.

The primary indication for lung transplantation is that the patient is expected to die as a result of lung disease. Not all patients are candidates for lung transplant, or they may choose not to pursue this option. The indications and exclusion criteria for lung transplantation have been described.^{47,61,62} The patients most likely to benefit from transplantation include those with a low 5-year predicted survival rate, hypercapnic respiratory failure, pulmonary hypertension, rapidly worsening lung disease, FEV₁ less than 30% of predicted, massive hemoptysis, increasing malnutrition, and increasing hospitalizations.^{47,61,62} The allocation of donor lungs takes some of these factors into consideration, so that transplantation occurs for those most likely to benefit.⁴⁷ Other factors that are important to the success of transplantation include the patient's social support system, compliance, and psychological stability.

The role of the RT may never seem as important as it is with the patient with advanced stage lung disease and respiratory failure. As stated above, therapies used to treat exacerbations are implemented as they are thought to be palliative, and airway clearance is perhaps most important. In my experience, this is when patients often request a return to hands-on therapy with standard chest physiotherapy. Perhaps they find it most effective, or perhaps they just want additional contact. These patients may have more frequent admissions and longer hospital stays, and in many ways, the hospital team becomes a second family. The RT is an important member of that family and can provide critical emotional support for the patient and family.

Summary

CF is a chronic disease with a history of early demise for patients. The success that we have seen over the last decades, including patients living longer and with a better quality of life, has been the result of new medications and more aggressive therapeutic approaches. However, the disease remains progressive and the patients will face a number of complications associated with the disease. Clinicians must remain cognizant of the potential pulmonary complications that result from the chronic infection and inflammation, notably pneumothorax, hemoptysis, and eventual respiratory failure. The clinician should be able to recognize and manage these complications, as well as understand the implications of these complications in the long-term planning in the care of patients with CF.

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Discussion

Rubin: I will take the prerogative of co-chair to ask the first question. And I do have an addition to your manuscript that I'd like you to include, based on this question. You discussed specifically, massive hemoptysis, pneumothorax, and respiratory failure in patients with CF. For the RTs, you are one of the gurus of airways clearance; I still use your commandments. Airway clear-

ance: should it be used in patients with pneumothorax? Is it safe? Is it safe if it's not severe, and, if so, is there a safer way to do this? You suggested PEP [positive-expiratory-pressure therapy] may not be safe, but is there a safe way? Same question for hemoptysis. Airway clearance: is it safe? Is there a degree of hemoptysis that you would or wouldn't do? And is there a safer way to do it? Respiratory failure with very poor cough: is there a value in

airway clearance? Is there a danger in doing this if they can't expectorate?

Flume: I'll start with how we're going to tackle our guidelines when we get to the subject of complications. For airway-clearance therapies and long-term medications the systematic reviews found evidence in support of those therapies, but none exist for the management of pneumothorax and hemoptysis, so for those we use an ap-

proach akin to the Delphi method,¹ which is more rigorous than the usual consensus approach. We poll the experts for their opinions *and* their degree of confidence in those opinions.

Regarding my approach to airway clearance in patients with those complications, I don't stop airway clearance for anything. I don't stop it for pneumothorax, massive hemoptysis, or for a patient near the end of life. Patients with pneumothorax who have pain and a chest tube do not tolerate some therapies, such as percussion, but we (especially RTs and patients, and occasionally physicians) have the creativity to come up with methods that can work for these patients. For example, active cycle breathing, autogenic drainage, Acapella, perhaps: these are methods that don't inflict the same degree of pain. We try to relieve the fear among RTs and physicians, who can develop an unwillingness to lay their hands on these patients, for fear that they are too complicated and delicate.

I would make the same argument for massive hemoptysis. I wouldn't use IPV [intrapulmonary percussive ventilation] or maybe not even the Vest on someone with massive hemoptysis, because it could break free a clot. But I think you can use gentler methods, such as active cycle of breathing and Acapella. I've seen some RTs who have a remarkable ability to work with the patient and coax out an amazing amount of phlegm.

Regarding patients who are near the end of life, it's been my experience that if there's ever a time that a patient really wants physical contact, this is the time. We discourage the use of the Vest or IPV in patients who have very severe disease; instead, we tend to use percussion and postural drainage. These patients, especially at the end of life, want people to touch them; they don't want to be left alone. They come to the hospital not merely for the therapies we do, but in some respects because the hospital staff have become close, trusted friends. It's been

my experience that these patients with very advanced disease seem to prefer percussion and postural drainage.

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Lester: The end of life tends to be a very isolating time. These patients are home and they're not seeing many people. I don't know if the CF center staff become their *friend*, as much as people whom they trust. When they come in to the hospital, they want to be taken care of and touched, so we tend to go to hands-on therapies at end of life.

Marshall: I don't think we know very much about end-of-life care for patients with CF. There's a lot of literature on the quality of end-of-life care, but I don't think it's been extensively applied in the CF community. My sense is that we probably do a better job than what occurs in general health care, but I think it would be nice to document that, and I think there's room for improvement.

Regarding the work you did with the CF patient registry,^{1,2} did you do any more sophisticated statistical work to adjust for disease severity, to try to draw out those associations a bit more?

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Flume: We had a difficult time trying to match control patients with patients who had complications. When we would select patients in a given year, there was a high potential that a selected control (matched for age, sex, severity of disease, or whatever) would become an incident case years later. We were not able to adjust the selec-

tion without creating biases, so we used the odds ratio. I hesitate to call them "risk factors"; they are actually "associated factors," because we're not implying that there is a cause-and-effect relationship.

Ratjen: About end-of-life care and respiratory-failure data, because of this tricky interaction with lung transplantation, we changed our approach. Now we have the palliative-care team get involved initially when we contact them about transplantation, to make this more of a continuum, because questions about end-of-life care need to be discussed early on, to avoid these patients dying on the respirator, which is the worst scenario.

Regarding pneumothorax, Waters and I did the Cochrane review¹ on that, which was the easiest review I've done, because there were no data to review. How do you feel about it? Is pneumothorax enough of a problem that we need to study it and interventions, or are we doing a good enough job that it doesn't need further research?

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Flume: I think it would be almost impossible to do a study that would answer the questions. The incidence is low enough that it would require many centers to participate or a very long study. For example, should we perform pleurodesis after the first pneumothorax? Would all the centers have a surgeon available to perform the correct procedure? There would be so many problems and it would take so long, such a study is unlikely.

Davies: Are there any guidelines on how long to wait after a pneumothorax before doing forced expiratory maneuvers, such as spirometry? If not, what is your practice?

Flume: There are no guidelines I'm aware of, nor any case reports of pneumothorax during spirometry. I will write that down as a potential question to put to our experts.

Rosenblatt: During a forced expiratory maneuver, wouldn't the pleural pressure be higher than the airway pressure? If so, I am not sure why there would be a relationship between pneumothorax and obtaining spirometry.

You indicated that in massive hemoptysis you go directly to embolization. But what about a patient whose hemoptysis is not massive, but is recurring? I think the literature suggests that about 30% of these patients have to be embolized more than once. What is your experience?

Flume: The typical approach with patients who have more than just rare, scant hemoptysis is to treat as if it were a pulmonary exacerbation. As for when to use bronchial-artery embolization, I think there must be a large amount of blood, or frequent substantial blood, say 100 mL a day for several days. I would put our interventional radiologists up against any others. But embolization has another potential complication. We've never had a major complication; the worst was a pseudo-aneurysm at the insertion site, which required maintaining pressure there for a long time. But re-

peated embolization is associated with a loss of lung function. We had an individual who had repeated embolization and got a chest-wall deformity, which I believe was because of an infarction to her lung over time.

On the one hand you must be ready to "pull the trigger" very quickly, but in most cases the bleeding will stop without embolization. Even if a patient comes in and says she has coughed up half a liter of blood, I don't necessarily go to embolization right away. I admit the patient to the hospital, initiate therapy as if treating an exacerbation, and observe before making the decision about embolization. The recurrence rate of massive hemoptysis may be more than 30%, even following embolization.

Rosenblatt: The definition of massive hemoptysis has been variable. Some use 240 mL of blood as the definition of massive hemoptysis, but others may use 100 mL, and the therapy is prompted by how sick the physician thinks the patient is. There is so much variability. I am concerned when I hear about such a high hemoptysis recurrence rate; it suggests we should be more aggressive. But I don't think there are enough solid data on the recurrence rate.

Ratjen: The only data I'm aware of were from Sweezey and Fellows, in Boston.¹ That study was not com-

pletely controlled, but the recurrence rate after embolization was the same as the recurrence rate in a population that was not embolized. My reading was that embolization helps control the acute episode, but it doesn't necessarily affect the recurrence rate.

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Lester: I've known a couple of lung-transplant patients who had one or more great years after a transplant, and they hope they're going to get another transplant. Do patients with CF ever get a second transplant?

Rosenblatt: I don't know, but the data clearly show that after re-transplantation, most of which is for bronchiolitis obliterans syndrome, the survival is distinctly lower than it is with the initial transplant.¹ Some programs have decided not to perform re-transplants. I do not know the difference in survival in re-transplantation between CF and other patients.

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