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CONSENSUS CONFERENCE PULMONARY COMPLICATIONS OF CYSTIC FIBROSIS

Management of complications of cystic fibrosis (CF) are the subject of perennial controversy and ongoing change. The literature reflects only partially the wealth of experience accumulated by caregivers and has become rapidly outdated.

A group of physicians representing a vast array of disciplines joined in discussion to arrive at a set of recommendations that reflect the current trend of management of complications of the pulmonary disease of CF.

Consensus documents represent the combined wisdom and clinical experience of a group of experts in the field, rather than a mere distillation of the literature. We expect the opinions herein to evolve with time, as new therapeutic approaches are developed, in the same manner as this document has emerged from a critical review of what is known and published.

PNEUMOTHORAX IN CYSTIC FIBROSIS

Introduction

Pneumothorax, or "air in the pleural space" can cause dangerous pressure on the lung. In patients with CF, this is most often caused by rupture of subpleural blebs through the visceral pleura. Another, much less common cause is "traumatic pneumothorax" secondary to lung puncture during procedures such as intravascular line insertion, or barotrauma (e.g., during mechanical ventilation).

Incidence

The approximate incidence of pneumothorax is one percent per year (Cystic Fibrosis Foundation Patient Registry data). Five to eight percent of all CF patients will eventually experience a pneumothorax. The incidence increases with age and severity of disease. Approximately 16 to 20 percent of adults (over 18) with CF will experience a pneumothorax at some time in their lives.

Diagnosis

Pneumothorax should be suspected in patients with CF who experience the sudden onset of chest pain and respiratory distress. Other patients can be completely asymptomatic and the pneumothorax is detected on a chest roentgenogram obtained for other reasons.

Common signs and symptoms of pneumothorax include: tachypnea, tachycardia, dyspnea, pallor, and cyanosis. On physical examination these are found: decreased breath sounds, vocal fremitus, and decreased thoracic excursion of the affected hemithorax. Tension pneumothorax may, in addition, cause signs of mediastinal shift, including deviation of the point of maximal impulse of the heart and deviation of the trachea from the midline. Subcutaneous emphysema and signs of circulatory compromise also are more likely during tension pneumothorax.

The most important laboratory examination is the chest radiograph which should include frontal and lateral views. In addition, inspiratory, expiratory and lateral decubitus views may help detect free air in the pleural space when pneumothorax is difficult to detect in a plain film. Air will become evident as the lung deflates on expiration or when the affected side is up (i.e., the air will rise and a rim of air will become evident on the left lateral decubitus film on a right sided pneumothorax).

Treatment

Every patient with a newly diagnosed pneumothorax, even if asymptomatic, should be hospitalized and observed for a minimum of 24 hours. For an asymptomatic patient in whom pneumothorax is an incidental finding, a chest radiograph should be obtained 24 hours after admission. If this patient remains stable, asymptomatic, and the chest radiograph shows no increase in the

size of the pneumothorax, the patient can be discharged and followed as an outpatient (Figure 1). However, if the pneumothorax has increased, full treatment should begin (Figure 2).

If the patient is symptomatic, or the pneumothorax appears to be 20 percent or more of the total affected hemithorax volume, a chest tube should be inserted. Negative pressure of no more than -20cm of water should be applied. Because the lung re-expands by itself once free air is evacuated, higher negative pressure does not necessarily cause faster pneumothorax resolution.

Furthermore, many physicians feel that application of high negative pressure causes laceration of the lung secondary to apposition of a high negative pressure source (tube) to the visceral pleural surface.

Large pneumothoraces are best managed by applying no suction to the chest tube initially and letting the lung re-expand slowly. This cautionary maneuver should avoid both patient discomfort and edema of the affected lung when suddenly reinflated. Some practitioners administer 100 percent inspired oxygen to facilitate reabsorption. This method is not universally accepted and is probably ineffective beyond the neonatal period. No controlled studies have clarified these controversies.

After chest tube insertion, a new chest radiograph should be obtained. If a substantial collection of air persists, insertion of additional chest tubes should be considered. Such procedures can be aided by diagnostic imaging guidance such as fluoroscopy, ultrasound, etc. Following reduction of the size of pneumothorax, a waiting period of 24-48 hours is prudent. However, if after this waiting period pneumothorax is still present, surgery must be considered.

Once the pneumothorax is resolved and the air leak stops (i.e., apposition of the visceral pleura to the thoracic wall) the chest tube can be removed.

If the patient remains asymptomatic and the lung stays up, the pneumothorax is considered resolved. If the lung stays up but the air leak persists, observation of the patient should continue. If after approximately five days there is no resolution of the air leak, suction should be discontinued and the tube should be left to underwater seal. A new radiographic and clinical evaluation should be carried out. If air reaccumulates in the pleural space, surgery should be considered.

No full agreement has been reached as to whether tubes should be clamped before removal, or whether tubes should be removed as soon as the pneumothorax is considered resolved. Most practitioners will clamp the tube for approximately 12 hours prior to withdrawing it. Reoccurrence of pneumothorax indicates the need for surgery.

Sclerosing agents have been used as a treatment for pneumothorax in CF patients. The most popular sclerosing agents are quinacrine and tetracycline. In a large unpublished study (Denning et al, 1991), instillation of quinacrine into the pleural space resolved pneumothoraces unresponsive to chest tube insertion and air drainage alone in about 90 percent of all cases. In that same series, tetracycline was successful in 58 percent of pneumothoraces, whereas open thoracotomy was successful in 96 percent of the instances (Table 1).

Instillation of sclerosing agents has two advantages. First, no surgical intervention is required. Second, it can be accomplished in gravely ill patients without general anesthesia. The disadvantages include: lack of direct visualization of the distribution and effect of the chemical; unpredictable results and variable success rate. Finally, both quinacrine and tetracycline are no longer being manufactured by U.S. pharmaceutical companies and access to these products has become extremely difficult.

Talcum powder is a very effective and readily available sclerosing agent. A major drawback in using talcum is the high probability of causing lung adhesions to the parietal pleura. This complication is particularly serious if it involves the diaphragmatic pleura because it may render the diaphragm unable to contract properly.

Thoracoscopy and CO_2 laser abrasion, with or without stapling of blebs or instillation of chemical agents, has recently emerged as another treatment modality for pneumothorax.

Thoracoscopic stapling and abrasion is facilitated by collapse of the lung. Patients with CF tend not to fully collapse their lungs following pneumothorax because of pleural adhesions and poor elastic recoil. Thus, adequate visualization may be less than opti-

mal for thoracoscopic management in some of these patients.

Data concerning the use of thoracoscopy in CF are scant. Successful management of pneumothorax in five CF patients using talc insufflation through thoracoscopy was recently reported. No data are available on the long-term outcome of this procedure in CF.

Recommendations

1. Treatment options for pneumothorax unresponsive to chest tube drainage are: thoracotomy, limited surgical pleurodesis, oversewing or stapling subpleural blebs, and chemical pleurodesis.

2. The benefits of surgery to manage persistent pneumothorax far outweigh the risks of this procedure for most patients.

3. Needle aspiration is an emergency procedure which can precede but never replace chest-tube insertion. Needle aspiration is only indicated when patients are severely compromised upon presentation and require immediate intervention. Otherwise, needle aspiration is not appropriate in the management of pneumothorax in CF.

4. Heimlich valves have a limited role in the temporary control of pneumothorax. They could be used during patient transport and for patients awaiting an imminent lung transplantation. These valves are not always effective in completely evacuating air but provide a temporary method of preventing tension pneumothorax.

5. Chemical pleurodesis should be reserved for patients whose clinical condition is such that the risk of surgery outweighs its benefits (e.g., extremely poor anesthetic risks, patients in heart failure or respiratory failure), or for patients who absolutely refuse surgery. Availability of chemical agents may limit the performance of these procedures.

Technical Considerations

Chest Tube Placement

The chest tube should be of adequate size to evacuate the air and allow for sufficient flow to accommodate air leak from the ruptured bleb(s). In general, a 24 French size tube should suffice for an adult-sized patient. Smaller tubes may be adequate for smaller patients.

The site of insertion of the chest tube will depend on the location of the pneumothorax. Consideration must be given to the fact that surgery may ultimately be required. Since the preferred surgical approaches are transancillary (third intercostal space) or anterior (fourth or fifth intercostal space) the chest tubes should not be placed in these locations.

The optimal insertion site is in the mid-axillary line in the fifth or sixth intercostal space below the axillary tail of the breast in females. It is important to direct the tube to the apex of the chest and to insert a sufficient length so that the end of the tube sits in the apex.

High anterior chest tubes (second intercostal space) are sometimes useful. However, they are difficult to position and maintain properly, and are more painful to insert. Also, their insertion risks injury to the internal mammary artery if placed too far medially. Diagnostic imaging may help position the tube, particularly when placement of a second tube becomes necessary.

Several commercially available pleural drainage units offer closed suction systems. Connections should be air-tight with appropriate pleural pressures. Occasionally, these units can malfunction if they are overturned or if the negative inspiratory force exerted by the patient exceeds -30cm. In these situations, fluid can be expelled via a valve designed to ensure egress of air. For patients with restrictive lung disease this, can be a frequent occurrence and therefore mandates diligent surveillance.

Chest tube removal may cause recurrence of pneumothorax when the tract formed by the tube remains in communication with the pleural space. A purse string or mattress suture can be used to assure a proper skin seal.

Technique of Pleurodesis (Production of Adhesions)

The area of air leak is identified through a small thoracotomy. Identifiable blebs are usually excised after their base is stapled. The parietal pleural surface is then abraded with a gauze sponge. By rubbing the sponge over the pleural surface, the surgeon can see the inflammation that this causes because the pleura

become erythematous to the naked eye. By manipulating the lung the surgeon has the ability to see and control the extent and location of the area of abrasion.

Pleurodesis and Lung Transplantation

Pleurodesis is not an absolute contraindication for lung transplantation. The transplant coordinator at the specific center should be contacted with questions concerning management of pneumothorax if referral is planned.

Patients who experience pneumothorax while awaiting transplantation (on a transplant list) should be managed as other CF patients. It is prudent, however, to contact the transplant team at the referral institution before beginning pleurodesis.

Complications

Complications of pneumothorax include: respiratory compromise, shock, hemorrhage (due to shearing of vessels), and empyema. Efforts should be made to continue physical therapy. The performance of this technique will not interfere with pneumothorax resolution. Efforts should be made to relieve discomfort resulting from the presence of a chest tube or a thoracotomy with adequate analgesic therapy.

Prognosis

Spontaneous pneumothorax in CF is, generally, a bad prognostic sign. Available data indicate that survival after the onset of a pneumothorax is approximately 30 months.

Prevention

To prevent pneumothorax, CF patients should avoid maneuvers or situations which will create marked fluctuations in intrapleural pressure. These include power weight lifting, intense isometric exercises, and scuba diving. During scuba diving, individuals are subjected to increased pressure followed by decompression, which may create changes in lung parenchyma that could cause pneumothorax. Underwater swimming in pools and shallow diving probably do not increase the risks of pneumothorax.

No air travel or pulmonary function testing should be undertaken for at least two weeks following resolution of pneumothorax.

HEMOPTYSIS IN CYSTIC FIBROSIS

Minor Hemoptysis ("Blood Streaking")

Blood streaking of the sputum is common in CF patients and requires no specific treatment. Persistent streaking however, may indicate a pulmonary exacerbation requiring appropriate therapy. The physician should determine that there are no other potential contributing factors to this condition such as the chronic use of aspirin.

Major Hemoptysis ("Major Bleed")

Major hemoptysis is defined as acute bleeding of a large amount of blood (often defined as 240 cc in a 24-hour period) which could be life-threatening due to asphyxiation from airway obstruction and/or could lead to acute hypotension.

Recurrent bleeding of substantial volume (e.g., more than 100 cc/day) over a short period of time (e.g., 3-7 days) are also termed "major hemoptysis." These recurrent episodes may have the following characteristics:

- Threaten life due to asphyxiation
- Produce airway obstruction
- Produce hypotension
- Produce anemia
- Produce chemical pneumonitis
- Trigger a pulmonary exacerbation.

Incidence

About one percent of CF patients have one episode of major bleeding each year, according to the Cystic Fibrosis Foundation Patient Registry data which defines hemoptysis as a bleed more than 240 cc/24 hours or requiring transfusion. Obviously, the number of patients with major hemoptysis, as defined above, will be somewhat larger. The vast majority of patients with major hemoptysis are 16 years or older (Registry data).

Pathogenesis

Major hemoptysis in CF patients is nearly always of systemic arterial origin. The bleeding usually arises from markedly enlarged and tortuous bronchial arteries which vary greatly in number and origin. Two-thirds of bronchial arteries arise from the ventral surface of the aorta with the remaining one-third arising from other arteries including the internal mammary and intercostal arteries. Major hemoptysis also can be produced by non-bronchial arteries which collateralize with the bronchial circulation or enter the lung through granulation tissue. Such arteries include the phrenic, intercostal, internal mammary, thyrocervical, costocervical, and branches of the subclavian and axillary arteries.

Evaluation/Diagnosis

1. It is essential to differentiate major hemoptysis from bleeding from the upper airway or from the gastrointestinal tract. In addition, the examination should rule out the presence of a foreign body. A careful history may help to localize a pulmonary bleed by the patient noticing localized gurgling, warmth, discomfort, fullness, etc. Physical examination may reveal new, localized pulmonary findings or bleeding from an upper airway site. Differentiating a pulmonary bleed from bleeding from other sites may require assessing associated symptoms, measuring pH of the expectorated blood, placing a nasogastric tube, endoscopy, etc.

2. Use of other drugs which could contribute to the bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAID), penicillin, etc. should be ascertained.

3. A chest radiograph should be obtained for several reasons: to determine if there have been any acute changes in the lungs; to try to localize the site of the bleeding; and to determine if there are any other unusual findings which could explain the bleeding such as a new thick wall cyst, (suggesting infection with an unusual organism such as atypical mycobacteria), or localized or unilateral hyperinflation (suggesting a foreign body).

4. The following laboratory tests should be obtained: complete blood count with platelet count; prothrombin time (PT) and partial thromboplastin time (PTT); liver function tests; type and cross the patient's blood for possible transfusion.

5. A sputum for culture and sensitivity should be obtained. If the clinical situation and radiographic findings suggest other potential infections, the sputum should also be stained and cultured for organisms such as mycobacteria and fungi.

6. Bronchoscopy may help localize the site of bleeding; however, the procedure is not always successful. This occurs when the patient has stopped bleeding or when massive bleeding prevents adequate visualization of the airways.

   The vast majority of major pulmonary bleeds in CF patients are acute, self-limited, and may not require diagnostic tests such as bronchoscopy.

   Bronchoscopy is indicated when the acute bleeding continues, appears to be progressive or frequently recurs, or if surgery or local airway therapy will be used. It is strongly recommended that both rigid and flexible bronchoscopes be available since either or both may be required to assess and manage the bleeding. If the site of bleeding is known, it is acceptable to embolize only the artery(ies) to that area. If embolization of bronchial arteries is determined to be the therapy of choice and the site of bleeding is unknown, all large and tortuous bronchial arteries may be embolized since collaterals often have developed from mediastinal and contralateral vessels.

7. When the patient is admitted a surgeon and a radiologist experienced in interventional angiography should be notified. If such personnel are not readily available, referral to another center should be considered.

Treatment

Many CF patients with major hemoptysis will stop bleeding spontaneously in less than four days. This may occur with no change in their usual therapy and/or without specific treatment for the bleeding.

There are almost no scientific data to support most of the therapeutic options noted below for treatment of hemoptysis in CF patients. The recommendations are based on the clinical observations and experiences of the physicians at the Consensus Conference, case reports in the literature, published studies and theoretical considerations derived from the literature.

1. First, the patient should be reassured and calmed. Psychological support may be necessary. Occasionally, sedation may be required.

2. Drugs which could interfere with coagulation should be discontinued. These include: aspirin, penicillin, NSAID, etc. Inhaled drugs which may be pulmonary irritants should also be discontinued such as N-acetylcysteine and aerolized antibiotics. *In vitro* and animal studies have demonstrated that inhaled ß-adrenergic drugs may dilate the bronchial circulation whereas anticholinergic drugs may constrict the bronchial circulation. There are no data in humans. Therefore, the decision to continue or discontinue any of the inhaled bronchodilators is based on theoretical considerations. No specific recommendations are made with respect to their use.

3. Coagulation defects should be corrected with Vitamin K, fresh frozen plasma or specific factors as indicated. If intravenous Vitamin K is used, the drug should be given slowly to avoid hypotension and anaphylaxis. Since the PT and PTT may not always reflect low levels of clotting factors, intramuscular Vitamin K is often given during a major bleed, in spite of a normal PT and PTT.

4. Acute blood loss should be corrected with transfusions as clinically indicated.

5. A majority of major pulmonary bleeds appear to be associated with pulmonary exacerbations and, therefore, should be treated with appropriate intravenous antibiotics and other usual therapies (as discussed earlier, penicillins probably should not be used).

6. Placing the lung which appears to be bleeding in the dependent position may help to prevent contamination of the non-bleeding lung. However, individual patients may respond to various positions with increased bleeding and/or increased breathing difficulties. Thus, the positioning of patients with major hemoptysis needs to be individualized.

7. The patient should be encouraged to cough to maximize blood expectoration and, thereby keep the airways as patent as possible. There is no evidence that discontinuing chest physiotherapy is beneficial or harmful. The decisionof whether to continue chest physiotherapy or not is left to the physician and patient.

8. Placing ice packs on the chest has no demonstrable benefit and may be uncomfortable for the patient.

9. Intravenous premarin (water-soluble, conjugated estrogen) may rapidly stop pulmonary bleeding by enhancing platelet aggregation, decreasing capillary permeability, interfering with tissue reactions to bradykinin, and by other poorly understood mechanisms. This medical treatment may warrant consideration before more invasive therapy. Dose: 10-25 mg over 10-15 minutes every 4-6 hours for 3-4 doses.[21,26,32,39]

10. Intravenous pitressin (vasopressin and desmopressin) may rapidly stop bleeding by enhancing arteriolar smooth muscle contraction and the release of coagulation factors from the vascular endothelium. This medical treatment may warrant consideration before more invasive therapy. With the use of pitressin, there may be considerable water retention and diuretics may need to be given. Dose: (1) Vasopressin — 20 units over 15 min; then continuous infusion of .2 units/min. (2) Desmopressin—4 ug intravenously; then infusion of 0.3 ug per km over 12 hours.[33,37,38]

11. Local/topical treatment may be indicated when the bleeding appears to be immediately life-threatening. Such therapy may include some or all of the following:

    - Endobronchial tamponade with a catheter/balloon system
    - Direct airway tamponade with gel foam pledgets
    - Iced saline lavage
    - Topical therapy with alpha-agonists or thrombin
    - Selective or double-lumen intubation
    - Removal of clots (while removing clots may improve ventilation, it can also lead to a marked increase in bleeding).

Topical or local treatment is usually not indicated in non-emergency situations.

12. Arterial embolization may be indicated for major hemoptysis (as defined above) as well as for persistent hemoptysis of lesser volume when it either interferes with a patient's lifestyle and/or medical management. While embolization often produces acute cessation of bleeding, the procedure has potential major complications including paralysis, organ infarction, and death. Therefore, this procedure should only be performed by an experienced angiographer and interventional radiologist who have experience with this specific procedure. If such a physician is not available, the patient should be referred to an institution where the embolization can be performed.

12. Recurrence of bleeding is relatively common following embolization and should be managed as a *de novo* event. If bleeding does not stop acutely after embolization, re-embolization should be considered. It is important at this time to remember the anatomic variability of the bronchial vessels and the role other arteries play in producing major hemoptysis. A theoretical complication of embolization is airway ischemia which could affect subsequent lung transplantation.

13. In rare cases where bleeding cannot be stopped by the methods described above, including embolization, local pulmonary resection may be indicated. In these situations, it is mandatory to localize the site of bleeding prior to surgery. If surgery is seriously contemplated, other factors such as the patient's baseline lung function and overall clinical status must be considered.

Prognosis

Recent data indicate that an episode of major hemoptysis does not necessarily change the long-term prognosis for any individual patient.

RESPIRATORY FAILURE IN CYSTIC FIBROSIS

Introduction

Respiratory failure in patients with CF is a sign of severe lung disease and is defined by hypoxemia and/or hypercapnia associated with obstructive airways disease. The topic merits review for several reasons. Over the past 20 years, we have developed a better understanding of the treatment of hypoxic respiratory failure with supplemental oxygen, and we have observed technical advances in modes of ventilatory support. Further, the availability of lung transplantation makes the short-term treatment of respiratory failure of CF patients pertinent, because their long-term quality of life may be improved with transplantation. This section will describe our current understanding of the pathophysiology of respiratory failure in CF and the state of the art for therapeutic interventions. These concepts rely, in part, on information gleaned from treatment of non-CF patients with obstructive airways disease and respiratory failure.

Pathophysiology of Respiratory Failure

Retained airway secretions and bronchiectasis are major features of the obstructive airway pathobiology in CF. Pathogenic factors in the development of respiratory failure include: 1) thickened airway secretions with bacterial infection and mucus hypersecretion; 2) bronchoconstriction; 3) airway mucosal edema and inflammation; and 4) respiratory muscle weakness and fatigue. These features contribute to the development of respiratory failure, and hypoxemia usually precedes hypercapnia. Figure 3 displays the pathophysiologic consequences of airway obstruction that contribute to respiratory failure. Obstruction of airflow in small and large conducting airways results in hypoxemia due to altered matching of ventilation and perfusion, and this results in hypercapnia due to alveolar hypoventilation.

Treatment of Respiratory Failure: Initial Approach

Goal

The goal of treatment is to correct hypoxemia and to achieve adequate pulmonary carbon dioxide elimination and a stable acid-base status, thereby retarding the development of pulmonary hypertension and cor pulmonale and prolonging functional life. The treatment of respiratory failure must target the pathogenic factors, i.e., abnormally thickened airway secretions, bacterial infection, bronchoconstriction, mucosal edema and inflammation, and respiratory muscle weakness and fatigue.

General Principles

The initial approach to the treatment of respiratory failure is to intensify the usual regimen used to treat the pulmonary disease in CF patients, i.e., clearance of retained airway secretions and control of bacterial

infection with parenteral antibiotics. This approach should involve more intensive and more frequent sessions of chest physical therapy with postural drainage, including intensive care resources if necessary. It may also involve higher doses and/or longer durations of multiple anti-pseudomonal drugs and, sometimes, antistaphyloccocal therapy, even if *staphylococcus is* not recovered from sputum cultures. The use of inhaled or systemic bronchodilators may assist clearance of airway secretions. Anti-inflammatory agents, particularly systemic corticosteroids, may play a useful short-term role for reducing mucosal inflammation, edema, and bronchospasm, and improving clearance of airway secretions. The long-term benefit of anti-inflammatory agents however is undefined. Adequate nutrition is mandatory to provide appropriate muscle strength and endurance. Nutritional supplementation may be required. Exercise rehabilitation may be useful, not only to improve cardiovascular conditioning, enhance oxygen delivery, and improve respiratory muscle strength and endurance, but also to assist in mechanical clearance of airway secretions. The initial therapeutic approach also should include a search for unusual pathogens such as non-tuberculous mycobacteria, and for other etiologies such as pneumothorax, allergic bronchopulmonary aspergillosis, or reactive airways disease.

Treatment: Oxygen Supplementation

Chronic (Daily) Hypoxemia

If intensification of the standard therapeutic regimen does not correct hypoxemia (room air $PaO_2 < 55$ torr at rest), continuous supplemental oxygen is mandatory to limit the development of pulmonary hypertension and cor pulmonale.[40,41] Although supplemental oxygen for 12 hours per day is better than no oxygen supplementation, continuous oxygen therapy (18-24 hours per day) reduces mortality in patients with chronic obstructive pulmonary disease (COPD) by 50 percent when compared to nocturnal oxygen alone.[42] Oxygen supplementation should be aimed at achieving a $PaO_2 > 60$ torr without significant adverse effect on arterial $PaCO_2$ and pH. In patients who chronically retain CO_2, oxygen supplementation should be initiated cautiously and $PaCO_2$ rechecked. The usual mode of oxygen supplementation is by a nasal cannula. Although transtracheal oxygen delivery is being used in patients with COPD, there is little experience in CF patients, in whom transtracheal oxygen may dry airway secretions and impair the clearance of airway secretions. Many patients will require increased amounts of oxygen at night to overcome the effects of hypoventilation with REM sleep and worsening ventilation to perfusion (V/Q) mismatch secondary to airway closure.[43-47] Patients on exercise rehabilitation programs also are likely to require increased levels of oxygen supplementation during exercise.[45,46,48] The dosing requirement for additional oxygen supplementation during sleep or exercise must be determined empirically (Table 2).

Nocturnal Hypoxemia

Some CF patients may have adequate daytime oxygenation, but experience hemoglobin desaturation during sleep that is associated with less REM sleep, shorter total sleep time, and increased pulmonary artery pressures.[43-47] These patients should receive supplemental oxygen at night because it improves functional well-being and reduces the frequency of hospital admissions; further, nocturnal hypoxemia may contribute to pulmonary hypertension and vascular remodeling.[49,50] The prevalence of nocturnal hypoxia in CF patients who have adequate daytime oxygenation is not well defined, but secondary polycythemia is not a reliable index of nocturnal desaturation in CF patients. Assessment by oximetry is required, and screening for nocturnal hypoxemia should be considered in patients with saturation less than 92 percent when awake. Patients who exhibit evidence of pulmonary hypertension or right heart failure should be evaluated for the possibility of nocturnal hypoxemia, even if they have adequate PaO_2 during the daytime (Table 2).

Treatment: Other Medications

If oxygen therapy is satisfactorily instituted, there is little role for diuretics, digitalis, or pulmonary vasodilators for the treatment of hypoxic respiratory failure in CF patients.[51,52] Diuretics may have an adverse effect by decreasing systemic vascular volume without reducing pulmonary vascular pressures; this leads to a decrease in right heart filling, and cardiac output may be adversely affected since the right ventricle is a "volume" pump.[53] Cardiac glycosides provide little benefit for right-sided cardiac failure,[54] and may be associated with arrhythmias, particularly when pulmonary hypertension is present. The use of pulmonary vasodilators (other than supplemental oxygen) is discour-

aged because they may induce larger reductions in systemic vascular resistance than in pulmonary vascular resistance, leading to decreased cardiac output, hypotension, and even death.[55] The use of theophylline may contribute to improved diaphragmatic muscle function,[56] but it is not routinely beneficial and may be associated with increased risk of gastroesophageal reflux, which is common in CF patients.

Treatment: Mechanical (Assisted) Ventilation

Introduction

The general goal of medical therapy in patients with CF is to improve longevity and quality of life. Initial experience with mechanical ventilation in CF patients in the 1960's and early 1970's yielded poor results; few patients were successfully weaned from ventilators, and those weaned had short survival.[57] However, assisted ventilation may be appropriate when there are reversible causes of respiratory failure, or when lung transplantation is imminent (Table 3).

Infants

Early experience with mechanical ventilation in CF infants (less than 12 months) with respiratory failure was associated with an 80 percent mortality rate,[57] but recent studies indicate that infants and young children with CF may have greatly improved acute survival (~80 percent) with current methods of ventilatory support, and significant long-term survival (50-60 percent for several years).[58,59] Thus, infants and young children with CF should be afforded mechanical ventilatory support as indicated; many will survive and achieve long-term functional status.

Acute/Reversible Respiratory Failure

CF patients with potentially reversible respiratory failure due to an acute illness, e.g., bronchospasm, viral pulmonary infection, pneumothorax, hemoptysis, massive aspiration, or with possibly reversible respiratory failure due to suboptimal medical therapy, should be treated with mechanical ventilatory support as indicated. The majority of these patients will survive short-term ventilatory support, and overall prognosis is more closely linked to the underlying severity of the lung disease than to the episode of respiratory failure. Several general principles should be carefully observed. First, the period of intubation should be as short as possible. Second, there should be aggressive attention to mechanical removal of airway secretions to prevent impaction of secretions. Third, respiratory and skeletal muscles should be exercised (including patient ambulation with Ambu-bag) to prevent muscle deconditioning and atrophy.

Chronic Respiratory Failure in Patients Accepted for Lung Transplantation

In some CF patients, the possibility of lung transplantation increases the likelihood of long-term improved quality of life, and adds another potential indication for assisted ventilation. However, the evolving criteria for candidacy for lung transplantation, and the limited availability of donor organs, make it difficult to define specific recommendations at this time. In general, CF patients receiving assisted ventilation will not be accepted as transplant candidates. The criteria for use of assisted ventilation in CF patients previously accepted as lung transplantation candidates will be defined by the experience of individual lung transplant centers. This situation requires consideration of the possible duration and complications of mechanical ventilation, the availability and assignment of donor organs, and the likelihood of successful transplantation in mechanically ventilated patients.

Chronic Respiratory Failure in Patients Not Accepted for Lung Transplantation

CF patients who develop respiratory failure despite aggressive treatment consistent with standard measures in a CF Center should be advised that mechanical ventilation is unlikely to provide long-term benefit. Unless there is an acute and potentially reversible component to the respiratory failure, the great majority of these patients will not be successfully weaned from mechanical ventilation, and the survival time and functional capability of any patient successfully weaned are likely to be limited. A time-limited trial of intubation and mechanical ventilation is occasionally appropriate to accomplish last wishes, but this approach should be discouraged by educating the patient about terminal respiratory complications of the disease. Recent experience suggests that noninvasive (i.e., face or nasal mask) ventilatory support may be useful in selected patients,[60-62] but this does little to improve functional status. It improves or stabilizes the blood gases so that patients

do not have continuing increase in $PaCO_2$ or acidosis without otherwise changing the pulmonary function.

Methods: Ventilatory Support

Goal

Assisted ventilation in CF patients is usually directed at the treatment of hypercapnic respiratory failure; hypoxemic respiratory failure can usually be treated successfully with supplemental oxygen. The goal of mechanical ventilatory support is to increase alveolar ventilation sufficiently to sustain life and permit treatment of the underlying cause of hypercapnic respiratory failure.

General Principles

Because clearance of secretions from small airways by endotracheal suctioning is less effective than cough, all possible measures should be instituted to limit the duration of intubation and thereby prevent irreversible "impaction" of secretions and loss of lung function. Particular attention should be paid to correcting any acute or reversible components of respiratory failure, and the usual regimen of care for CF lung disease must be intensified. This includes use of frequent (every 1-4 hours) and aggressive chest physical therapy and other techniques to clear airway secretions. Bronchoscopy is occasionally useful to diagnose and treat central mucous plugging, but is not usually beneficial for clearing secretions from small airways. Parenteral antibiotics should be used intensively, with multiple drugs and high doses. Parenteral bronchodilators and/or corticosteroids should be considered for bronchospasm/mucosal edema unless contraindicated; for example, corticosteroids may be contraindicated in lung transplant candidates. Maintenance of adequate nutrition is essential, and must be balanced with the associated increase in CO_2 production.

In contrast to some patients with severe COPD or status asthmaticus, sedation and paralysis to reduce CO_2 production are not generally appropriate; sedation should be minimized. CF patients should exercise respiratory and skeletal muscles, even walking (while intubated) with Ambu-bag assisted ventilation. Aggressive therapy to reduce production of and to remove airway secretions should be rapidly instituted. Rapid treatment of reversible etiologic factors and early extubation is essential, since prolonged positive pressure ventilation tends to worsen small airways obstruction and reduces the likelihood of successful extubation.

Techniques

Positive pressure ventilation through cuffed endotracheal tubes is the current standard of care for hypercapnic respiratory failure. Negative pressure ventilatory devices have not been effective in CF, in part because of their interference with chest physiotherapy. The endotracheal tube should be as large as possible to permit adequate suctioning and, occasionally, bronchoscopy. Tracheostomy generally is not necessary, and may compromise candidacy for lung transplantation in some patients. Many volume- and pressure-limited ventilator modes and waveforms are available on positive pressure mechanical ventilators. The modes selected must be adapted to the individual patient and situation. However, some general principles apply in virtually all situations:

1) Ventilatory modes that permit and encourage patient use of respiratory muscles (e.g., pressure support ventilation) are more useful for adults and children.

2) Waveform and inspiratory flow rate must be adjusted to allow adequate expiratory time and to minimize the additional air-trapping that may occur in patients with obstructive lung disease.

3) Maximal and mean airway pressures should be minimized because of the high incidence of pneumothorax in CF patients. The benefits of continuous or expiratory positive airway pressure to maintain airway patency and improve clearance of secretions during expiration are unproven, and their use must be tailored to the individual case.

4) It is essential to maximize intensity of therapy, and attempt to minimize time on mechanical positive pressure ventilation, since this type of ventilation makes clearance of small airways secretions particularly difficult. Most CF patients demonstrate gradual deterioration of lung function while on positive pressure ventilation.

Use of tight-fitting face masks or nasal masks to provide positive airway pressure or assisted ventilation may be an alternative technique to treat hypercapnic respiratory failure in selected individu-

als, and may permit more effective clearance of airway secretions. These techniques may improve alveolar ventilation by stenting airways open during expiration, and by providing mechanical assistance for weak or fatigued respiratory muscles. These masks can be used to provide continuous or cycled positive airway pressure, and can be removed transiently to permit coughing and physical therapy to assist in clearance of airway secretions. Preliminary reports are promising,[61,62] but controlled studies have not been carried out. The general principles outlined above for care of hypercapnic respiratory failure are applicable to face/nasal mask ventilators. The relative benefits and complications of nocturnal or intermittent mask ventilation have not been established.

Summary

Respiratory failure in CF can be summarized as follows:

1) Initial treatment of respiratory failure in CF patients should be an intensification of the usual therapeutic maneuvers employed to treat CF lung disease, i.e., intensive maneuvers to remove airway secretions, aggressive antibacterial therapy, adequate nutrition, and a search for other contributing etiologies such as bronchospasm.

2) Supplemental oxygen is the treatment of choice for hypoxic respiratory failure refractory to intensification of the usual therapeutic regimens. For patients exhibiting daytime hypoxemia, i.e., PaO_2 < 55 torr, continuous supplemental oxygen is mandatory to limit the development of pulmonary hypertension (cor pulmonale) and right heart failure. Oxygen supplementation may need to be increased at night or during exercise.

3) The prevalence of nocturnal hypoxia in CF patients who have adequate daytime oxygenation is not well defined, but patients with an oxygen saturation of < 92 percent while awake may merit study by oximetry for the possibility of nocturnal hypoxemia. Patients who exhibit evidence of pulmonary hypertension or right heart failure should also be assessed for nocturnal hypoxemia. Nocturnal oxygen supplementation in appropriate patients improves functional well-being and reduces the frequency of hospital admissions.

4) If oxygen therapy is instituted in an effective manner, there is little role for diuretics, digitalis, or pulmonary vasodilators for the treatment of hypoxic respiratory failure in CF patients.

5) Infants and older patients with potentially reversible respiratory failure, due to acute illness or suboptimal therapy, should be afforded mechanical ventilatory support by standard techniques employing specific principles pertinent to CF patients (see above, Methods: Ventilatory Support).

6) CF patients on a waiting list for lung transplantation occasionally may be afforded ventilatory support while awaiting a lung donor; the method of assisted ventilation will depend on clinical circumstances. This situation requires consideration of the likelihood of successful transplantation in patients undergoing mechanical ventilation, and the distribution of limited resources, i.e., donor lungs, among the list of transplant candidates.

7) CF patients with progressive respiratory failure who are not transplant candidates and who have been aggressively treated with standard therapy in a CF Center should be advised that mechanical ventilation is unlikely to provide long-term benefit.

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Table 1. Unpublished Data from a Retrospective Review of Treatment of Pneumothorax in 192 Patients. Denning et al, 1991.

Treatment	*Success*	
Open thoracotomy	50/52	(96%)
Quinacrine Sclerosis	31/35	(89%)
Tetracycline Sclerosis	21/36	(58%)

Table 2. Hypoxemic Respiratory Failure: Guidelines for Oxygen Therapy

*Daytime, breathing room air:

$PaO_2 < 55$ torr

or

$PaO_2 < 59$ torr, plus one of the following:
a) Edema

b) Hematocrit > 55%

c) p- Pulmonale on EKG

Nocturnal: oxygen saturation < 88-90% for > 10% of total sleep time.

Exercise: Hemoglobin O_2 saturation < 88-90%.

*Used by third-party payers for reimbursement.[42]

Table 3. Hypercapnic Respiratory Failure: Guidelines for Assisted Ventilation

INDICATED	Infants (most cases)
	Reversible or potentially reversible complications
	Pneumothorax
	Bronchospastic obstruction
	Central mucous plugging
	Suboptimal therapeutic regimen
POSSIBLE	Patients accepted as lung transplant candidates
NOT INDICATED	Progressive respiratory failure, unresponsive to intensive standard therapy

FIGURE 1

Management of Small Pneumothorax

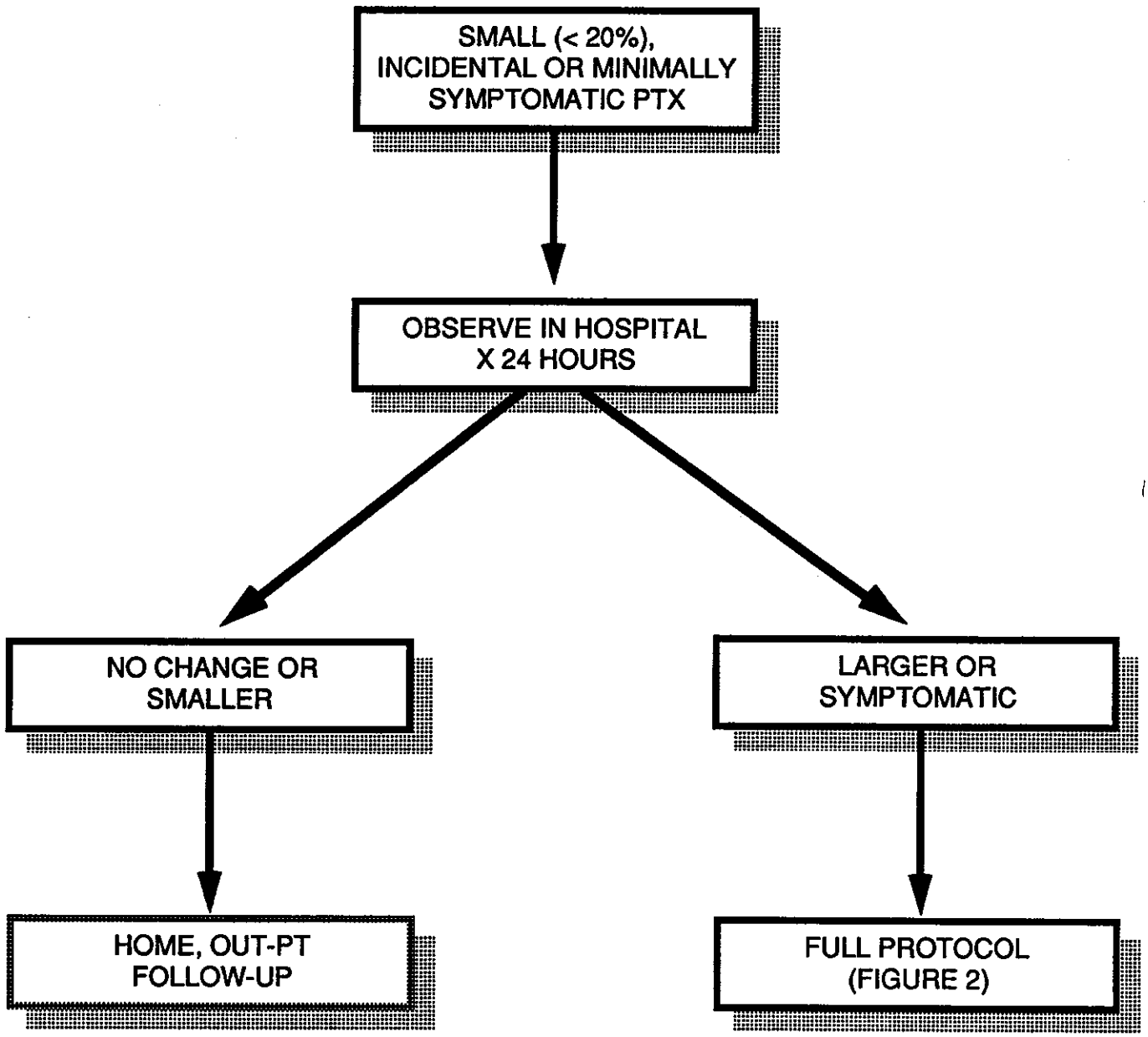

FIGURE 2

Management of Large Pneumothorax

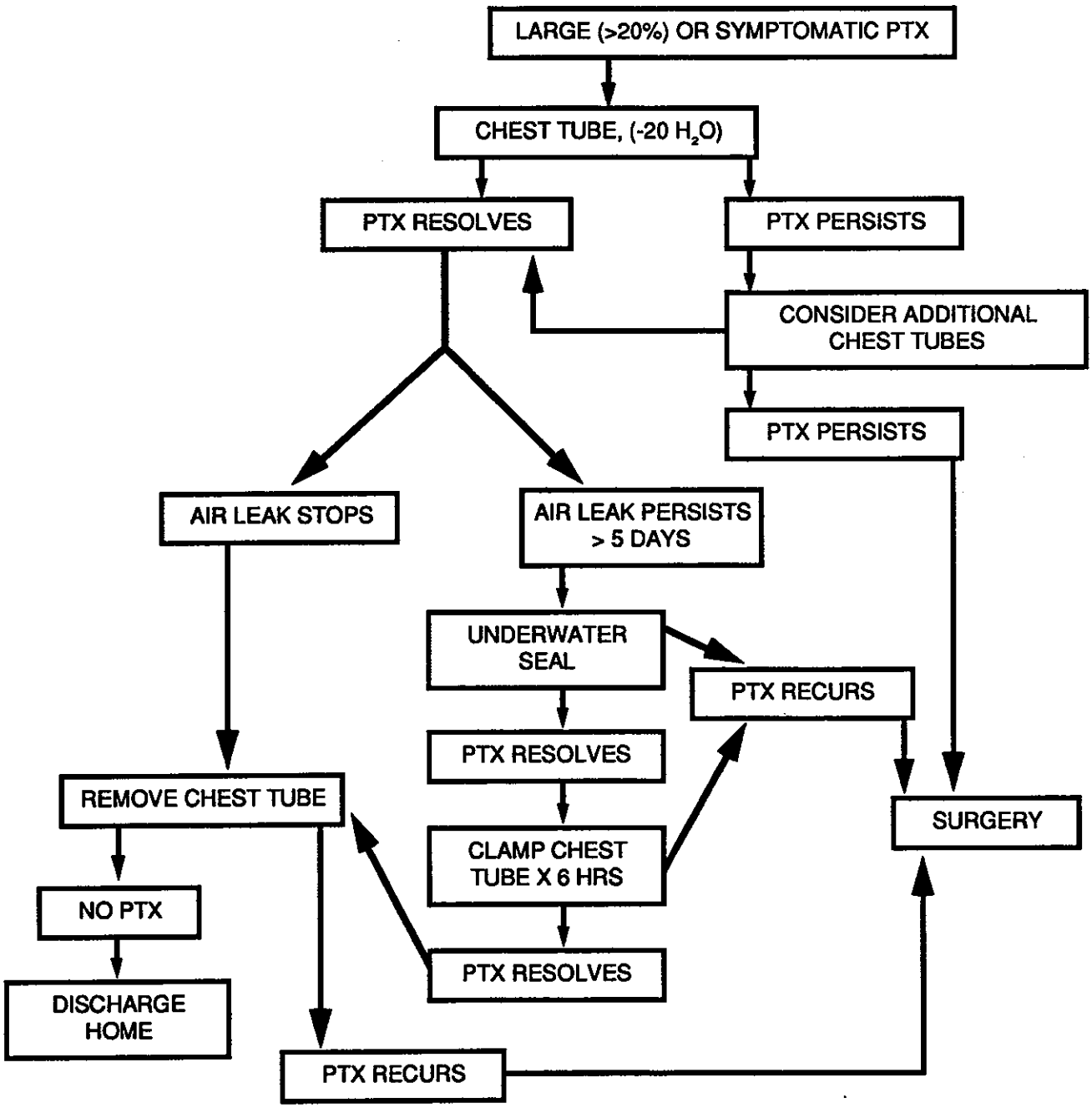

FIGURE 3

Major Pathophysiologic Derangements Associated with Hypoxemic and Hypercapnic Respiratory Failure in Cystic Fibrosis