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With advances in medical science, patients with serious congenital diseases are living into adulthood. A previous issue of Emergency Medicine Reports *dealt with adults with congenital heart disease. This issue deals with another group of survivors, those who have survived with cystic fibrosis. Where once patients died in infancy, patients now live into their 40s. Although many of the standard treatments for COPD apply to cystic fibrosis, there are specific differences in management, which this monograph highlights.*

—Sandra M. Schneider, MD, FACEP, Editor

Emergency Department Care of Adult Cystic Fibrosis Patients

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Introduction

A 19-year-old Caucasian male who was diagnosed with cystic fibrosis as a child presents to the emergency department in respiratory distress. His parents are at his bedside. The patient is thin, pale, chronically ill-appearing, and is in moderate distress with coughing and mild wheezing. His blood pressure is 110/60 mm Hg, heart rate 120, respiratory rate 48, temperature 99.5°F, and oxygen saturation 88% on 15 liters oxygen. The patient tells you that he was just discharged from the hospital last week and does not want to be readmitted or intubated. He says he is tired of being sick. His distraught parents are at his bedside and are asking you to do everything possible to help their son. What can you do? What should you do?

Overview

'The child will soon die whose forehead tastes salty when kissed," appeared in an 1857 Almanac of Children's Songs and Games from Switzerland 100 years before the sweat test was first used in the 1950s to help diagnose cystic fibrosis (CF), a disease that is characterized by abnormal salt transport, and, in previous years, death in infancy. Cystic fibrosis (CF) was first described as a disease entity in 1938.[1,2]

The important developments of the past few decades in cystic fibrosis care have led to the tremendous growth of the adult CF

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population. Cystic fibrosis has classically been defined as a pediatric disease since, at the time of discovery, it was invariably fatal in infancy, and in the 1950s median survival was 6 months. The median predicted survival was 16 years in 1970s. For patients born in the 1990s, median survival is predicted to be over 40 years.[3,4] More than 36% of patients in the U.S. Cystic Fibrosis Registry are 18 years of age or older.[5] Advances in medications and overall aggressive approach to the disease have led to this. Improved patient outcomes have been associated with comprehensive CF care centers and a multidisciplinary approach to patient care.[1]

Genetics and Epidemiology

Although there are reports dating from the 1650s of infants who likely had CF, the first report identifying the disease as a distinct clinical entity was published in 1938 by Dorothy Hansine Andersen, a pathologist at the Babies' Hospital in New York.[2] She reported mucus plugging of the ducts of the pancreas in infants dying of malnutrition. She also first hypothesized that CF is a recessive disease. During the 1948 heat wave in New York, Paul di Sant'Agnese recognized that many of the infants presenting to the emergency department with heat-related illness and hyponatremic dehydration had CF. In subsequent summers, he determined that these patients had abnormally high sodium and chloride content in their sweat. In 1953, Dr. di Sant'Agnese and a colleague developed the sweat test, which measures for abnormal chloride levels in perspiration and, in 1959, standardization of the sweat test established this as the gold standard of CF diagnosis. In 1983, chloride transport was identified as the basic physiologic CF defect, accompanied by increased sodium reabsorption. In 1989, the discovery of the CF gene demonstrated the basic defect to be in a cAMP-regulated chloride channel.[6,7]

The CF trait results from a mutation of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) found on chromosome 7. Most homozygotes for the disease have the classic triad of chronic pulmonary disease, malabsorption secondary to pancreatic insufficiency, and elevated concentration of sweat electrolytes. Although this disease affects multiple organ systems and varies greatly in severity and progression, most morbidity and over 90% of mortality results from chronic lung disease.[3]

Cystic fibrosis is the most common lethal inherited disease among Caucasians in the United States with an incidence of 1 in 2000-3000 whites affected. About 1 in 20-25 whites carry mutations of the CFTR gene. African Americans are affected at a rate of 1 in 15,000 and Asian Americans at 1 in 31,000. All together, approximately 30,000 children and adults have CF in the United States. Cystic fibrosis is diagnosed in males and females equally. For unclear reasons, males tend to have a longer life expectancy than females.[1]

Pathophysiology

The CFTR is located in the apical membrane of epithelium in the pulmonary airways, pancreatic duct, intestine, biliary ducts, and the sweat glands. The CFTR protein crosses the membranes and acts as a channel connecting cytoplasm to the surrounding fluid. This channel is the primary means for controlling the movement of chloride across the cell membrane. The CF phenotype is expressed when the patient inherits two copies of the defective gene that encodes the CFTR protein. The most common mutation associated with CF is the deletion of three base pairs that code for phenylalanine at position F508 in the 1480 amino acid sequence of the CFTR protein.[8] Once the deletion occurs, the mutant protein does not fold properly, so it is degraded. The exocrine glands are primarily affected because a lack of CFTR gene encoded transport proteins leads to the trapping of chloride inside the cells of the glands and on the surface of the skin. Without enough functional copies of the CFTR protein in their cell membranes, epithelial cells cannot pump enough water into the mucus and other products they secrete. Therefore, the secretions are too dry, thick, and sticky and they obstruct the small airways of the lungs and ducts of various organs. The abnormally viscous mucous secretions create a nutrient rich environment that is protected from the host immune system. This leads to chronic infection, inflammation, or both and eventually leads to tissue destruction and remodeling, resulting in bronchiectasis.[8] Bronchiectasis refers to localized, irreversible dilatation of bronchi. Involved bronchi are dilated, inflamed, and

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Table 1. States that Have Newborn Screening Programs for CF[5]

Alabama	Maryland	Ohio
Alaska	Massachusetts	Oklahoma
Arizona	Michigan	Oregon
California	Minnesota	Pennsylvania
Colorado	Missouri	Rhode Island
Connecticut	Mississippi	South Carolina
Delaware	Montana	South Dakota
District of Columbia	Nebraska	Virginia
Florida	New Hampshire	Washington
Georgia	New Jersey	Wisconsin
Illinois	New Mexico	Wyoming
Iowa	New York	
Kentucky	North Dakota	

easily collapsible, resulting in airflow obstruction and impaired clearance of secretions.

Diagnosis

Although diagnosis through DNA analysis is becoming a standard of care in CF, the sweat test is still the diagnostic gold standard. It is the only method of diagnosis recognized by the Cystic Fibrosis Foundation as an adequate test for definitive diagnosis of CF.[5] The test involves collection of sweat by pilocarpine iontophoresis coupled with chemical determination of the chloride concentration.[9,10] At least 50 mL of sweat must be collected in a 30-minute period. Using a chloride threshold of 60 mEq/L in sweat appears to distinguish nearly all adults with CF from those with other lung conditions.[11] However, normal values of sweat chloride do rise with age, so higher levels may be considered normal in some patients. One to two percent of patients have clinical features consistent with CF but have normal sweat chloride levels. These patients can be diagnosed by detecting mutations in the CF gene.[6]

Clinical Presentation

CF runs a highly varied course, ranging from death due to complications from meconium ileus in the first days of life or death from severe respiratory tract problems within the first few months of life to minimally symptomatic course for 10 to 20 years and extended survival. An increasing number of patients with CF live into the sixth and seventh decades of life.[6,7,12]

Cough is usually the earliest symptom and is usually worse at night. At first it is intermittent and occurs with what appears to be an acute respiratory illness. The coughing is sometimes accompanied by wheezing, especially in infants and young children. Episodes of coughing persist longer than expected for a routine respiratory illness and occur more frequently with time. As the disease progresses, the cough becomes productive of thick purulent sputum. Symptoms consistent with bronchitis may occur for several years before diagnosis. Eventually the exacerbations of productive cough are accompanied by dyspnea, anorexia, and weight loss. Physical findings depend on the stage of the disease. At first crackles are intermittent and occur with exacerbations. Lung sounds may be decreased because of hyperinflation. As the disease progresses, rales and rhonchi are common and continuous.[8] The majority of adults with CF die of respiratory failure.

Patients who have not yet been diagnosed with CF may initially be seen at any age and can present with a variety of complaints. Many symptoms can mimic those found in a variety of other diseases. Failure to thrive and a history of chronic respiratory, and/or gastrointestinal problems are the most common symptoms in children. A child may have persistent cough or recurrent pneumonia and atelectasis. Atypical asthmatics with digital clubbing (which occurs in nearly all patients with CF), bronchiectasis, or cough producing sputum may potentially have CF. Undiagnosed cystic fibrosis patients may have been seen in the emergency department or primary care physician's office multiple times for respiratory or GI complaints, yet the diagnosis remains elusive. CF won't be diagnosed in patients with mild disease or older patients unless someone puts the pieces together and refers the patient for testing. This is an important role for the emergency physician.

Patients diagnosed with CF as adults usually present with chronic respiratory problems. As a group, they have milder lung disease, less Pseudomonal infection, and are more likely to be pancreatic-sufficient than patients diagnosed at an earlier age.[13-15] Adult patients come to attention with atypical presentations such as chronic/recurrent pancreatitis, recurrent pneumonia, or bronchitis.[3,16-18]

A newborn may have a meconium ileus while older children and adults can present with frequent passage of pale, bulky, loose, and excessively foul-smelling stool that is characteristic of CF. Young patients are often misdiagnosed as having milk allergy or chronic diarrhea and may have tried multiple different formula preparations. Edema and hyponatremia may develop in children with CF, especially those taking a soy protein formula. Bleeding problems resulting from vitamin K malabsorption may be seen. Many patients presenting with less severe symptoms may not require emergency treatment at all. These patients, however, must be referred for further diagnostic evaluation if the suspicion of CF is high.

Pulmonary Disease. Changes consistent with airway obstruction appear first in the small airways along with evidence of airway hyperactivity. Arterial oxygenation decreases with time. As the disease progresses, untreated hypoxemia and progressive loss of functional lung may produce pulmonary artery hypertension and right ventricular failure (cor pulmonale). Hypercarbia and chronic respiratory acidosis are apparent in late stage disease. Respiratory failure becomes increasingly difficult to manage at this point.

The lung function in adults with CF is highly variable. FEV1 expressed as the percentage predicted of a healthy nonsmoking reference population is accepted as the single most useful objective measure of pulmonary status.[19] Thirty-six percent of adults with CF have normal or mild lung dysfunction (FEV1 > 70% predicted). Thirty-nine percent have moderate dysfunction

Table 2. Phenotypic Features Consistent with the Diagnosis of Cystic Fibrosis[6]

Chronic Sinopulmonary Disease
- Persistent colonization/infection with typical CF pathogens (*S. aureus*, nontypable *H. influenzae*, mucoid and nonmucoid *P. aeruginosa,* and *B. cepacia*)
- Chronic cough with sputum production
- Persistent chest radiograph abnormalities (i.e., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Airway obstruction (wheezing, air trapping)
- Nasal polyps and CT abnormalities of the paranasal sinuses
- Digital clubbing

GI and Nutritional Abnormalities
- Intestinal: DIOS and rectal prolapse
- Pancreatic: pancreatic insufficiency and recurrent pancreatitis
- Hepatic: focal or multinodular cirrhosis
- Nutritional: failure to thrive, hypoprotenemia, edema

Salt Loss Syndromes
- Acute salt depletion and chronic metabolic alkalosis

Male Genitourinary Abnormalities and Obstructive Azoospermia

Table 3. Complication Rates in CF Patients: Adults and Children[23]

COMPLICATION	ADULT %	CHILDREN%
P. aeruginosa colonization	79	47
Ciprofloxacin resistance	22	4
Tobramycin resistance	15	6
B. cepacia colonization	6	2
Massive hemoptysis	1.8	0.1
Pneumothorax	1.4	0.2
Require continuous O2	6	1
CFRD requiring insulin	16	2.5

(FEV1 < 40% to 69%). The remainder have severe dysfunction (FEV1 < 40% predicted).[3]

The lungs of CF patients are colonized and infected by bacteria from an early age. *Pseudomonas aeruginosa* is the most common pathogen, infecting most of the CF population.[20] In fact, persistent bacterial pulmonary infection, especially with *Pseudomonas aeruginosa*, is the hallmark of CF. The mucoid strains of Pseudomonas are associated with more rapid clinical deterioration. Although mucoid *P. aeruginosa* is occasionally cultured from patients with other lung diseases, its presence in the sputum should immediately alert the physician to the possibility of cystic fibrosis. Other common pathogens encountered include *S. aureus*, *H. influenzae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia,* and non-tuberculous mycobacteria.[21] As the disease progresses, infection with antibiotic resistant bacteria and concomitant infection with more than one organism are likely.[8] *Burkholderia cepacia* is a multiple resistant gram negative organism that carries the worst prognosis. Some patients who develop a sepsis-like syndrome with severe necrotizing pneumonia called cepacia syndrome have rapid deterioration and death.[1]

The most frequent fungal infection seen is Candida, affecting 50-70% of patients. Aspergillus is isolated from 25% of patients and can be associated with significant allergic manifestations such as wheezing, pulmonary infiltrates, and worsening of bronchiectasis and fibrosis.[22] More than 50% patients have antibodies to *Aspergillus fumigatus*, but only a small percentage develop allergic bronchopulmonary aspergillosis. This is characterized by rusty brown sputum plugs.[8]

These organisms, which often spread among individuals with CF, thrive in the altered mucus in the small airways of the lungs. This mucus encourages the development of bacterial microenvironments called biofilms that are difficult for immune cells and antibiotics to penetrate. CF disease progresses from bronchiolitis at a young age to bronchitis and eventually bronchiectasis as a consequence of persistent obstruction and inflammation. Bronchiectatic cysts are prominent in 50% of lungs in end stage patients and may contribute to the 3-19% reported incidence of pneumothorax.[1,8]

In general, adults with CF have more severe pulmonary disease than children. Adults are at higher risk for serious complications such as pneumothorax and massive hemoptysis.

Chronic airway infection leads to significant, persistent neutrophilic inflammatory response that destroys small airways, leading to bronchiectasis. Angiogenesis in areas of intense inflammation predisposes patients to hemoptysis, which occurs in about 3% of adult patients per year. Hemoptysis, which usually presents as blood-streaked sputum, becomes more common as bronchiectasis develops. Significant hemoptysis is 30-60 cc of blood and is due to the erosion of an area of local bronchial infection or bronchiectasis compromising a bronchial vessel. Hemoptysis is usually self-limited, but embolization or lobectomy may be required in severe cases.[1] Hemoptysis may require supplemental vitamin K if the prothrombin time is prolonged due to inadequate absorption.[24]

Pneumothorax is a well-known complication whose incidence increases with age. Sixteen to 20% of CF adults have a pneumothorax at some point, often as the result of rupture of a subpleural bleb. The patient usually presents with chest pain, dyspnea, and hemoptysis. CF patients with a pneumothorax of greater than 10% should be treated with a tube thoracostomy as 30% of these patients are reported to experience a tension pneumothorax.[1,8]

Additional diagnoses such as asthma, allergic bronchopulmonary aspergillosis, sinus disease, and gastroesophageal reflux should be considered in patients whose clinical course of respiratory decompensation or response to treatment are atypical for CF.

Loss of CFTR function also affects the upper airway epithelium, so chronic rhinitis is common. The sinuses are universally involved but acute/chronic sinusitis is uncommon.

Cardiac Disease. Patients with CF who have moderately severe pulmonary insufficiency and some degree of hypoxia will eventually develop right ventricular hypertrophy secondary to pulmonary hypertension (cor pulmonale). Increased hypoxia dur-

ing an exacerbation of pulmonary symptoms in such patients may precipitate an episode of congestive heart failure. In addition to cyanosis, tachypnea, and tachycardia, other associated symptoms may include an enlarged, tender liver and ascites.[25]

Gastrointestinal Disease. Failure to secrete enough chloride and fluid in the intestine leads to reduced water content of the fecal stream, which results in meconium ileus in many infants with CF. The abnormal intestinal mucus in CF patients leads to a decrease in mobility that, combined with a decreased amount of abnormal pancreatic and biliary secretions, results in a dry, thick stool that cannot pass from the terminal ileum to the cecum. This may cause recurrent abdominal pain, obstruction, volvulus, or intussusception. In older patients, distal intestinal obstruction syndrome or "meconium ileus equivalent" can produce intermittent recurrent episodes of partial small bowel obstruction in 15% of patients and may lead to complete obstruction.[1] Distal intestinal obstruction syndrome can be relieved with intestinal "flushes" with a balanced salt solution of 1-2 liters instilled into the stomach. Rectal prolapse may be seen in adults and can usually be reduced voluntarily by using abdominal, perianal, and gluteal muscles.[6]

Gastroesophageal reflux disease (GERD) is common in CF patients, and is seen in more than 20%.[26] Many factors contribute, such as head down position for airway clearance, medications that decrease lower esophageal sphincter tone, and hyperexpansion of the lung that flattens the diaphragm and impairs the physiologic sphincter.[27]

Destruction and loss of pancreas function occurs at birth or in early infancy. Exocrine pancreas disease affects most CF patients; 91% are on pancreatic replacement therapy.[27,28] Obstruction of the ducts, loss of acinar cells, and pancreatic enzyme deficiency leads to malabsorption of protein, fat, and fat-soluble vitamins. This leads to bulky, foul-smelling stool and weight loss.[8] Abnormal CFTR function in the ducts of the pancreas causes a decreased volume of secretions with reduced bicarbonate concentration. Autoactivation of retained digestive proenzymes leads to destruction of pancreatic tissue. Consequently, absorption of fat soluble vitamins A,D,E, and K is reduced. The presence of pancreatic insufficiency portends a worse overall prognosis.

Symptoms of pancreatitis occur in a small percentage of adolescents and adults, especially in those who have retained pancreatic function. There is a strong association between idiopathic pancreatitis and having one CFTR mutation.[29] Although the Islets of Langerhans are relatively spared, destruction of the pancreas can cause endocrine pancreatic dysfunction leading to diabetes. This rarely develops before the age of 10 and usually manifests after the second decade of life. The prevalence of CF-related diabetes increases with age from 9% (age 5-9) to 43% for patients over 30 years of age.[30] Hyperglycemia can occur at any age but is generally a problem of the second and third decades of life.[31] Diabetic ketoacidosis is rare in CF-related diabetes. Most patients with sustained hyperglycemia require insulin, but oral agents may work in some patients.

Liver disease is the second most common cause of death in CF patients.[28] Many CF patients have some form of liver or biliary disease.[8] This may manifest as elevated transaminases, hepatosteatosis, or gall stones. Frank liver disease with cirrhosis and liver failure can occur in childhood and is progressive. As patients are living longer, chronic obstruction of the ducts may lead to liver damage and biliary cirrhosis. Hematemesis is a severe complication that may develop from esophageal varices due to portal hypertension. The severity of liver disease varies widely from mild elevation of alkaline phosphatase in many patients to hepatomegaly and persistently elevated liver enzymes to jaundice, ascites, and edema in severe cases. However, few patients develop clinical cirrhosis. Thirty percent of adult CF patients have a hypoplastic, poorly functioning gallbladder and may develop gallstones.[1,3]

There is an increased risk of Crohn's disease by 12-fold in CF patients over the general population as well as a 6-fold increase risk of malignancy.[32,33]

Genitourinary Disease. Atrophy of the Wolffian duct structures is almost universal in CF patients. Ninety-five percent of young men with CF are infertile because of bilateral absence of the vas deferens, abnormalities of the seminal vesicle, or both.[34] It is believed that the vas deferens becomes occluded during gestation and is reabsorbed. Spermatogenesis is retained, however, and retrieval of sperm for in vitro fertilization can be performed. Females with CF have decreased fertility because of thick secretions at the cervical os and poor nutritional status.[34-36]

Emergency Department Evaluation and Treatment

Radiographs. Hyperinflation is often the earliest change seen on chest radiograph. Subsequent peribronchial thickening creates peribronchial cuffing. As the disease progresses, mucus impaction and bronchiectasis are seen as well as variable amounts of fluffy infiltrates. The right upper lobe is usually the first and most severely involved. Widespread bronchiectasis may be seen on CT before it appears on plain chest radiographs.[8]

A chest radiograph is indicated for patients with suspicion for an acute complication, such as pneumonia or pneumothorax. Comparison to old films is important to note acute changes. Chest CT is indicated for patients presenting with complications such as loculated pleural effusions, lung abscess, or other potentially surgical problems.

Laboratory evaluation is complaint-specific may include complete blood count, basic metabolic panel, transaminases, coagulation studies, and arterial blood gases.

The cornerstones of emergency treatment in CF are similar in adults and children. This includes oxygen, airway support, antibiotic treatment (acute, chronic, or suppressive), airway clearance, mucolytic therapy, anti-inflammatory agents, and bronchodilators.

Oxygen. Supplemental oxygen should be used as needed to maintain adequate oxygenation in the acute setting. Supplemental oxygen in accordance with the guidelines established for chronic COPD is recommended.[37,38] The most important chronic therapy for the prevention of pulmonary hypertension is supplemental oxygen.

Antibiotics. Pulmonary exacerbations are common in adults with CF and usually are associated with bacterial infections. There is evidence that early, aggressive use of antibiotics in decompensated CF patients produces better results than delaying the administration of antibiotics until symptoms are well developed or advanced.[39] The choice of antibiotics and the use of single or combined therapy are controversial areas in the treatment of respiratory infection in CF. A recent Cochrane review investigated single vs. combination intravenous antibiotic therapy for CF patients. The results were inconclusive due to multiple trials, variable antibiotic choices, and significant methodological issues.[40]

Although *P. aeruginosa* is rarely eradicated once it becomes chronic, an important benefit is gained by decreasing the net bacterial load with intensive parenteral antibiotics. As the number of organisms decreases, airway inflammation is reduced, thus decreasing the airway destruction and the airway symptoms. Azithromycin has no direct killing effect against Pseudomonas but it can adversely affect Pseudomonas virulence factors and it is active against *H. influenzae* and *S. aureus*.[41] There is evidence that the macrolides demonstrate acute inflammatory effects such as modulation of signaling pathways, inhibition of proinflammatory cytokines, limiting influx of neutrophils to the lung, mucus secretion, and altering the formation of the biofilm matrix.[41-43]

Long-term macrolide antibiotics effectively treat diffuse panbronchiolitis and produce clinical improvement in patients chronically infected with Pseudomonas. Azithromycin has been shown in 4 randomized controlled trials to improve lung function and reduce the frequency of pulmonary exacerbations,[42,44-46] even prior to infection with Pseudomonas.

Antibiotics are selected on the basis of recent sputum cultures, if available, although this is not often the case in the emergency department. Therapy with fluoroquinolones is often used for mild to moderate exacerbations in adults. Two antipseudomonal antibiotics are used in combination (ie. Beta lactam and aminoglycoside) for the treatment of moderate to severe exacerbations.[3] (*See Table 4 for suggested antibiotic regimens*.)

Aminoglycosides have been the mainstay of anti-Pseudomonas therapy for many years and may still have a role in some patients. A major advantage is the ability to monitor and adjust blood levels. Disadvantages include oto- and nephrotoxicity. A drug like gentamycin or tobramycin is usually paired with one of the penicillin derivatives or with ceftazidime.[26] Clearance of aminoglycosides by the kidney is increased in CF. The required doses are often two to three times higher than in non-CF patients.[8]

Inhalation antibiotics are attractive because high concentrations can be attained at the airway surface and in mucus, thereby minimizing systemic toxicity. Aerosolized high-dose tobramycin (TOBI) can reduce the density of *P. aeruginosa*, improve FEV1, and reduce length of hospitalization.[47]

Chronic suppressive antibiotic therapy is increasingly becoming a standard part of care.

Aerosolized tobramycin is the most thoroughly studied chronic suppressive therapy. In two large double blind placebo controlled trials, treatment with TOBI was found to produce significant improvement in pulmonary function, to decrease the density of *P. aeruginosa* in the sputum, and to decrease the number of days the patients were hospitalized.[45] Chronic, continuous, low-dose azithromycin also improves lung function and reduces the frequency of exacerbations.[48,49]

CF patients require higher doses of antibiotics and shorter dosing intervals. In general, the highest recommended doses are given to achieve penetration into the respiratory secretions. Both total body clearance and volume of distribution are considerably greater for CF patients than other patients.[50] In addition, large doses are needed to achieve therapeutic levels in the infected and mucus- or pus-filled endobronchial space. Longer courses of 2-4 weeks of antibiotics are often used.

Chest Physiotherapy. Excessive bronchial secretions contribute to the airway obstruction in CF, which leads to atelectasis and hyperinflation. For 40 years, chest physiotherapy (CPT) was the major airway clearance strategy in CF. The goal of CPT is to improve pulmonary status and prolong survival via removal of tenacious bronchial secretions, reduce airway resistance, and improve ventilation over the short term.[51] Chest PT facilitates loosening and expectoration of mucus. CPT is often initiated in asymptomatic patients to try to slow the progression of the disease.

The most compelling argument for the use of postural drainage with chest percussion (based on the concept that cough clears mucus from large airways but chest vibrations are necessary to move secretions from the small airways where expiratory flow rates are low) comes from a study of older children with mild-moderate airflow limitation.[52] When patients were receiving CPT on a regular basis, the only immediate effect was an increase in peak expiratory flow rate 30 minutes after therapy. However, after 3 weeks without CPT, both functional vital capacity (FVC) and flow rates were significantly reduced. A meta-analysis of 35 studies concluded that standard CPT increases sputum production and improves expiratory airflow (FEV1).[39]

A widely used device for chest compression therapy is called the vest. It is a chest wall compression and oscillation system that is composed of a fitted vest and oscillation system coupled to a pneumatic compressor. Therapy is delivered to the entire chest at the same time with the patient in a seated position. This allows for the administration of nebulized medications during therapy and also affords independence to the patient.[3]

CPT may be utilized as part of acute therapy in the emergency department. This may be performed by a respiratory therapist or trained family member.

Bronchodilators. The majority of CF patients have bronchial hyperreactivity/bronchospasm at least some of the time.[42] Bronchodilators are a standard component of the therapeutic regimen, and most emergency physicians are very familiar with the use of these medications. They are often used in conjunction with CPT to facilitate airway clearance. There is some evidence that maintenance albuterol reverses the progressive downhill course in lung function in CF patients.[53-55]

Table 4. Antibiotics Used to Treat Pulmonary Exacerbations in Cystic Fibrosis Patients[6,64]

(Route of administration is intravenous unless noted)

AGENT	DOSE	
	Children	**Adults**
Piperacillin/Tazobactam	300 mg/kg/d divided q6 (max 24 g/day)	2-4 g q6
	OR	
Ticarcillin/Clavulanate	200-300 mg/kg/d divided q4-6	1-4 g q4-6
	OR	
Ceftazidime	200 mg/kg/d divided q6	250 mg-2 g q8-12
	OR	
Cefepime	50 mg/kg/d divided q8	2 g q12
	OR	
Aztreonam	50 mg/kg/dose q6-8	2 g q8-6
	OR	
Imipenem/Cilastatin	45-60 mg/kg/dose q6	same as peds
	OR	
Meropenem	40 mg/kg/dose q8	2 g q8
	OR	
Aztreonam	300 mg/kg/day divided q6-12 (max 12 g/day)	same as peds
	PLUS	
Ciprofloxacin	20-30 mg/kg/d divided q8*¶	250-750 mg q12¶
	OR	
Gentamycin	3 mg/kg/dose q8	3 mg/kg/dose q8
	OR	
Tobramycin	3 mg/kg/dose q8	3 mg/kg/dose q8
Inhaled tobramycin		300 mg via jet nebulizer q12
If MRSA is suspected, add:		
Vancomycin	15 mg/kg/dose q8-12	same as peds
	OR	
Linezolid	10 mg/kg/dose q12†	600 mg q12†

* Not the preferred agent for pediatric patients but can be used in certain situations
¶ Route of administration is PO or IV
† Route of administration is PO

Anticholinergic bronchodilators may be helpful in some patients with CF. Ipratropium may be more effective than beta agonists in adults with CF. Adults often have less bronchospasm, but more secretions than children. The airway of the adult CF patient may closely mimic that of the adult with chronic bronchitis and, therefore, may be more responsive to the effects of a parasympathomimetic agent. Combination therapy with a beta agonist may also be effective.[56-58]

Hypertonic Saline. The excessive absorption of salt from the airway lumen of CF patients carries water with it, dehydrating airway mucus secretions and depleting the volume of liquid on the airway surface. These changes disrupt the mucociliary mechanism, and the retained mucus becomes a nidus for chronic infection.[59] Therefore it is hypothesized that the use of hypertonic saline should be helpful in CF patients.

Over the short term, hypertonic saline (HS) improves the transportability of sputum and hydration of the airway surface[60,61] and mucociliary clearance and lung function[62,63] in patients with CF. Treatment with hypertonic saline for one year had no significant effect on the rate of decline in lung function, but it was associated with a moderate yet sustained improvement in the level of lung function. More dramatic were the reductions in the number of exacerbations, antibiotic use for exacerbations, and absenteeism from school/work.[59]

In a double blind study of 164 patients 6 years old or older with stable CF, patients inhaled 7% saline or normal saline twice a day for 48 weeks. The hypertonic group had significantly higher functional vital capacity (FVC) (by 82 cc, 95% CI 12-153) and FEV1 (by 68 cc, 95% CI 3-132). In addition, the hypertonic saline group had fewer pulmonary exacerbations (relative reduc-

tion of 56%, p = 0.02) and a higher percentage of patients without exacerbations (76% vs 62%, p = 0.03).[59]

Hypertonic saline, usually preceded by a bronchodilator, is inexpensive, safe, and effective therapy for patients with CF and can safely be used as part of the treatment in the emergency department.

Mucoactive Therapies. The most characteristic feature of inflammation in the lung is the persistent infiltration of massive numbers of neutrophils into the airway. Although neutrophils help control infection, when present in excess, they may cause more harm than good.[65] Neutrophils infiltrating the airways and degenerating are the major source of the DNA and filamentous actin that makes CF sputum so tenacious.[66,67] Augmentation of DNA content is directly associated with an increase in mucus viscosity.[68] Mucoactive therapies reduce viscosity and tenacity of the sputum via degradation of the excess DNA. The most widely used agent for this purpose is dornase alpha (Pulmozyme).[51]

DNase is produced naturally in humans. More than 50 years ago, it was shown that bovine pancreatic deoxyribonuclease I (DNase I), an enzyme that cleaves DNA, reduced the viscosity of lung secretions in vitro.[69] It was approved for human use in 1958. The agent lost popularity over time due to severe pulmonary reactions, possibly allergic in etiology. Recombinant human DNase (also known as alpha-dornase or Pulmozyme,) was sequenced in 1990 and used in aerosolized form. It decreases the viscosity of CF sputum by catalyzing extracellular DNA into smaller fragments.[70] This preparation has better tolerability, with the most common adverse effects being respiratory such as pharyngitis and hoarseness with minor allergic reactions.[51] The drug can be started safely during an acute pulmonary exacerbation, as well as during a stable period.[71]

A study of rhDNase in patients 3-16 years old showed that one-third children had sustained improvement in spirometry greater than 20% over 1 year, but one-third deteriorated.[72] The effects of rhDNase on lung function diminish over time. Another study showed that after stopping rhDNase, lung function dropped markedly below the initial baseline level.[51] The concern is that rhDNase only effects a superficial removal of secretions while deeper down below the mucosal surface, tissue damage continues as before. The dose is 2.5 mg nebulized once or twice daily.[51]

Ballman, et al., compared nebulized rhDNase to hypertonic saline in a short-term study of 14 patients with mild to moderate CF. They demonstrated comparable short-term effects and noted that hypertonic saline was much cheaper. A longer trial with 48 patients demonstrated that rhDNase produced significantly greater improvement in FEV1 from baseline compared with hypertonic saline.[73]

There are no other well-validated alternative mucolytic agents available presently. IV acetylcysteine reduces the viscosity of sputum in vitro but can be very irritating to the upper airway and can cause bronchoconstriction.[74] Further investigation is ongoing.

To the authors' knowledge, no randomized controlled studies exist to support the efficacy of nebulized DNase in the emergency department for acutely decompensated pulmonary disease in CF patients. However, it is a reasonable addition to acute therapy in a CF patient in whom intubation is an undesirable option.

Steroids. Oral corticosteroids have a wide range of anti-inflammatory effects, one of which is to prevent the conversion of neutrophils to the activated state. They also prevent the production of toxic metabolites.[41] Two randomized controlled trials in CF patients with mild to moderate disease treated with 1 or 2 mg/kg prednisone on alternate days for a 2-4 year period showed improvements in lung function and reduction in frequency of pulmonary exacerbations compared to placebo.[75,76]

Short-term treatment (3 weeks) with daily corticosteroids in stable patients with severe obstructive disease showed no benefit,[77] but patients with less severe disease showed some improvement.[78] The 1 mg/kg group vs placebo for 4 years had benefit with respect to pulmonary function at the expense of growth impairment and bone density.[79,80]

The long-term adverse effects are well-described and include glucose intolerance, cataracts, and growth impairment. An increase in the rate of infection is not seen.[76,81] Inhaled steroids have less systemic effects. Low doses of inhaled beclomethasone showed no effect on various markers of airway inflammation.[82] Higher doses of inhaled steroids have shown promise in preliminary studies.[83,84] Larger trials with long-term data are needed.

Advanced Airway Management. Hypercapnic and hypoxemic respiratory failure in CF is primarily due to progressive obstructive airway disease with alveolar hypoventilation with ventilation-perfusion mismatch. When a CF patient presents in respiratory failure, the management decisions become difficult. CF patients in general do not respond as well to and have more complications from mechanical ventilation compared to COPD patients.[25] However, ventilatory assistance is effective in CF patients with acute respiratory failure caused by reversible insults,[40] but produces few long-term benefits in patients with respiratory failure due to irreversible bronchiectasis.[85] The difference between these two entities may not be easy to determine the emergency department setting. Aggressive ICU care for adults with CF who have respiratory failure as a consequence of progression of their disease can be beneficial.[86] If an acute episode such as pneumonia or bronchospasm precipitates respiratory failure in a CF patient who had good pulmonary function before the episode, mechanical ventilation should be considered.[25] Factors to consider when making the decision: the patient's level of activity and pulmonary function before the episode, the cause of the patient's decompensation, and the expectations of patient and his or her family. Ventilatory support is appropriate for a patient when lung transplant is planned.[86] Consult with the patient's personal physician before electing not to intubate a patient.

Avoidance of endotracheal intubation and mechanical ventilation is desirable to limit possible airway complications of intubation, including nosocomial pneumonia and deleterious cardiovascular effects of positive-pressure ventilation such as decreased cardiac output or pneumothorax. Alternative ventilatory support in the form of BIPAP may be useful. Bilevel positive airway pressure (BIPAP) is a noninvasive mode of ventilation administered through a tight-fitting mask to assist spontaneously breathing patients. The BIPAP system regulates the pressure supplied

to patients, delivering different pressures during inspiration and exhalation. As the patient initiates a breath, the system delivers air with a positive pressure gradient, thus increasing tidal volume and minute ventilation.[87,88]

BIPAP has been used in cystic fibrosis as a bridge to transplantation. It has been shown that the use of BIPAP is associated with improvement in ventilation and arterial blood gases as well as improvement in subjective symptoms such as headaches, activity level, and quality of sleep in CF patients with end-stage lung disease awaiting lung transplant.[89,90] In a small study, Efrati, et al., demonstrated a significant improvement in survival of CF patients after lung transplant for patients who used BIPAP in the months before lung transplantation compared with those who did not use BIPAP. This improvement was thought to be due to improvement in respiratory muscle strength and nutritional status.[87]

Patient cooperation is crucial to the success of BIPAP. It is not recommended for patients with altered mental status, abnormal gag reflex, inability to protect airway, or inability to effectively clear respiratory secretions or protect their airway.

Heliox has been used with some success in asthmatic patients with severe airway obstruction.[19,91] The literature describing the use of heliox in cystic fibrosis is very limited. It was used in conjunction with noninvasive high-frequency percussive ventilation in a 5-year old child with severe acute respiratory failure resulting from advanced cystic fibrosis lung disease. The patient had dramatic improvement and avoided intubation in that case.[19] Another case report details the successful use of heliox in a teenage girl with severe acute respiratory compromise from cystic fibrosis.[92] The mechanism of action is thought to be improvement of gas exchange by enhancing molecular diffusion and by favoring laminar flow throughout the upper and lower airways. Further study is needed, but this seems like a reasonable therapeutic alternative for an acutely decompensated cystic fibrosis patient.[19,86,91]

Promising Therapies. Over the last 50 years the Cystic Fibrosis Foundation has been at the forefront of research efforts for the development of potential CF therapies. CF, however, is still a complicated and uniformly fatal disease. Novel treatments can be divided into two basic categories: those aimed at correction of the CFTR dysfunction and those aimed at mitigating the effects of having a limited number of CFTR channels. Definitive cure for CF would involve correcting the deficit left by the CFTR gene mutation. Restoration of even 5-10% of airway epithelial cells could correct the electrolyte transport defect.[8] There has been a significant amount of promising research in this direction, including gene therapy, activation of alternate chloride channels, and improving function of native CFTR.[1]

Ibuprofen can slow the effects of CF by reducing inflammation, but long-term use of this drug at the high doses required for improvement can negatively affect the kidney and gastrointestinal tract as well as other organs. The use of N-acetylcysteine as an alternate method to reduce inflammation is being investigated. High-dose oral N-acetylcysteine (NAC), a glutathione prodrug, modulates inflammation in cystic fibrosis. NAC has been tested with some success in patients with other inflammatory lung problems, including chronic bronchitis, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis.[93] Oral NAC treatment not only increased the amount of glutathione in circulating neutrophils, it also decreased the number of neutrophils and the levels of elastase and interleukin-8 in the airways. In 2006 the researchers began a 24-week placebo-controlled Phase II trial of NAC in cystic fibrosis patients to confirm these findings.[93]

In the terminal phases of the disease, lung transplantation often becomes necessary for individuals with CF as lung function and exercise tolerance declines. A pancreatic or liver transplant may be performed at the same time to alleviate liver disease and/or diabetes. Lung transplantation is considered when lung function approaches a point where it threatens survival or requires assistance from mechanical devices.

Disposition

The literature describing emergency department care of the acutely decompensated cystic fibrosis patient is sparse. Many pediatricians and pulmonologists work diligently to keep the patients out of the emergency department with care in the clinic and at home. If the patient needs to come to the ED, hospital admission is usually the goal.

The most important indications for admission would include need for intravenous antibiotics and/or advanced airway management. The disposition of the patient should include input from the patient's primary care physician or pulmonologist.

End-of-Life Issues

For patients who are not transplant candidates and have progressive respiratory failure, it may be difficult to decide whether to offer intubation. Potentially reversible aspects of the disease, short-term goals, and the wishes of the patient and the family are important to consider.[86] In patients who are not transplantation candidates, the decision to proceed with mechanical ventilation should be undertaken with the understanding that there is a limited chance for a good outcome.[94] For terminal patients in whom mechanical ventilation is not planned, the primary palliative care issue is the management of dyspnea. Morphine infusions have been successfully used in these cases to provide comfort care.[94] Advanced directives are helpful in this situation and should be sought.

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Physician CME Questions

91. What is the current life expectancy for cystic fibrosis patients born in the 1990s?
    A. 6 months
    B. 14 years
    C. 30 years
    D. Greater than 40 years

92. Regarding the diagnosis of CF, which statement is true?
    A. The sweat test is no longer used.
    B. Rarely, symptomatic patients who test positive for CF on genetic testing will have a normal sweat test.
    C. The sweat test can only be used up to age 2.
    D. CF is routinely screened for in all infants born in the United States.

93. Which of the following is the most common infecting pathogen in the lungs of CF patients?
    A. *H. influenzae*
    B. *Burkholderia cepacia*
    C. *Staph. aureus*
    D. *Pseudomonas aeruginosa*
    E. *Stenotrophomonas maltophilia*

94. Which organism causes a sepsis-like syndrome in CF patients with a severe necrotizing pneumonia?
    A. *Pseudomonas aeruginosa*
    B. *Burkholderia cepacia*
    C. *Stenotrophomonas maltophilia*
    D. *Achromobacter xylosoxidans*
    E. *E. coli*

95. Which of the following is a known complication of pulmonary disease in CF?
    A. Pneumothorax
    B. Hemoptysis
    C. Bronchiectasis
    D. Bronchospasm
    E. All of the above are known complications of CF

96. Regarding gastrointestinal dysfunction in CF patients, which statement is true ?
    A. Distal intestinal obstruction syndrome is only seen in children.
    B. Most CF patients do not require pancreatic enzyme replacement.
    C. CF-related diabetes often results in diabetic ketoacidosis.
    D. Liver disease is the second most common cause of death in CF patients.
    E. There is no increased risk of Crohn's disease in CF patients.

97. What is the earliest change seen on chest radiograph in CF patients?
    A. Peribronchial cuffing
    B. Bronchiectasis
    C. Infiltrates
    D. Hyperinflation

98. Regarding antibiotic treatment in cystic fibrosis, which of the following statements is *false*?
    A. Early aggressive use of antibiotics in decompensated CF patients produces better results than delaying antibiotics.
    B. Azithromycin has a direct killing effect against Pseudomonas.
    C. Aerosolized tobramycin is the most thoroughly studied chronic inhalation antibiotic therapy.
    D. CF patients require higher doses and shorter dosing intervals of antibiotics.
    E. All of the above are true.

99. Regarding treatment of decompensated CF lung disease, which statement is *false*?
    A. Beta agonists and anticholinergic agents are not indicated in the treatment of CF bronchospasm.
    B. Hypertonic saline is useful as a nebulized agent in CF.
    C. Aerosolized DNase helps decrease viscosity of the secretions.
    D. BIPAP may be helpful in a cooperative patient.

100. Which of the following statements is true?
    A. Crohn's disease and malignancy are more common in patients with CF than in the general population.
    B. In general, chest CT provides no more information than an AP plain x-ray of the chest.
    C. Chest physiotherapy is passe and has no role in the treatment of CF.
    D. Patients with CF are *not* candidates for transplant because the disease is systemic.

CME Answer Key

91. D; 92. B; 93. D; 94. B; 95. E; 96. D; 97. D; 98. B; 99. A; 100. A

Emergency Medicine Reports®
The Practical Journal for Emergency Physicians

Adult Cystic Fibrosis Patients

Antibiotics Used to Treat Pulmonary Exacerbations in Cystic Fibrosis Patients

(Route of administration is intravenous unless noted)

AGENT	DOSE	
	Children	**Adults**
Piperacillin/Tazobactam	300 mg/kg/d divided q6 (max 24 g/day)	2-4 g q6
	OR	
Ticarcillin/Clavulanate	200-300 mg/kg/d divided q4-6	1-4 g q4-6
	OR	
Ceftazidime	200 mg/kg/d divided q6	250 mg-2 g q8-12
	OR	
Cefepime	50 mg/kg/d divided q8	2 g q12
	OR	
Aztreonam	50 mg/kg/dose q6-8	2 g q8-6
	OR	
Imipenem/Cilastatin	45-60 mg/kg/dose q6	same as peds
	OR	
Meropenem	40 mg/kg/dose q8	2 g q8
	OR	
Aztreonam	300 mg/kg/day divided q6-12 (max 12 g/day)	same as peds
	PLUS	
Ciprofloxacin	20-30 mg/kg/d divided q8*¶	250-750 mg q12¶
	OR	
Gentamycin	3 mg/kg/dose q8	3 mg/kg/dose q8
	OR	
Tobramycin	3 mg/kg/dose q8	3 mg/kg/dose q8
Inhaled tobramycin		300 mg via jet nebulizer q12
If MRSA is suspected, add:		
Vancomycin	15 mg/kg/dose q8-12	same as peds
	OR	
Linezolid	10 mg/kg/dose q12†	600 mg q12†

* Not the preferred agent for pediatric patients but can be used in certain situations
¶ Route of administration is PO or IV
† Route of administration is PO

States that Have Newborn Screening Programs for CF

Alabama
Alaska
Arizona
California
Colorado
Connecticut
Delaware
District of Columbia
Florida
Georgia
Illinois
Iowa
Kentucky
Maryland
Massachusetts
Michigan
Minnesota
Missouri
Mississippi
Montana
Nebraska
New Hampshire
New Jersey
New Mexico
New York
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island
South Carolina
South Dakota
Virginia
Washington
Wisconsin
Wyoming

Complication Rates in CF Patients: Adults and Children

COMPLICATION	ADULT %	CHILDREN%
P. aeruginosa colonization	79	47
Ciprofloxacin resistance	22	4
Tobramycin resistance	15	6
B. cepacia colonization	6	2
Massive hemoptysis	1.8	0.1
Pneumothorax	1.4	0.2
Require continuous O2	6	1
CFRD requiring insulin	16	2.5

Phenotypic Features Consistent with the Diagnosis of Cystic Fibrosis

Chronic Sinopulmonary Disease
- Persistent colonization/infection with typical CF pathogens (*S. aureus*, nontypable *H. influenzae*, mucoid and nonmucoid *P. aeruginosa,* and *B. cepacia*)
- Chronic cough with sputum production
- Persistent chest radiograph abnormalities (i.e., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Airway obstruction (wheezing, air trapping)
- Nasal polyps and CT abnormalities of the paranasal sinuses
- Digital clubbing

GI and Nutritional Abnormalities
- Intestinal: DIOS and rectal prolapse
- Pancreatic: pancreatic insufficiency and recurrent pancreatitis
- Hepatic: focal or multinodular cirrhosis
- Nutritional: failure to thrive, hypoprotenemia, edema

Salt Loss Syndromes
- Acute salt depletion and chronic metabolic alkalosis

Male Genitourinary Abnormalities and Obstructive Azoospermia

Supplement to *Emergency Medicine Reports*, April 28, 2008: "Emergency Department Care of Adult Cystic Fibrosis Patients." *Authors:* **Lisa Freeman Grossheim, MD, FACEP**, Assistant Professor, Department of Emergency Medicine, University of Texas Medical School at Houston; **Keith S. Gates, MD, EMT-P**, Resident, Department of Emergency Medicine, University of Texas Medical School at Houston.
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Trauma Reports

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May/June 2008

Pediatric Concussions

Authors: **Mara S. Aloi, MD, RDMS,** Assistant Professor of Emergency Medicine, Drexel University School of Medicine, Program Director, Emergency Medicine Residency, Allegheny General Hospital, Pittsburgh, PA; and **Brian Rempe, MD,** Assistant Professor of Emergency Medicine, Drexel University School of Medicine, Assistant Program Director, Emergency Medicine Residency, Allegheny General Hospital, Pittsburgh, PA.

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Traumatic brain injury (TBI) is an important public health problem. It has the potential for long-term complications with persistent morbidity, and also can result in missed school and workdays. The medical literature is replete with studies defining the management of moderate to severe TBI, but much controversy still exists concerning the management of mild TBI. Most of the literature deals with adult patients; therefore, less is known about mild TBI in children.

Some of the problems that may result from a concussive injury are subtle and are often missed or attributed to something else, such as psychogenic factors. This can result in further injury when a child is prematurely allowed to return to play.

With nearly 60% of all high school students in the United States participating in organized sports, there is a huge population at risk for concussive injury.[1] The rate of hospital admission for children with mild TBI has been decreasing despite increases in estimated rates of emergency department visits for TBI.[2] This suggests that the burden of managing these cases is being shifted toward emergency physicians and other healthcare providers in outpatient settings. It is crucial that acute care providers accurately identify pediatric patients with mild TBI who may be at risk of developing the symptoms of postconcussive syndrome (PCS).

— The Editor

Epidemiology

Much of the literature on concussion indicates significant underdiagnosis and underreporting.[3] It is estimated that 1 million cases occur annually, with 80-90% being classified as mild TBI.[4] According to the Centers for Disease Control and Prevention, more than 500,000 pediatric TBI patients are treated and released annually.[5] It is estimated that an additional 250,000 cases are seen in outpatient, non-hospital settings. It is unknown how many patients never seek medical attention because they deem their injury to be mild, even

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though they may have suffered a concussion. Patients with mild cases may not seek medical care if they do not experience any limitation of daily functioning;[6] thus, their cases may go unreported. In one self-report study, many athletes described concussive injuries without realizing they had sustained a concussion.[7] Even if patients do present for care, many healthcare providers rely on the Glasgow Coma Scale for assessment; this tool is insensitive for mild cases of TBI. Therefore, the true incidence of mild TBI and PCS is unknown.

The highest-risk sports for TBI and PCS are boxing, football, hockey, wrestling, and soccer.[8] More than 60,000 high school athletes suffer PCS injuries each year.[9] The majority of these are football players. In almost every age group, the incidence of concussion is higher in males than in females, but this gap is narrowing as more females join organized sports.

Pathophysiology/Risk Factors

The term "postconcussion syndrome" was first used in 1934 to describe the "subjective post-traumatic syndrome due directly to the blow on the head."[10] Since that time, much discussion and controversy has arisen concerning attempts to further delineate and categorize this disease process. The word "concussion" refers to mild TBI that is caused by an impact or jolt to the head. All concussive injuries involve rotation, acceleration, and/or deceleration forces that result in stress to brain tissue and associated vascular and neural tissues.[11] Concussion also may result from a direct blow elsewhere on the body from which force is transmitted to the head.[12] The exact mechanism of injury will depend on the sport or activity. In animal models of concussion, changes include neuronal depolarization; release of excitatory neurotransmitters; and impairment of glucose metabolism, axonal function, and cerebral blood flow.[13,14]

Although there are more data on adult patients, several interesting findings have been published on the unique characteristics of the pediatric brain. In the past, it was believed that the pediatric brain was more resilient and could more easily recover from injury than the adult brain. However, it has been discovered that the immature brain is actually more vulnerable to injury.

The developing brain is 60 times more sensitive to glutamine-mediated N-methyl-D aspartate (NDMA) excitotoxic brain injury.[15] This NDMA-hypersensitivity may make the young brain more susceptible to injury from excitatory amino acids (EAAs), which are present after brain trauma. The injury induced by these EAAs results in post-traumatic dysautoregulation and a subsequent decrease in cerebral blood flow. These effects may not be seen until 2-3 days after injury and may persist for up to 1 week. It is during this period, when the brain is hypersensitive and autoregulation has not normalized, that the brain may be more vulnerable to another concussive injury. In fact, previous injury has been shown to impart a 3- to 6-times higher risk of sustaining a subsequent concussion.[16,17]

The pediatric brain may be more prone to diffuse and prolonged cerebral edema after injury than the adult brain.[1,18] This may result in a longer recovery time and render the child susceptible to more severe damage or permanent deficit if another injury occurs while edema is still present. More protracted recovery rates have been reported in high school athletes suffering from PCS than in college athletes, suggesting that younger athletes take longer to return to baseline.[15]

The significance of head injury also may be greater in children because their young brains are still developing skills. Impact to areas of the brain important for skill acquisition is more likely to affect developing skills than well-established ones. Injury in preschool-age children (< 5 years) may be even worse because this age is critical for the development of many important skills. Research has shown that mild TBI in preschool children may affect their ability to learn to read.[19] Early diagnosis of injuries in these children may allow for early intervention that focuses on these affected skills, as well as teacher notification. Normal neurobehavioral and neurobiological development may depend on a precise balance of chemical and anatomic factors, so any derangement of these factors may have serious consequences. The hippocampus is especially sensitive to repeated injury, which may account for memory disturbance seen after concussion.[20]

There may be a chemical and biological basis for the development of PCS. The apolipoprotein E epsilon-4 (*apoE*) gene has been implicated as a susceptibility gene for Alzheimer's disease. This gene is involved with neuronal repair and antioxidant activity and has been associated with poor outcomes after TBI.[12] The *apoE* gene has been shown to be a risk factor for chronic traumatic encephalopathy in boxers.[21] Despite this evidence, there is no role at present for routine genetic screening as part of sports physicals. Pre-morbid behavioral disorders (such as attention-deficit/hyperac-

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tivity disorder) may affect vulnerability to concussion as well.[4] There is some evidence that greater force is required to bring about symptoms after TBI in children.[22,23] Fortunately, younger athletes are smaller in size and in strength than their adult, professional counterparts, which reduces the force of collisions.

Diagnosis

Clinical Features of Concussion. Clinical features associated with concussion vary significantly. Detecting the often subtle signs and symptoms is important to the clinician as there are no objective radiographic tests to diagnose a concussion. Recognition is particularly important in sports, where a re-injury could result in postconcussive syndromes or the second impact syndrome, which involves a second head injury while the patient is still symptomatic from the original injury. The second impact syndrome, addressed more thoroughly later in this discussion, is rare but can lead to devastating outcomes that include brain damage and death.

Currently, the American Academy of Neurology (AAN) defines concussion as "a trauma-induced alteration in mental status that may or may not involve a loss of consciousness."[24] These alterations cause a spectrum of signs and symptoms that can be divided into three categories:[1,25,26]

Somatic: headache, fatigue, sleep disturbance, nausea, visual changes, tinnitus, dizziness, balance problems, light/noise sensitivity.

Emotional/Behavioral: lowered frustration tolerance, irritability, increased emotional lability, depression, anxiety, clinginess, personality changes.

Cognitive: slowed thinking or response speed, mental fogginess, poor concentration, distractibility, memory/learning difficulty, disorganization, problem-solving difficulties.

Two commonly used diagnostic guidelines come from the International Classification of Diseases, 10th revision (ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV). The ICD-10 criteria are: history of TBI plus three of the following eight symptoms: headache; dizziness; fatigue; irritability; insomnia; intolerance of stress, emotion, or alcohol; difficulty concentrating; and memory impairment.

Critics of this method fault the lack of requirement of objective cognitive deficit or exclusion of other disorders.[27]

The DSM-IV criteria require a history of TBI causing "significant cerebral concussion" and:

1) cognitive deficit in attention or memory;
2) the presence of at least 3 out of 8 symptoms (fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, personality changes, apathy) that appear after injury and last > 3 months;
3) symptoms that begin or worsen after injury; and
4) interference with social role functioning.

The DSM-IV also requires the exclusion of dementia or other disorders that might account for symptoms.

Unfortunately, there is limited agreement between the DSM-IV and the ICD-10 criteria. For example, in one study, only 17% of patients who met the criteria for PCS using the ICD-10 set also met the DSM-IV requirements.[27] When healthcare workers have multiple diagnostic criteria sets to choose from, with varying inclusion criteria and reliability, the result may be inaccurate classification of patients.

The symptom pattern seen after concussive injury is multifactorial. The mechanism and force of injury, as well as the patient's genetic makeup/susceptibility, gender, previous injury history, preexisting conditions/learning difficulties, psychiatric status, and psychosocial factors, all contribute to the severity and duration of symptoms.[28-30] This is where much of the controversy regarding the diagnosis of PCS arises. Some authors believe that symptom-based diagnosis may include those with pre-injury symptoms, malingering, or post-injury psychological factors that may exacerbate symptoms.[4] Many of the criteria listed above are subjective and nonspecific. Patients and their parents can report these complaints even in the absence of history of brain trauma, leading some authors to question the validity of diagnosis based purely on reported symptoms.[31] The symptom expectation factor cannot be underestimated. Parents of head-injured children are up to 3 times more worried about "brain damage," which may result in unintentional false reporting of PCS symptoms. Even if symptoms exist, are they attributable to the brain trauma or the overall stress from the trauma? At least one study found that symptoms developed with the same frequency in head-injured and non-head-injured trauma patients.[31] This calls into question whether objective symptoms specifically related to brain concussion actually exist.

Loss of consciousness was once considered a cardinal feature of concussion, but research has shown it to be somewhat less important clinically.[32-35] Particularly in sports-related concussion, post-traumatic amnesia (PTA) is probably more important prognostically.[26,36] PTA may be associated with a worse functional outcome. Specific symptoms of depression and cognitive deficits vary significantly based on the duration of PTA. Amnesia of any duration after trauma is associated with a greater incidence of dizziness.[37] Asplund and coworkers reported that more than 3 hours of headache, difficulty concentrating, retrograde amnesia, and loss of consciousness may be predictive of a more prolonged recovery.[26] Patients experiencing PTA for more than 30 minutes may have a more severe concussion than others. However, determination of the actual duration of PTA is difficult and usually relies on a retrospective account of recent events (obtained by asking the patient how far back he or she can remember). At present, there is no standardized method of determining the duration of PTA.

The Glasgow Coma Scale, a well-known 15-point scale used to assess head injury, is insensitive for detecting milder degrees of impairment. There is a limited role for its use for sideline testing. Computerized testing has some benefit over symptom-report diagnosis because it also can assess reaction time. This has been shown to be very sensitive in detecting mild TBI.[38] Several well-validated neuropsychological tests are available as computer models and allow both baseline (pre-injury) and post-trauma testing. This may be a more objective method of evaluating PCS. Many athletic organizations require baseline neuropsychological testing at the start of the season so that after injury, the player can be retested and scores compared with the baseline.

Table 1. Commonly Used Concussion Guidelines

CONCUSSION GRADE	CANTU 1986/REVISED	COLORADO MEDICAL SOCIETY	AMERICAN ACADEMY OF NEUROLOGY
1	No LOC, PTA < 30 min / No LOC, PTA, PCSS < 30 min	Confusion, no LOC	Transient confusion, no LOC, symptoms resolve in < 15 min
2	LOC > 5 min or PTA > 30 min / LOC < 1 min or PTA > 30 min but < 24 h, PCSS > 30 min but < 7 d	Confusion, amnesia, no LOC	Transient confusion, no LOC, > 15 min of symptoms
3	LOC > 5 min or PTA > 24 h / LOC > or equal to 1 min, or PTA > or equal to 24 h, PCSS > 7 d	LOC of any duration	LOC of any duration

Data from references 15,24,40,41

Abbreviations: LOC, loss of consciousness; PTA, posttraumatic amnesia; PCSS, Postconcussion Signs/Symptoms; min, minute; h, hour; d, day

Concussion in Sports, Management on the Sidelines. Concussion is a common occurrence in sports activities. Issues include recognition and sideline testing, management of concussion, and when to allow athletes to return to play. This is still the subject of much debate and controversy. Several sets of guidelines have been presented that are meant to grade concussions and then direct return-to-play decisions accordingly.[39] However, there is no universally accepted grading system, and no guideline has been scientifically established. Lovell and co-workers wrote, "At the current time, there is no consensus on the definitive diagnosis of concussion, parameters regarding return to sport participation following injury and the short-term and long-term neurologic consequences associated with concussion."[27] This has led to the general rule: "When in doubt, sit them out."[1]

Three of the most commonly used guidelines are discussed. *(See Table 1.)* It should be mentioned that these guidelines are generalized to all genders, ages, and levels of skill. A "one-size-fits-all" application of these guidelines does not take into account the differences between the pediatric and adult brain.

Cantu published sport-related concussion guidelines in 1986. The symptoms measured in his guidelines include loss of consciousness and post-traumatic amnesia.[40] He, as well as those publishing later guidelines, divides concussion into three grades based on severity. Grade 1 involves no loss of consciousness and post-traumatic amnesia lasting less than 30 minutes. Grade 2 involves a loss of consciousness for less than 5 minutes and amnesia of more than 30 minutes but less than 24 hours in duration. Grade 3 involves post-traumatic amnesia lasting more than 24 hours or loss of consciousness for more than 5 minutes. Later, Cantu created another set of guidelines including assessment based on the duration of concussive systems other than amnesia, including loss of consciousness and confusion.[15]

In 1991, the Colorado Medical Society published guidelines again utilizing amnesia and loss of consciousness. Grade 1 concussions involved transient confusion without PTA or loss of consciousness. Grade 2 added PTA, and Grade 3 involved any loss of consciousness.[41]

The AAN guidelines, published in 1997, also split concussion into three grades,[24] but they involve confusion rather than amnesia and consider any loss of consciousness very serious. Grade 1 involves no loss of consciousness, only transient confusion, and all symptoms resolving in less than 15 minutes. Grade 2 involves similar symptoms lasting more than 15 minutes. Grade 3 includes concussion with any loss of consciousness.

The guidelines summarized in Table 1 also have associated return-to-play recommendations based on the grade of the concussion. *(See Table 2.)* These recommendations for return to play are similar for a given grade of concussion, but differ widely in the grade assigned to specific symptoms. All allow individuals with grade 1 concussions to return to play if symptoms resolve and the results of examination on the sidelines are normal. Unfortunately, objective neuropsychological testing of reaction time and cognitive function has shown that, even in athletes with grade 1 concussions whose symptoms resolve within 15 minutes after injury, deficits may persist until day 6.[42]

Athletes with grade 2 concussion are removed from play and may return in one to two weeks if symptoms resolve. For grade 3 concussions, The Colorado Medical Society and AAN recommend hospital evaluation as well as a delayed return to play. Cantu recommends removal from play for a month with a grade 3 concussion. He also recommends longer play restriction in athletes with recurrent injury. Particularly, he recommends ending the season for an athlete sustaining his/her third concussion even if it is mild.[27,40,41] These guidelines rely heavily on the presence or absence of symptoms to guide decision-making. The use of quick sideline testing may result in neurocognitive deficits being missed and may place the athlete at risk if he or she is allowed to return to play prematurely. In addition, practitioners should bear in mind that some patients might minimize or deny symptoms to get clearance to play. There also exists the mentality that athletes are expected to "tough it out" or "play through an injury."

Traditionally, many athletes have not been allowed to return to play for 7 days. There is evidence that this one-week recovery time may not be long enough. McClincy et al studied recovery

Table 2. Return to Play Guidelines

CONCUSSION GRADE	AAN	COLORADO MEDICAL SOCIETY	CANTU (1ST CONCUSSION)
1	Same day if sideline assessment including exertion testing is normal, otherwise in 1 week if no symptoms	Remove and reassess for 20 minutes, may return if asymptomatic.	Must be asymptomatic for 1 week
2	1 week; 2 weeks if multiple concussions	May return after 1 week without symptoms.	Must be asymptomatic for 1 week
3	1 week if only brief LOC; 2 weeks if LOC for more than 1 minute; 1 month if multiple grade 3 concussions	May return after 2 weeks.	No play for 1 month assuming asymptomatic for at least 1 week

Data from references 21,24,40,41

Abbreviations: AAN, American Academy of Neurology; LOC, loss of consciousness

times in 104 high school and college athletes who sustained concussions.[43] They graded concussions using AAN scales, and also used neuropsychological testing before and repeatedly after a concussive event. Neurocognitive defects persisted for up to 14 days. Alarmingly, concussion recovery times had little to do with AAN grade; 80% of concussed athletes would have returned to play with persistent neurocognitive defects. This is potentially dangerous, as research has demonstrated risks associated with repeated injury prior to full recovery.[15]

The International Conference on Concussion in Sport met and published guidelines in Vienna in 2001 and in Prague in 2004.[21] They offered a new definition for sports concussion as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces." Their consensus was that loss of consciousness had likely been overstated as an indicator of injury severity, and that amnesia was possibly a valuable indicator of severity. The group abandoned previous concussion grading based on initial symptoms and instead separated concussion into two groups, simple and complex, based on pattern of recovery. They also indicated that in contrast to statements from previous grading scales, any child with concussion mandated an evaluation by a physician.

A *simple concussion* is defined as one that "resolves without complication over a 7-10 day period." A graded increase in activity is recommended before these patients return to full sport participation. A *complex concussion* is one that leads to persistent symptoms or involves seizure or prolonged loss of consciousness (more than 1 minute). This category also includes those with recurrent injury. Formal neuropsychological testing is recommended for this group, as well as more intensive evaluation by physicians who specialize in concussion. *(See Table 3.)*

To address the concerns that symptom-based guidelines were resulting in athletes being returned to play prematurely, the conference statement from Prague made several additional recommendations:[21] A key instruction is that no player goes back into the current game after a concussion. This differs significantly from the previously mentioned guidelines, which may allow return to play after a short rest (15-20 minutes) and sideline testing. Another recommendation is the return to play in a stepwise fashion. This begins with light activity and progresses to sport-specific exercise; followed by drills; full-contact practice; and finally, return to game play. If any symptom occurs during this process, the athlete should return to the level of exercise not associated with symptoms. The athlete may then attempt a higher level of activity after 24 hours. The statement also recommended cognitive rest, which had not been mentioned in previous return-to-play guidelines.

In addition, the Prague statement included the Sport Concussion Assessment Tool (SCAT), which is meant to be used for the sideline assessment of athletes and also for pre-season assessment.[21] The SCAT card is available from the *Clinical Journal of Sport Medicine* (www.cjsportmed.com, search for "Sport Concussion Assessment Tool") and consists of a scorecard for concussion symptoms, as well as an organized outline of a neurocognitive assessment tool. However, unlike professional sports organizations that require the presence of on-site trainers or sports medicine physicians, amateur sporting events may not have these resources present at each game. If an assessment by a trained individual cannot be done on the sidelines, the patient should be removed from play until a proper evaluation has been completed.[4]

ED Management: When to Order a CT Scan

Perhaps the most important step in evaluating the emergency department patient with concussion is ruling out more significant pathology such as brain hemorrhage. Some common symptoms of concussion also may indicate more severe pathology. Concussed patients often complain of a headache,[26] but severe headache may indicate a more serious intracranial injury.[44,45] Some vomiting may be present in the setting of concussion, but recurrent or projectile vomiting may be an indication that further testing is warranted.[46,47]

The question of when to obtain imaging to exclude an intracranial injury has been the topic of numerous studies over several years, yet there is not a clear consensus.[44-52] Computed

Table 3. Recommendations of the International Conference on Concussion in Sport[21]

TYPE OF CONCUSSION	RECOMMENDATION
Simple	No return to play in current practice or game; stepwise return to play
Complex	Formal neuropsychological testing with return decision made by a physician with specialized training in concussion

tomography (CT) is expensive, and it also exposes patients to significant doses of radiation, which may increase the future risk of cancer. The risk of cancer death in a 1-year-old who undergoes a CT scan of the brain approaches 1/1000.[53] Unfortunately, the youngest members of the pediatric population are the most difficult to assess for more serious injury and also may suffer the greatest risk of radiation exposure.[44,53,54]

In 1999 the American Academy of Pediatrics, in concert with the American Academy of Family Physicians, published a consensus guideline on the management of minor closed head injury in children older than age 2. For the patient with a normal neurological exam following a mild head injury without a loss of consciousness, they recommend only observation. If there is a brief loss of consciousness, then a CT scan or observation is appropriate. The period of observation should be 24 hours, but that can include at-home observation by a reliable caregiver as well as time in the emergency department, physician's office, or hospital. Notably, this guideline is meant to include those who have symptoms of concussion including episodes of vomiting or lethargy, but it excludes patients with evidence of a skull fracture, as well as those with multiple traumas, intentional trauma, intoxication, or bleeding diathesis.[55]

Later investigation has attempted to close the 0- to 2-year-old age gap with the development of criteria to determine when these youngest of patients should receive brain CT scans.[45,47,48] This group traditionally has been considered at higher risk and more difficult to assess.[48,54] In addition to brain injury, other complications such as growing skull fractures and leptomeningeal cysts must be considered in this age group.[54] In 2001, Schutzman and colleagues published guidelines for those younger than age 2.[48] The recommendations included exceptions to the previously mentioned AAP guidelines. They advocated dividing patients into four groups depending on risk. In their guidelines, risk is determined by age, with lower ages at higher risk. Symptoms such as vomiting, loss of consciousness, and lethargy are considered, as is the mechanism of injury. Lower-risk infants can be discharged. Radiographs are considered for those with potential skull fracture. Those with intermediate risk are scanned or observed, and all high-risk patients receive CT scans.[48] Notably, the authors pointed out that loss of consciousness and vomiting had not been demonstrated to be predictive of intracranial injury (ICI). The guidelines do not offer strict cut-offs between their risk groups, which could lead to clinician judgment playing a very significant role.

In 2003, Palchak et al published a decision rule for determining when to scan those age 2 or younger.[44] They studied 2043 children who underwent CT scan following a head injury. The decision rule involved the following:

- Abnormal mental status;
- Clinical evidence of skull fracture;
- History of vomiting;
- Scalp hematoma in those younger than age 2; and
- Headache.

The authors demonstrated a sensitivity of 99% for detecting lesions present on CT scans and 100% sensitivity for lesions requiring intervention. There was a specificity of 42.7% for those requiring intervention.

More recently, NEXUS II data have yielded more specific criteria for use in children in general and in the difficult 0- to 2-year-old group.[47] Published in 2006, this study involved 1666 children, 309 of whom were younger than age 3. The authors began by analyzing 19 variables potentially associated with significant ICI. They selected eight variables based on the association with ICI in the study cohort, including:

- Evidence of significant skull fracture;
- Altered level of alertness;
- Neurological deficit;
- Persistent vomiting;
- Presence of scalp hematoma;
- Abnormal behavior;
- Coagulopathy; and
- Age older than 65.

Utilizing the NEXUS II cohort, the authors reported 98.3% sensitivity with 100% in the population younger than age 3, but noted that these criteria should be validated in a separate cohort of patients. Specificity was only 13.7% for the group, but these data could still be used to decrease unnecessary CT scan utilization.

In 2007, Sun et al used the NEXUS II cohort data to validate a slight modification of the Palchak et al rule (the UC-Davis Pediatric Head Injury Rule).[45] They demonstrated a sensitivity of only 90.4% and specificity of 42.7%. This Modified UC-Davis Pediatric Head Injury Rule involves five elements, including:

- Abnormal mental status;
- Signs of skull fracture;
- Scalp hematoma in children younger than age 2;
- High-risk vomiting; and
- Severe headache.

High-risk vomiting in this scenario refers to recurrent, forceful, or projectile vomiting, according to the authors. This was only a slight modification of the UC-Davis Pediatric Head Injury Rule, which had demonstrated a sensitivity of 100%.

To date, there is no universally accepted guideline to instruct physicians when to order CT scans on children with concussion or head injury. Physicians should use their clinical assessment of

the patient along with knowledge of the currently available guidelines in determining which patients to scan.

Adjunctive Tests. Conventional neuro-radiologic studies are usually normal in mild TBI, although CT scan is still used liberally in the acute setting to rule out serious pathology such as intracranial bleed or subarachnoid hemorrhage. Magnetic resonance imaging (MRI) can be used for certain situations including prolonged recovery time, focal neurologic deficits, or worsening symptoms. In rare cases, delayed or slowly developing intracerebral hemorrhage (ICH) has been detected by MRI.

Single photon emission computerized tomography (SPECT) and positron emission tomography (PET) scanning may be useful as diagnostic modalities. They can assess regional blood flow and cerebral blood volume.[56] SPECT also can evaluate blood-brain barrier integrity. SPECT and PET are much more sensitive than CT or MRI, which are negative in the majority of patients with PCS. They have been found to have a sensitivity of 90%.[57] SPECT is much more readily available and less costly. Using these modalities, researchers have found a high incidence of medial temporal hypo-perfusion (MTH) in children with mild TBI.[57,58] This may account for the memory impairment seen with PCS because the hippocampus is located in the medial temporal lobe. Researchers hypothesize that this hypo-perfusion results in ischemic injury. Symptoms of PCS correlated with abnormal SPECT scans. SPECT may prove to be a useful screening tool to determine if any hypo-perfusion has occurred in children who have suffered a concussive injury, but at present, it is not widely used for that purpose.

Electroencephalogram (EEG) may show abnormal slowing after concussion.[59] This can be coupled with low-resolution brain electromagnetic tomography (LORETA), which localizes areas of slowing to pathologic areas found on SPECT scan. It is currently unclear if these abnormalities are associated with the symptoms of PCS.

Ideally, serum biochemical markers could be used instead of expensive radiologic studies, some of which incur the risk of radiation exposure. It is presumed that if the blood-brain barrier is damaged by a traumatic injury, brain-related proteins may be identifiable in the peripheral circulation. Astroglial protein (S100B) may indicate brain injury, but diagnostic tests for it are still experimental. S100 protein is released from astrocytes. However, this isoform is not isolated to brain tissue. In addition, its relationship to outcome after TBI is variable. Recent investigations suggest that using a creatine kinase correction factor may aid in accounting for extracranial S100B release.[60] Further research needs to be undertaken to determine if this is a useful tool in the evaluation of patients with mild TBI. Neuron-specific enolase (NSE) is an enzyme important for glycolysis in neurons. It is not isolated to the brain. Cleaved tau protein (CTP), found in axons, is presumed to be released after mild TBI when diffuse axonal injury has occurred. This marker may be useful in combination with S100B protein.[61] At present, the value of these markers is questionable.

It should be mentioned that objective measures of brain injury, such as radiologic tests and serum markers, cannot be used as the only predictors of mild TBI outcome. Numerous other factors come into play, such as pre-morbid characteristics (e.g., attention-deficit/hyperactivity disorder, socioeconomic setting) and coping mechanisms, which account for the variability in symptom severity and duration in patients with seemingly similar injuries. It has been shown that children with persistent symptoms of concussion have poorer pre-injury behavioral adjustment than children without persistent symptoms.[62] The emotional and behavioral symptoms of PCS may be affected by post-injury parent and family adjustment, family stressors, and resources unrelated to the injury.[63] Below-average parenting skills and family functioning may worsen the negative effects of PCS, but higher-functioning families may be able to lessen these effects, especially the behavioral symptoms.[4] Children who have adjustment difficulties may not have the necessary coping skills to deal with the acute stress of an injury. Families who function poorly may not serve as a resource to help children cope. There is a significant relationship between the number of problems reported and the level of parental stress.[64] Failure to reasonably cope with the acute stress of injury may result in persistent symptoms, even when the tangible effects on brain function have resolved as evidenced by neuropsychological testing.

Clinical Management

The individual's recovery course is more important than the initial grade of concussion. Grading concussions immediately after injury may not be an accurate assessment because individual recovery varies. Loss of consciousness is one indication of concussion severity, but it is by no means the most important. Many recover quickly despite suffering a loss of consciousness; conversely, others who do not lose consciousness may experience a prolonged recovery period.[65]

It is crucial to identify patients who are at risk for developing PCS early so that treatment can be started and assistance can be offered with psychosocial and family issues.

Optimal management requires ongoing assessment to make sure secondary problems have not developed (such as depression, family dysfunction, post-traumatic stress disorder, attention-deficit/hyperactivity disorder). Therefore, appropriate follow-up instructions and referrals should be offered.

To reduce some of the negative psychosocial effects of PCS, it is important to educate families and school personnel. They may be able to adjust the child's schedule and their own expectations while healing is occurring. Specialized educational help can be arranged. This and other early psychosocial intervention, such as cognitive-behavioral therapy, may lessen the severity of some of the emotional and behavioral symptoms resulting from PCS.[66,67] If a patient is not improving as expected, referrals to specialists in neuropsychology, neurology, rehabilitation, sports medicine, or behavioral health should be considered.

Pharmacologic Therapy. Several medications have been recommended for PCS based on their efficacy in treating similar symptoms in the non-concussed population. Few have been studied. Levels of dopamine and serotonin are reduced in the cerebrospinal fluid of TBI victims,[68] which is the basis for use of antidepressants in patients with TBI. Methylphenidate and sertra-

line have been found to be better than placebo for treating depression. Their efficacy in treating the other neuropsychological symptoms of PCS, including sleep disturbances and cognitive function, has not been proven. Sertraline has been found safe for use in children as young as age 6. Symptomatic relief of headache can be achieved with acetaminophen or non-steroidal anti-inflammatory agents.

Investigative studies have explored the role of functional neurogenesis. Using a rat model, fibroblast growth factor-2 and epidermal growth factor have been found to encourage repopulation of hippocampal neurons in an area of injury.[69] To document similar results in humans, researchers may need to use SPECT scanning, as histopathology tests of treated human subjects cannot be done.

Disposition. Hippocrates once said, "No head injury is too trivial to ignore."[70]

The emergency department physician should not halt treatment and assessment of a child following a negative head CT scan. Parents should be educated about the symptoms and natural history of concussion, and appropriate follow-up should be recommended. Parents often want to know when their child can return to sports or to physical education class, but children should be managed very conservatively. Field and colleagues compared collegiate and high school athletes and determined that the younger athletes took longer to recover, particularly in memory testing.[15] As previously mentioned, it also is suspected that the pediatric brain is more susceptible to second insult until injury has fully resolved. The Concussion in Sport Group recommends guidelines for stepwise return to play.[21] The athlete/student can advance through each level if symptoms do not develop with the activities described. If PCS symptoms develop at a particular level, the patient should return to the previous level for 24 hours before attempting that level again. The group recommends the following steps for return to play:[21]

1) No activity. Complete rest while still symptomatic. When symptoms have resolved, proceed to level 2;
2) Light aerobic exercise (walking, stationary bike), no resistance training;
3) Sport-specific exercise (e.g., running for soccer or football);
4) Non-contact training drills;
5) Full-contact training after medical clearance; and then
6) Game play.

Retirement From Play

Retirement from play should be considered for athletes with a persistently abnormal neurologic exam or persistent concussive symptoms, and those with neuropsychological testing scores that are not at the patient's baseline.[40] Also included are those with abnormal neuroimaging studies, those with increasing recovery times after successive injuries, and those who require less force to suffer a concussion after subsequent injuries.[71] There are no absolute numbers of concussions to guide clinicians at this point. Cantu has recommended retiring players for the season if they've had two to three lower-grade concussions or one to two grade 3 concussions.[40] Patients should be referred to their primary care providers for further guidance on when they may return to play. Preseason concussion assessment and baseline neuropsychological testing could potentially identify those at high risk for injury.[21] If retirement from play is considered too extreme, recommendations for special protective gear or a change in playing position may be given, but this should be done with the cooperation of the primary care provider, coach, and family.

Complications

The risk of recurrent concussions also is subject to debate. It used to be accepted dogma that each concussion rendered the brain more susceptible to subsequent injury, but it has not been scientifically proven. A "three-strike rule" requiring removal of an athlete from play if he or she has sustained three concussions has been used.[72] Recent literature suggests that recurrent concussions have some cumulative effects. In one study of high school athletes, children who had suffered more than two concussions but were currently asymptomatic had neuropsychological test scores that were indistinguishable from those of children with recent concussions.[68] Academic grade point average was also lower in those with multiple concussions, although it is unclear whether this was a result of injury or if it indicates a predisposition of some children to concussive injury. In another study, memory deficits were found to be more pronounced in children with multiple concussions. The evaluation of a child after head injury should include a history of all prior head injuries, previous symptoms of PCS, and documented concussions. This may be difficult because many patients will not recognize all prior concussive injuries. Recollections of coaches or teammates can be unreliable. All previous injuries to the maxillofacial area and neck should be looked into, as these may have been associated with an undiagnosed PCS. The families of children who have sustained multiple concussions should be advised about the risks of repeated injury. Referral for further evaluation and neuropsychological testing should be considered after the patient is evaluated following an acute injury.

Chronic Postconcussive Syndrome (Dementia Pugilistica). Chronic postconcussive syndrome is an Alzheimer's-like condition seen in professional boxers. It is rarely described in other sports. A less severe form is persistent postconcussion syndrome, which is defined as the presence of PCS symptoms after 3 months post-injury. This may be seen in up to 30% of patients.[58] Due to the previous lack of objective, sensitive diagnostic tools, many physicians may have attributed persistent symptoms to a psychological origin rather than an organic one. Secondary gain issues have also been thought to come into play. Children with persistent symptoms have been grouped in with these even though secondary gain may play less of a role. Objective neuropsychological tests will aid in identifying those with true deficits.

Second Impact Syndrome. The second impact syndrome refers to fatal cerebral edema following relatively minor head trauma that occurs while a patient is recovering from a prior injury and is still symptomatic. The second blow to the head can be remarkably minor, with the patient becoming obtunded within a few seconds or minutes.[73] The syndrome is thought to relate to a disruption of the autoregulation of cerebral blood flow and is characterized by the abrupt onset of cerebral edema.[1,73] On most recent review, only 17 cases have been described and all patients were 13-18 years of age.[74] This syndrome is a rare occurrence

and the reported incidence is 1 to 2 in 1.5 million players. The prognosis for this condition is dismal. Potential interventions include osmotic agents. Surgery has no role.

Prevention

There is no proven medical therapy for concussion, so prevention is crucial.

Pre-participation Assessment. Baseline testing is currently recommended by the International Conference on Concussion in Sport.[21] They recommend conducting baseline cognitive assessment and symptom score as pre-participation evaluation in all players in high-risk organized sports, regardless of age or level of performance. This has sparked some debate. Some experts feel the immense output of resources needed to put all amateur athletes through baseline testing is not justifiable.[1] Comprehensive tests take hours and are costly. Many districts do not have access to the testing tools. It has been suggested that comprehensive testing be used only in certain situations, including: multiple concussions; no improvement within 1-2 weeks; and difficulty at school. Three widely available systems are the Immediate Post-Concussion Assessment and Cognitive Testing (IMPACT), the Concussion Resolution Index, and CogSport.

Proper Head Protection. The majority of concussive injuries are sustained while playing football or hockey, both of which require helmet use. Unfortunately, it has been found that only 15% of high school football players' helmets fit.[75] The American Academy of Pediatrics and the American Dental Association recommend the use of mouth guards in high school football players. Mouth guards not only protect the teeth but also realign the mandible. This allows the force of blunt trauma to the jaw and head to be absorbed by the cartilaginous cushion between the top of the jaw and the skull. The New England Patriots team has had no PCS since fitting players with mouth guards. It is presumed that similar protective effects will be seen in athletes playing other sports. The assessment of a head-injured child should include questioning about protective gear worn during injury, and is similar to assessment used for patients involved in motor vehicle or bicycle accidents. This may help guide modification of equipment to prevent future injury.

Education. Athletes, coaches, and families should be educated at the beginning of the season so they can recognize PCS and seek medical attention promptly. They also should be informed of the potential risks and long-term complications so they will take the problem seriously. It's important to note that many individuals in the lay public still believe loss of consciousness is required for concussion to have taken place. Whenever young athletes are seen for any trauma, clinicians should take the opportunity to educate them on the necessity of reporting injuries early and resisting the urge to be stoic and "play through the injury." This can be difficult because adolescents often have some feeling of indestructibility. They also may fear having to sit out of games, thereby losing potential opportunities for higher level of play or scholarships.

Professional athletes are subject to baseline assessment, education, and prevention. These standards also should apply to young amateur athletes, given the risks to brain development and the possibility of long-term complications. Educational programs targeting young athlete groups should be developed. To deliver appropriate care after an acute injury, healthcare providers must be cognizant of the ramifications of concussion.[7]

Resource Note from the authors: *A new resource from the CDC is available free to physicians. It is a kit called "Heads' Up: Brain Injury in Your Practice" and includes fact sheets to prevent concussions and a palm card on the management of on-field sports-related concussions.*

It is available at www.cdc.gov/ncipc/pub-res/tbi_toolkit/toolkit.htm

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CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

CNE/CME Questions

1. Which of the following is true regarding traumatic brain injury (TBI) in children ?
   A. The majority of children who suffer a concussive injury present for medical evaluation.
   B. With the use of protective head gear, football, hockey, and wrestling now have the lowest risk of concussive head injury.
   C. Most medical research on head injury has been focused on adult patients.
   D. The Glasgow Coma Scale is a sensitive tool for the evaluation of mild traumatic brain injury.

2. Which of the following is true regarding injury to the pediatric brain?
   A. The developing brain is remarkably resilient and can more easily recover from traumatic brain injury.
   B. The injured pediatric brain remains edematous for a longer period than the adult brain.
   C. NDMA plays a role in the release of protective amino acids that may aid in the regrowth of neurons after injury.
   D. The amygdala is a region of the brain that is particularly sensitive to injury from head trauma.

3. Which of the following is true regarding diagnostic studies used in the evaluation of postconcussive syndrome?
   A. Alteration of medial temporal blood flow can be determined with single photon emission tomography (SPECT) and positron emission tomography (PET) scanning.
   B. CT scan and MRI are currently the most sensitive tools available

CNE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a letter of credit.** When your evaluation is received, a letter of credit will be mailed to you.

to physicians evaluating postconcussive syndrome.

C. Astroglial protein (S100B) is unique to brain tissue; therefore, can be used as a serum marker of brain injury.

E. Chaotic or increased activity can be seen with EEG tracings of injured brain.

4. Which of the following is true regarding the treatment of postconcussive syndrome in children?
   A. The diagnosis of postconcussive injury is best kept confidential so that the child is not subject to any stigma at school.
   B. Loss of consciousness is the most reliable indicator of concussion.
   C. Sertraline is useful for the treatment of depression associated with concussion.
   D. Methylphenidate has proven to be the most effective medication to treat sleep disturbances and cognitive dysfunction resulting from concussion.

5. A 16-year-old high school football player has suffered a concussive head injury. As the team physician staffing the game, which of the following would you recommend based on the International Conference on Concussion in Sport Guidelines?
   A. Remove from play, return following a graded increase in activity as long as all symptoms resolve over a 7-10 day period
   B. Return to play in the same day, as long as exertion testing is normal
   C. Return to play if asymptomatic for a week
   D. Return to play as long as there was no loss of consciousness

6. Which of the following is true regarding prevention of postconcussive syndrome?
   A. Comprehensive pre-participation baseline cognitive testing is only recommended for athletes in high-risk sports who are younger than age 12.
   B. The use of a mouth guard is useful for preventing dental and maxillofacial injury but it has had little impact on the prevention of concussion.
   C. Medical providers should educate patients and families that loss of consciousness is not required for a concussion to occur.
   D. Recommendations on the use of proper head protection is best left to the discretion of coaches and athletic trainers.

7. According to the Palchak et al decision rule for identifying patients younger than age 2 who are at risk for brain injury after head trauma, the following were identified as risk factors:
   A. Clinical evidence of skull fraction or scalp hematoma
   B. History of Vomiting
   C. Headache
   D. All of the above.

8. According to current literature, the presence or absence of what factor could be the most important prognostic factor in patients following head injury?
   A. Loss of Consciousness
   B. Post traumatic amnesia
   C. Vomiting
   D. Blurred vision.

9. According to the International Conference on Concussion in Sport, the following factor would suggest a complex concussion:
   A. Repetitive concussions, loss of consciousness for more than a minute, concussion involving seizure
   B. A single concussion with *no* loss of consciousness and *no* amnesia.
   C. A concussion with vomiting.
   D. A blow to the head *without* a scalp laceration and dizziness.

10. Following the criteria utilized in the Sun et al modified prediction instrument for identifying significant head injury in the pediatric population after blunt head trauma, which patient would be considered low risk?
   A. An 18-month-old with mild headache, normal level of consciousness, and no scalp hematoma.
   B. A 2-year-old with no scalp hematoma but multiple episodes of vomiting.
   C. An 8-year-old with normal mental status, complaining only of severe headache.
   D. A playful 1-year-old with an egg sized parietal hematoma.

Answers: 1. C; 2. B; 3. A; 4. C; 5. A; 6. C; 7. D; 8. B; 9. A; 10. A

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