



## Pulmonary Complications of Cystinosis

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Increasing longevity of patients with cystinosis<sup>1</sup> has led to an appreciation that a variety of disease manifestations that are infrequent in childhood are becoming more prevalent as patients age. One set of complications targets the respiratory system and contributes significantly to morbidity and mortality of older patients with cystinosis.<sup>2</sup> This section will address the pulmonary complications of cystinosis, namely, respiratory failure from muscle weakness, aspiration because of swallowing abnormalities, and sleep apnea.

### Muscular Weakness

Muscle weakness is the major factor underlying the respiratory problems in cystinosis. A description of the myopathy that occurs in cystinosis is presented below. Relevant to the respiratory system, the myopathic process involves the muscles used for ventilation that can become functionally important. During quiet breathing, approximately two-thirds of the work of inhalation is done by the diaphragm, a sheet-like muscle that forms a dome separating the thorax from the abdominal compartment. When the diaphragm contracts, the dome descends and flattens thereby increasing the volume of the thorax and pushing the abdominal contents downward thereby drawing air into the lungs. During quiet breathing, exhalation is passive due to elastic recoil of the lung tissue that was stretched during inhalation.

Although the diaphragm differs from skeletal muscles by having a higher percentage of fatigue-resistant fibers, greater oxidative capacity, and a larger relative blood flow,<sup>3</sup> there is evidence that it too is damaged during cystinosis, as in other chronic myopathic conditions. Initially, ventilatory muscle impairment becomes apparent only during exercise. This is because relatively little muscular work is required to maintain ventilation at rest because of the lung being very compliant at tidal volumes. With increasing exertion, the work of breathing increases significantly because the lung becomes much less compliant as it is stretched to larger volumes. Furthermore, more energy is needed to overcome the frictional forces generated by more rapid airflow through the airways, resulting in dyspnea at high levels of physical activity. As the muscle becomes progressively weaker, dyspnea will become apparent at lesser levels of exertion, and with very severe myopathy this will occur at rest.

There has been relatively little study of the ventilatory impairment in cystinosis despite anecdotal reports of patients complaining of dyspnea on exertion. Most informative is the study published by Anikster et al<sup>4</sup> who evaluated subjects with cystinosis aged 20-40 years who were admitted to the National Institutes of Health Clinical Center in Bethesda, Maryland between July 1997 and June 1998.<sup>4</sup> Twelve of the 15 subjects studied had nephropathic cystinosis and were renal transplant recipients. The other 3 subjects had non-nephropathic cystinosis with ocular manifestations. All subjects had accumulated at least 17 years without cysteamine therapy.

Pulmonary function tests in the 3 non-nephropathic patients with cystinosis were all normal; however, significant abnormalities were seen in virtually all of the nephropathic subjects (Figure 1). Ten had reduced total lung capacity (TLC) (<80%), which is diagnostic of a restrictive ventilatory defect. The reduced lung volumes could not be attributed to lung scarring, which is the more common cause of restrictive ventilatory abnormalities. In particular, diffusion capacity measurements when corrected for low lung volumes were normal in these subjects and their high-resolution chest tomographic scans did not show evidence of significant fibrotic changes.

A more direct measurement of respiratory muscle strength can be obtained by determining the maximal inspiratory (MIP) and expiratory pressures (MEP) that a patient can generate while forcefully trying to inhale or exhale through an occluded mouthpiece. All of the 8 nephropathic patients who performed the maneuvers had low MIP and MEP. In that study, a combined pulmonary function test score calculated as the mean of TLC, forced expiratory volume, and forced vital capacity (FVC) was directly correlated with the extent of myopathy (Figure 2).

The distribution of muscle weakness in cystinosis is not uniform across all muscle groups. In cystinosis, there is an initial predilection for this to affect muscles of the distal limbs, particularly the small muscles of the hand, and the facial and swallowing muscles.<sup>5</sup> The appearance of weakness of the ventilatory muscles in cystinosis often parallels the involvement of other muscle groups.<sup>4</sup> Occasionally, the diaphragm becomes disproportionately

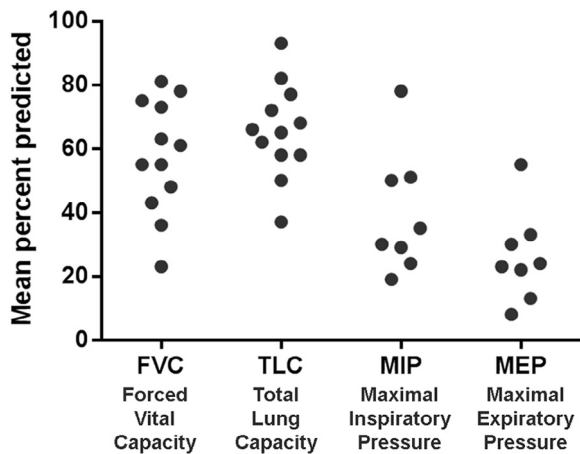
FVC	Forced vital capacity	MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure	TLC	Total lung capacity

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**Figure 1.** Pulmonary function characteristics in patients with cystinosis. Adapted from Anikster et al.<sup>4</sup>

weak. This manifests itself by patients noting that they become more dyspneic when lying supine than when sitting or standing.<sup>6</sup> This phenomenon occurs because when supine the diaphragm must work to push the abdominal contents downward as well as to stretch the lung. When sitting or standing, gravity holds the abdominal contents out of the chest so the diaphragm needs to do less work.

As stated above, progressive ventilatory muscle weakness first manifests itself during high levels of physical activity and, subsequently, during milder levels of exertion. In patients with a sedentary lifestyle who do not place demands on their ventilatory capacity, they may not recognize that they have lost considerable ventilatory function until the impairment becomes quite profound.

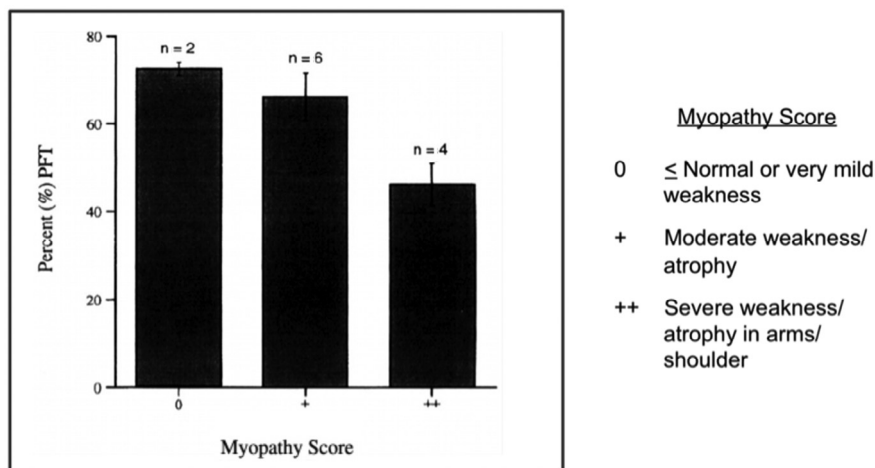
Respiratory muscle weakness also reduces the effectiveness of coughing that is needed to clear the airway of secretions. To generate high expiratory flow rates during a cough,

a person needs to inhale to high lung volumes. Strong intercostal and abdominal muscles and tight glottic closure are also required to generate high intrathoracic pressures that are released suddenly at the start of the cough. The myopathy of cystinosis impairs both inspiratory and expiratory muscle strength. Weakness of the pharyngeal muscles reduces the strength of glottic closure preventing attainment of high airway pressures.

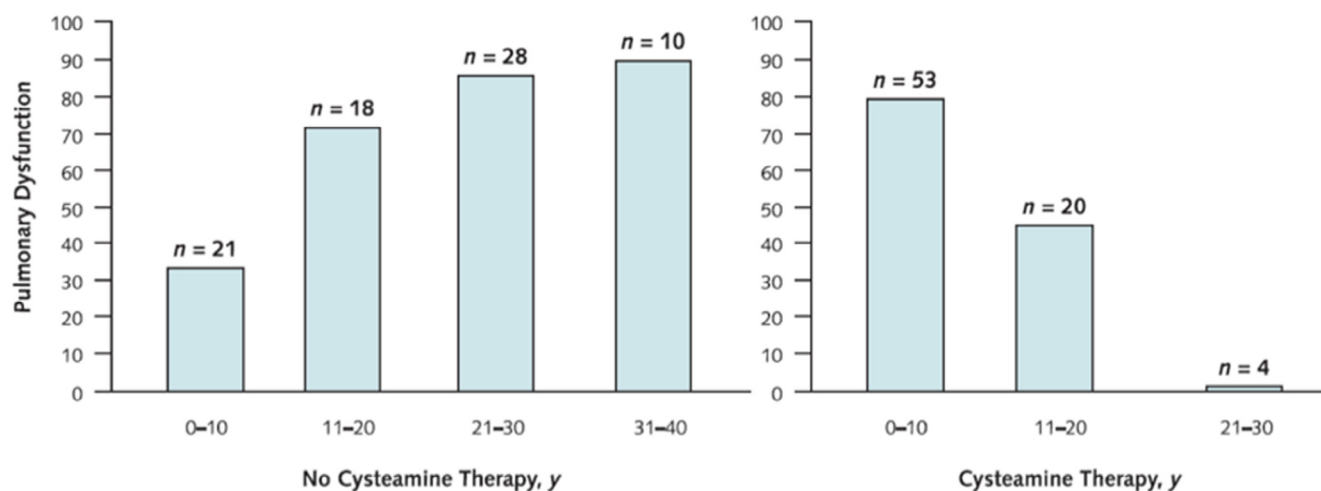
A weak cough increases the incidence and severity of lung infections. Microorganisms that are inhaled into the lungs are not effectively cleared allowing them to multiply and cause bronchitis and/or pneumonia. Once the lungs are infected, an inefficient cough allows secretions to accumulate, thereby increasing the severity and duration of the illness. In the extreme, an impaired cough increases the likelihood of progressing to respiratory failure with the need for assisted ventilation.

### Detection and Diagnosis of Cystinosis-Related Respiratory Muscle Weakness

Spirometry and measurement of maximal inspiratory and expiratory pressures are quite sensitive for detecting respiratory muscle weakness. They should be obtained in all patients with cystinosis when weakness in nonpulmonary muscles first becomes clinically evident. Testing should also be offered to patients who have shortness of breath during exertion that cannot be fully ascribed to other causes. Patients with orthopnea should be tested because it can be sign of diaphragmatic weakness. This positional effect can be quantitated during pulmonary function testing by comparing the patient's vital capacity in the supine and sitting positions. A decrement of >20% when going from sitting to supine suggests diaphragmatic weakness. Patients whose tests are mildly abnormal should have follow-up testing to determine the rate of decline. Annual testing is appropriate,<sup>7</sup> but more frequent testing is suggested if there is significant worsening in symptoms.



**Figure 2.** Relationship between the percentage of predicted pulmonary function test (PFT) and myopathy score in patients with cystinosis. Reprinted with permission from Anikster et al.<sup>4</sup>



**Figure 3.** Frequency of pulmonary dysfunction in patients with cystinosis by duration of oral cysteamine therapy.<sup>2</sup> Reprinted with permission from Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* 2007;147:242-50. Copyright © 2007 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

Arterial blood gas measurements are not a sensitive means to detect early respiratory muscle weakness. The weakness must be profound before a patient's resting minute ventilation decreases and causes arterial carbon dioxide tension ( $\text{PaCO}_2$ ) elevation. Similarly, arterial oxygen tension and hemoglobin oxygen saturation fall only when respiratory muscle weakness and hypoventilation are severe, unless there are other causes for impaired gas exchange in the lung. Some patients have experienced relief by nocturnal noninvasive positive pressure ventilation.<sup>6</sup>

Because there are many conditions that cause a low vital capacity, patients with cystinosis who have decreased vital capacity should be further evaluated to exclude other diagnoses. In addition to obtaining a detailed medical history and performing a respiratory-directed physical examination, further pulmonary function testing is indicated and should include measurement of absolute lung volumes by body plethysmography or gas dilution methods, diffusion capacity, and MIP/MEP. The pattern of results supportive of the diagnosis of respiratory muscle weakness are low vital capacity, low TLC, high residual volume, normal ratio of forced expiratory volume in 1 second to FVC, normal diffusion capacity corrected for alveolar volume, and low MIP and MEP. To further exclude other diseases that can cause a restrictive ventilatory pattern, high-resolution computed tomographic scans should be performed for the detection of parenchymal abnormalities, which should be absent in cystinosis.

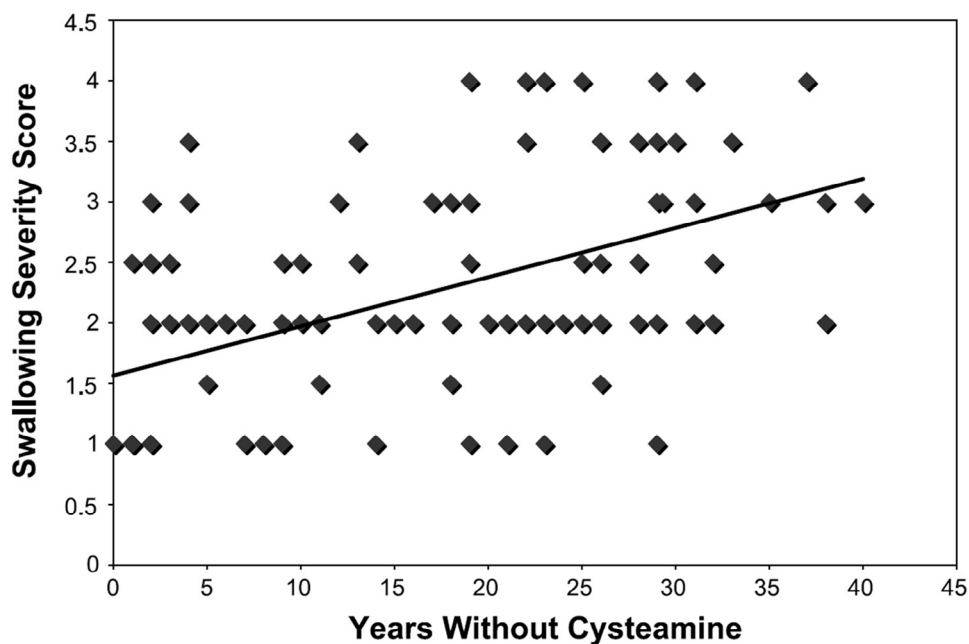
### Prevention and Treatment of Respiratory Muscle Weakness

Cysteamine therapy reduces cystine accumulation in skeletal muscles and has been reported to delay myopathic changes. It is likely that cysteamine has similar benefits for the muscles of

respiration. In support of this conclusion is a cross-sectional study reporting that the degree of pulmonary function impairment is dependent upon the number of years a patient is treated or not treated with cysteamine (Figure 3).<sup>2</sup> Seventy-seven patients had their pulmonary function test results plotted relative to the total number of years of life they were without cysteamine and the total number of years they received treatment. In short, pulmonary function was better in those accumulating more years of cysteamine treatment. None of the 4 patients who had taken cysteamine for over 20 years had respiratory impairment. These data strongly support the concept that cysteamine will delay and potentially prevent the respiratory muscle dysfunction in cystinosis. However, it is unknown whether cysteamine will reverse pre-existing muscle weakness.

As with any person who is susceptible to developing lung disease, it is critically important to avoid smoking. For those who are smoking, effective evidenced-based interventions should be used to assist cessation. Vaccination against influenza and *Streptococcus pneumoniae* should be offered according to guidelines. If other lung conditions are present (eg, asthma), the therapeutic plan should be reviewed frequently and optimized.

When respiratory muscle weakness becomes advanced leading to chronic ventilatory insufficiency, assisted mechanical ventilation is required to prolong life. Until recently, tracheostomy was the only long-term means by which a patient could be connected to a mechanical ventilator. However, there has been steady improvement with noninvasive methods to allow patients to use assisted ventilation and avoid or greatly delay the need for a tracheostomy. Masks that fit over the nose and sometimes include the mouth are commonly used. Small cannulas that fit into the nose are also used and preferred by some patients. Finding a comfortable interface for the patient can take a number of tries, but success is important.



**Figure 4.** Swallowing severity score vs years not on cysteamine: The swallowing severity score is a measure of deglutition function based on analysis of videofluoroscopy of swallowing. A score of 1.0 equals normal swallowing, and a score of 4 equals severe difficulty with aspiration of the bolus and a swallow duration of >5 seconds. Reprinted with permission from Sonies et al.<sup>11</sup>

There are no clinical studies that provide guidelines as to when a patient would benefit from starting assisted ventilation. From a practical standpoint, the decision is influenced by rules from insurance providers regarding whom they will cover for treatment. In the US, the Centers for Medicare and Medicaid Services will pay for assisted ventilation in patients with respiratory impairment because of neuromuscular disease in any of the following situations: PaCO<sub>2</sub> ≥45 mm Hg while awake; hemoglobin O<sub>2</sub> saturation ≤88% for ≥5 minutes during sleep; maximal inspiratory pressure <60 cm H<sub>2</sub>O; or FVC <50% predicted. When patients with neuromuscular disease meet at least 1 of these criteria, assisted ventilation is likely appropriate and is usually initiated first only during sleep. The rationale for starting treatment at night is the belief that supporting ventilation will improve tissue oxygenation and metabolism during sleep. It will also rest respiratory muscles that will improve their function and endurance during the day. As muscle weakness becomes more severe, assisted ventilation can also be used intermittently during the day to reduce dyspnea.

There are few published reports of using assisted ventilation in patients with cystinosis,<sup>6</sup> so the effects on quality of life and survival are unknown. However, there are data from studies of patients with ventilatory impairment because of other types of myopathy. For example, a cross-sectional study in patients with Duchenne's muscular dystrophy showed that noninvasive assisted ventilation was associated with improved survival.<sup>8</sup>

### Cystinosis-Associated Dysphagia

Dysphagia because of weakness of swallowing muscles is common in adults with cystinosis making them susceptible to

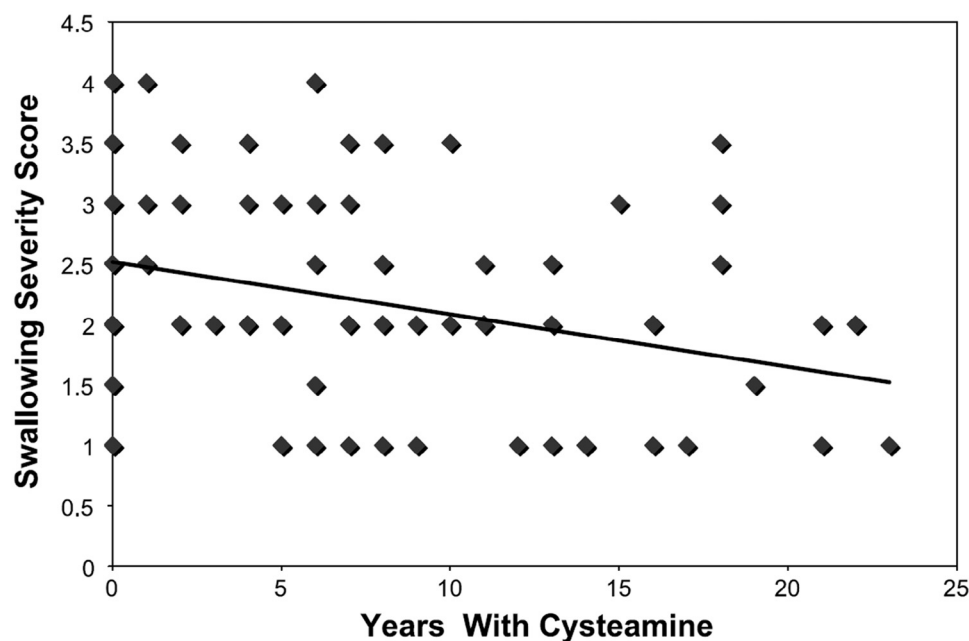
aspirating oral contents into the lungs.<sup>5,9,10</sup> On rare occasion, aspiration of a large bolus of food can obstruct the trachea leading to asphyxiation and death. The onset of swallowing difficulties often coincides with the appearance of weakness in the hands and distal muscles of the arms.<sup>5</sup> The severity of the dysphagia usually parallels the generalized myopathy.

Aspiration often leads to chronic cough because of irritation of the larynx and airways. Aspirated bacteria that are normally present in the mouth can cause bronchitis and pneumonia. The consequences of the infection are made worse for patients with respiratory muscle dysfunction because their weakened cough makes it difficult to clear the airway of secretions. In patients with marginal respiratory muscle function at baseline, the added work of breathing caused by bronchitis or pneumonia can precipitate acute respiratory failure requiring emergent use of assisted ventilation.

Of the 33 deaths that occurred in a study of 100 patients with cystinosis, 5 were respiratory-related, 4 had pneumonia, and 1 had refractory atelectasis.<sup>2</sup> All 5 had significant prior swallowing impairment.

### Prevention and Treatment of Dysphagia

A detailed study of dysphagia in nephropathic cystinosis evaluated the swallowing function of 101 such patients aged 6-45 years (Figures 4 and 5). The authors found more than one-half had significant complaints about swallowing. The abnormalities were linked to muscle dysfunction of the oropharynx, and, most importantly either showed improved or stabilized swallowing while on cysteamine.<sup>11</sup>



**Figure 5.** Swallowing score vs years on cysteamine. Reprinted with permission from Sonies et al.<sup>11</sup>

Early referral to a speech-language therapist with special expertise in swallowing disorders is advisable. Periodic evaluations to define the nature and severity of swallowing difficulties will dictate the appropriate therapeutic approach with the goals being to maintain nutritional status but minimize risk of aspiration. Interventions employed by speech therapists usually include learning safe swallowing techniques and modifying food consistencies to those that are more easily swallowed safely. If swallowing becomes too dysfunctional to maintain nutritional status, adequate intake can be guaranteed by gastrostomy tube feeding.<sup>12</sup>

## Sleep Apnea

Sleep apnea has been reported to occur in patients with cystinosis.<sup>6,9</sup> Although overall incidence of this is unknown, there are aspects of cystinosis that make older patients susceptible to developing it. The patency of the upper airway is maintained during inhalation by phasic contraction of the genioglossus and other pharyngeal dilator muscles. During sleep, the neural output to these muscles decreases but under normal circumstances the level of stimulation is still sufficient to maintain airway patency. Of importance, there are changes that occur in patients with cystinosis that can compromise the integrity of the airway during sleep. The myopathy of cystinosis with prominent involvement of the oral pharyngeal muscle can allow airway collapse to occur during inhalation. This has been described in other types of myopathy that involve pharyngeal muscle groups.<sup>13</sup> Also, alterations in craniofacial morphology have been described in patients with cystinosis that tend

to decrease the dimensions of the upper airway making airway obstruction during sleep more likely.<sup>14</sup>

Based on the predisposition of patients with cystinosis to develop sleep apnea, they should be periodically evaluated for signs and symptoms such as snoring with apneic episodes, morning headaches, and daytime hypersomnolence.<sup>7</sup> Neurocognitive impairment is a well-known consequence of untreated sleep apnea. With the recent appreciation that cognitive impairment can be seen in older patients with cystinosis it is important to insure that sleep apnea is not a contributing factor. To make a definitive diagnosis, patients should undergo formal sleep studies. If sleep apnea is detected, treatment usually begins with continuous or bilevel positive airway pressure breathing to maintain airway patency during sleep.

## Summary

The myopathy of cystinosis causes some patients of variable ages to be at risk for respiratory impairment because of ventilatory muscle weakness, aspiration because of oropharyngeal muscle weakness, and sleep apnea. Chronic cysteamine treatment provides the best approach to delay these complications; however, when present, each complication has treatment options that can be used to reduce their consequences with the goal of improving quality of life and survival. ■

## Author Disclosures

The author declares no conflicts of interest, real or perceived.

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