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Review

Cystic fibrosis: Myths. mistakes, and dogma

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EDUCATIONAL AIMS

The reader will come to appreciate:

1. How treatment of CF has persisted over time despite the evidence
2. Why treatment changes are difficult to implement when established beliefs are challenged
3. That good science can be trumped by poor adherence in the absence of effective communication with patients

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SUMMARY

As a student I recall being told that half of what we would learn in medical school would be proven to be wrong. The challenges were to identify the incorrect half and, often more challenging, be willing to give up our entrenched ideas. *Myths* have been defined as traditional concepts or practice with no basis in fact. A *misunderstanding* is a mistaken approach or incomplete knowledge that can be resolved with better evidence, while firmly established misunderstandings can become *dogma*; a point of view put forth as authoritative without basis in fact. In this paper, I explore a number of myths, mistakes, and dogma related to cystic fibrosis disease and care. Many of these are myths that have long been vanquished and even forgotten, while others are controversial. In the future, many things taken as either fact or "clinical experience" today will be proven wrong. Let us examine these myths with an open mind and willingness to change our beliefs when justified.

INTRODUCTION

Oscar Wilde wrote that, "Experience is simply the name we give our mistakes" [1] and mistakes can certainly be an opportunity to learn. However, entrenched mistakes become dogma that can paralyze progress. A *myth* is defined as a traditional concept or practice with no basis in fact. A *misunderstanding* is a mistaken approach or incomplete knowledge that can be resolved with better evidence, while entrenched misunderstandings can become *dogma*, which is a point of view put forth as authoritative without basis in fact. In this paper, I explore a number of myths, mistakes, and dogma related to cystic fibrosis (CF) disease and care. Many of these are myths that have long been abandoned and even forgotten, while others are controversial. I apologize if my perspective is controversial or troublesome to the reader, but I admit that I have certainly made some unintended mistakes in this manuscript. I am looking forward to correcting these as more data become available. And so we begin with mistakes from the past. Although some of these statements may seem odd to the enlightened reader in 2014, they have all been thought to be true at some time.

CYSTIC FIBROSIS GETS ITS NAME FROM THE PULMONARY FIBROSIS THAT DEVELOPS WITH CHRONIC DISEASE

The term "cystic fibrosis" was used by Dorothy Andersen in 1938, with the full name of the disease being "cystic fibrosis of the pancreas" [2]. Histologically, pancreatic tissue becomes scarred and fibrotic early in life, presumably because of auto digestion. While there can be pulmonary fibrosis that develops with advanced lung disease, the pulmonary manifestations of CF are

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more consistent with chronic and severe bronchiectasis, rather than fibrosis.

CF ALWAYS (OR ALMOST ALWAYS) OCCURS ONLY IN THE CAUCASIAN POPULATION

Although it is true that CF is more prevalent among Caucasians, the disease has been described among all races and nationalities. The estimated carrier frequency of common CF mutations has been estimated at 1 in 25 among Caucasians with a prevalence rate of 1 in 2500, a prevalence of 1:3500 among Hispanics, 1:15,100 among African/Americans, and approximately 1:31,000 to 1:100,000 in Asians, native Hawaiians or Pacific Islanders [3].

Physicians working in CF centers are aware of this and do not discount the possibility of CF in a patient with suggestive clinical findings because of that patient's ethnicity or race. Nevertheless, this pervasive myth does lead to less frequent and later referrals of non-Caucasians to CF centers, even in the presence of clear symptoms of CF [4]. Furthermore, although there are good CF centers in countries like Japan [5] and India [6,7], I have heard well trained pulmonary physicians from top medical centers in Asia, India, and Africa tell me that CF does not occur in their country, and therefore, there is no reason to test for this disease. This persistent myth, in the face of evidence to the contrary, recalls the familiar observation that, "the eye will not see what the mind does not know".

PATIENTS WITH CF USUALLY HAVE FAT MALABSORPTION LEADING TO LARGE BULKY FOUL SMELLING STOOLS, AND THEREFORE FAT SHOULD BE REMOVED FROM THEIR DIET

To pulmonologists completing their training in the last decade, this statement can seem to be beyond belief. How can anybody possibly consider that because fat is poorly absorbed it should be removed from the diet? Yet this was common and accepted practice in many CF centers until Gaskin and colleagues in Toronto demonstrated in the 1970s that restricting fat in the diet may "improve" the quality of stools but it worsens malnutrition, fat soluble vitamins stores, and survival in patients with CF [8,9]. One of the greatest advances in CF care has been to establish a high quality, high protein, high fat, and high caloric diet for persons with CF supplemented by pancreatic enzymes to aid digestion [10].

PANCREATIC ENZYMES ARE IMPORTANT FOR DIGESTING DIETARY FATS AND THEREFORE, PATIENTS WITH CONTINUED FAT MALABSORPTION SHOULD HAVE INCREASING AMOUNTS OF ENZYMES UNTIL FAT ABSORPTION IS NORMALIZED

It was once thought (by some) that pancreatic enzymes are digested as proteins in the intestines and therefore are safe at any dosage. It was not long after Gaskin and colleagues showed the benefits of increased dietary fat supplemented with pancreatic enzymes that some CF centers recognizing that this was a good thing, believed that more enzymes would be even better. Although some patients were able to ingest surprisingly large amounts of pancreatic enzyme without apparently suffering adverse consequences, the risk of severe fibrosing colonopathy increased with increasing dosage of pancreatic enzymes as shown by FitzSimmons and colleagues in the classic paper published in 1997 [11]. At a dosage of over 50,000 units per kg per day, the relative risk of fibrosing colonopathy was more than 200 times that of subjects taking less than 24,000 U/kg/day. Awareness of these risks has led to strict dietary guidelines related to the maximum amount of pancreatic enzymes that are safe.

BECAUSE PATIENTS WITH CF HAVE DIFFICULTY CLEARING SECRETIONS, IT IS BEST FOR THEM TO SLEEP IN MIST TENTS TO LOOSEN SECRETIONS AND AID EXPECTORATION

Tents containing high amounts of water vapor placed over the sleeping child's bed (so called mist tents), were routinely used to treat CF up until the 1970s [12]. In reality, mist tents were not effective in improving sputum clearance or pulmonary function [13,14], patients were lost in the fog and the mist tents quickly became contaminated by pathogenic bacteria leading to earlier acquisition of pseudomonas [15]. Although the dangers of mist tents were known in the CF community, it was often very difficult to get patients to "give up" their mist tents after becoming so comfortable sleeping in the clouds and told being how important these were in clearing secretions.

This naturally leads to a series of myths related to CF mucus and sputum.

CF SPUTUM IS VERY THICK AND VISCOUS

This is such a commonly accepted and pervasive myth that in many countries, CF is referred to as mucovisicosis. Viscosity is a specific measurement of the stress-strain relationship and the rate of energy loss in an ideal "Newtonian" liquid or a viscoelastic gel. This non-recoverable energy loss is referred to as viscosity. In gels, such as sputum and mucus, there is no single viscosity measurement that describes this behavior, but rather a range of viscoelastic behaviors over the range of applied stress. All of this is to say that although the term viscosity is often used loosely to mean something like "thickness", it has a very specific meaning to the rheologist. There have been many studies of sputum rheology in CF, and uniformly these have demonstrated that CF secretions are not exceptionally viscous, particularly when compared to secretions from patients with bronchiectasis, chronic bronchitis, and notably from fatal asthma [16,17]. Of note – and contrary to another myth that it is easier to expectorate secretions that are less viscous - it is often easier to expectorate secretions that are thicker as long as these do not adhere to the airway surface [18].

Although CF secretions are not especially adhesive, they are very adhesive and cohesive (sticky and stringy), and it is this combination, termed tenacity, leads to poor cough clearance and a sensation of "thickness" [19,20]. This has important implications for the next myth.

MUCOLYTICS AND EXPECTORANTS ARE BENEFICIAL FOR PATIENTS WITH CF

Although many different mucolytics have been used to "treat" CF, including N-acetylcysteine, carbocysteine, ambroxal, and expectorants like guaifenesin, none of these are proven to be beneficial [19]. At best, these are a waste of time and money, and theoretically these are potentially irritating and detrimental. The exception to this is dornase alfa (recombinant human DNase), which depolymerizes the secondary tenacious DNA and F-actin polymer network in CF sputum. Dornase has been shown to decrease the frequency of exacerbations and improve lung function in dornase naive persons with CF [21]. There is no proven role for other mucolytics in the treatment of CF nor for using dornase in any other disease [22].

THE PRIMARY PROBLEM IN THE CF AIRWAY IS IMPAIRED MUCOCILIARY CLEARANCE

This is a common myth, but decreased mucociliary clearance is unlikely to be the major cause of airway disease in CF. We know that mucociliary clearance in children with CF is normal in large