

Management of cystic fibrosis in adults

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SUMMARY

Cystic fibrosis is the most common lethal autosomal recessive disease. Mutations in a membrane protein cause secretions such as mucus and digestive juices to be abnormally thick and sticky.

Respiratory symptoms tend to dominate the course of the disease but other complications include gastrointestinal disorders, male infertility, osteoporosis, diabetes and rhinosinusitis.

Due to improved treatments in childhood, the life expectancy of patients with cystic fibrosis has increased. Doctors are now more likely to encounter adults with this disease so being aware of current and emerging therapies used in their management is important.

Introduction

The management of patients with cystic fibrosis has improved over the past 30 years and most people now survive into adulthood. In an Australian study, the mean age at death in 2005 was 26.6 years.¹ As a result doctors other than paediatricians are managing the complications of this disease.

Cystic fibrosis is the most common lethal autosomal recessive disease and occurs in 1 in 2000 people. A defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which regulates the transport of chloride and other electrolytes, causes secretions to be abnormally thick and sticky. These secretions build up in the upper airways and the ducts of various organs affecting the lungs, gastrointestinal tract, pancreas, liver, sinuses, sweat glands and reproductive system. Respiratory problems, such as chronic infection and inflammation, tend to dominate the clinical course and a patient's respiratory status ultimately determines their prognosis.

Managing respiratory disease

There are a number of respiratory complications including acute pulmonary exacerbations, asthma, haemoptysis, pneumothorax and pneumonia. *Pseudomonas aeruginosa* is the predominant organism, however other organisms may colonise the respiratory tract and warrant therapy on occasions.

Non-drug treatments

Because sputum of increased viscosity will lead to worsening airway obstruction, patients are strongly encouraged to perform active airway clearance techniques such as autogenic drainage or positive expiratory pressure to maintain their health. A flutter device can be effective in some patients. This is a hand-held oscillating positive pressure device (see Fig. 1). The patient breathes out through the device against an alternating resistance. Back pressure leads to small airway opening which in turn promotes increased airway clearance.

Mucolytics

Mucolytics are given to improve the viscosity of mucus and aid its clearance. Nebulised dornase alpha (2.5 mg) acts by breaking down DNA, which contributes to the high viscosity of the sputum.² Responses are variable so patients can only continue this treatment on the Pharmaceutical Benefits Scheme if their lung function improves by 10% (forced expiratory volume in 1 second – FEV₁) after a one month trial. There are very few adverse effects although haemoptysis has been reported.

Nebulised hypertonic saline, typically 5 mL of 6% solution twice a day, is also used to reduce mucus viscosity. The high salt content is thought to cause water to influx into the airway lumen and assist with mucus clearance. Many patients benefit from using this medication.³ However, some patients may not tolerate it because of severe bronchospasm or cough.

Inhaled mannitol powder has recently become available for cystic fibrosis.⁴ A standard dose is 400 mg twice a day. Its high sugar content elevates the osmolality within the airway leading to water influx into the lumen. Cough can be a limiting factor in adherence.

Antibiotics

Antibiotics are administered for several possible purposes:

- to eradicate or delay the onset of *P. aeruginosa* colonisation
- to maintain lung function
- to intensify treatment of a pulmonary exacerbation.

Eradication protocols contain intravenous antipseudomonal antibiotics followed by a prolonged course of nebulised colistin and oral ciprofloxacin.

Fig. 1 Flutter device



Picture courtesy of the author

Maintenance strategies include long-term treatment with oral azithromycin.^{5,6} Nebulised tobramycin or colistin cycling over some months to years, and other oral antibiotics sometimes given in a rotating fashion, are commonly used. However, there is no evidence for this practice.

Exacerbations

An exacerbation is difficult to define. One definition⁷ requires the patient to have two out of a possible seven symptoms – including fever, increased sputum volume (by 50%) and increased cough frequency (by 50%) as well as at least one of three additional clinical criteria such as a drop of 10% in forced vital capacity.

As the majority of adult patients are colonised with *P. aeruginosa*, therapies are directed at this organism. For mild exacerbations, oral ciprofloxacin (2 week course) and nebulised aminoglycoside (2–4 week course) are used. Typically, nebulised tobramycin 80–160 mg twice a day is given. Nebulised colistin (for example 1–2 million units twice a day) could be used as an alternative to tobramycin. This trial switch in therapy would be indicated if the patient was not responding to nebulised tobramycin or was intolerant (for example developing bronchospasm). Nebulised antibiotics rarely cause systemic adverse effects but with time can cause hearing impairment or balance problems in some patients.

If *P. aeruginosa* is not commonly isolated from the patient's sputa, a course of dicloxacillin (for example 500 mg four times a day) for *Staphylococcus aureus* colonisation or amoxicillin/clavulanic acid (for example 875/125 mg twice a day) may be used. Other pathogens that are sometimes isolated and need targeted therapy include *Stenotrophomonas maltophilia* (sulfamethoxazole/trimethoprim) and *Haemophilus influenzae* (amoxicillin).

For more severe exacerbations, patients are hospitalised and given intravenous antibiotics typically

with a combination of a beta lactam-derived antibiotic (for example ticarcillin/clavulanic acid or ceftazidime) with an aminoglycoside (for example tobramycin as a single daily dose). The duration of these treatments is about 10–14 days. This empirical approach is justified as studies have shown that sputum sensitivities are not a useful guide to choosing therapy.⁸ Often the choice of drugs is dictated by previous allergies or intolerances of various antibiotics. Because deteriorating patients require frequent courses of these antibiotics, they should be closely monitored for long-term complications such as renal and hearing impairment.

Inhaled bronchodilators

Many patients regularly use short-acting bronchodilators, such as salbutamol, to aid airway clearance and enhance delivery of other inhaled drugs. Research on tiotropium, a long-acting anticholinergic, is just beginning.

Inhaled steroids

Some patients with cystic fibrosis take these medications regularly to assist with asthma control or lung inflammation. Adherence and effectiveness are very variable. There is limited evidence for bacterial contamination of inhaler devices but it may occur.⁹

Rhinosinusitis

Rhinosinusitis is very common in cystic fibrosis and can be managed with a combination of saline sprays, inhaled steroids and sometimes oral prednisolone. Surgery may be required in some cases.

Managing gastrointestinal disorders

Maintenance of nutrition is critical for patients with cystic fibrosis. Mechanisms for weight loss include suboptimal pancreatic function, diabetes, chronic anorexia related to chronic suppurative lung disease, the catabolic effect of chronic respiratory infections and the increased work of breathing.

Patients can suffer from a range of gastrointestinal disorders including pancreatic insufficiency, liver disease (cirrhosis in 5% of patients), bacterial overgrowth and distal intestinal obstruction syndrome. About 15% of patients who are pancreatic sufficient can develop episodes of acute pancreatitis.

Pancreatic enzymes

Most patients have pancreatic insufficiency and thus require lifelong enzyme replacement. This is titrated to the fat content in each meal or snack with the aim being to control symptoms of abdominal cramping pain and steatorrhea and to maintain weight. A typical dose would be around 3–4 capsules with meals and 1–2 capsules with snacks, but this is highly variable.

Salt and fluids

Patients are strongly encouraged to take adequate salt and fluid throughout the whole year. Many patients take 4–8 salt tablets per day depending on the season. Fluids are generally electrolyte solutions (for example Glucolyte) with patients typically requiring 1–3 sachets per day.

Vitamins

Fat-soluble vitamins (namely vitamins A, D, E and K) are replaced by prescribing a combination therapy known as VitABDECK (2 tablets every morning).

Oral supplements

The most commonly used oral nutritional supplement is Ensure which is available as 200 mL tetrapaks. A number of patients would take about 2–4 of these per day. Other options include Ensure Plus (contains increased calories), Sustagen, Resource and Scandishakes.

Calcium and bisphosphonates

Patients with cystic fibrosis are at increased risk of osteoporosis and many take oral calcium and additional vitamin D. Osteoporosis is monitored by bone mineral densitometry twice a year and is treated with bisphosphonates (and testosterone when appropriate).

Proton pump inhibitors

Gastro-oesophageal reflux is very common and often requires chronic therapy with a proton pump inhibitor.

Enteral feeds

A significant minority of patients need to administer nutritional supplements via a self-inserted nasogastric tube (usually about 1 L per night) to maintain their body weight. Gastrostomy is occasionally required instead.

Ursodeoxycholic acid

A small percentage of patients with significant liver dysfunction are treated with ursodeoxycholic acid (500 mg twice a day) in an attempt to delay progression of liver disease to cirrhosis. However, evidence for this effect is lacking.

Diabetes

Diabetes is caused by destruction of the endocrine pancreatic glands from inflammation in the exocrine component of the pancreas. If diabetes develops, insulin is usually commenced.

Reproductive health

Male infertility is universal due to absence of the vas deferens. Men who want to start a family should be referred to a fertility centre for aspiration of sperm

which can then be used to fertilise the partner's eggs via *in vitro* fertilisation.

Pregnancy

Many women with cystic fibrosis can conceive naturally and should be using contraception until they decide to try for a pregnancy. We recommend that they discuss their intentions with their doctor before attempting to conceive. Genetic counselling is also important for couples planning to start a family.

Pregnancy poses a number of challenges. Often women have an increased frequency of respiratory exacerbations as the pregnancy progresses. Nutrition is harder to maintain so often additional supplements are required. Gestational diabetes may occur.

Adherence to therapy

As with other chronic diseases, adherence is a problem for many patients who often have a complicated therapy regimen. Team members work with the patient to enhance adherence using techniques such as motivational interviewing. Ongoing monitoring of adherence and appropriate advice and encouragement to address these problems are essential in managing the many challenges inherent in this chronic disease.

New therapies

As a result of ongoing research, new therapies have been developed targeting specific genetic mutations. For example, a randomised trial with a CFTR potentiator (VX770) has shown improvements in lung function and nutrition as well as demonstrating a partial correction of the electrolyte imbalance at the cellular level (chloride levels in sweat fell significantly).¹⁰ The compound is administered as a daily tablet which enhances the function of the abnormal CFTR in the membrane of epithelial cells throughout the body. It is used in patients with one or two G551D cystic fibrosis mutations in the genotype.

Conclusion

Cystic fibrosis is a complex multisystem disease which primarily affects the lungs and the pancreas. There are many therapies available to improve the health of the patient. Regimens tend to be quite involved so encouraging adherence is very important. Optimal management of these patients is achieved via a dedicated multidisciplinary team.

Patient survival has improved dramatically over a number of decades. However, new challenges are emerging because of antibiotic resistance and allergies. New treatments targeting the specific CFTR defect are becoming more available. ◀

Conflict of interest: none declared

**SELF-TEST QUESTIONS***True or false?*

- Cough may limit the use of hypertonic saline and inhaled mannitol powder in patients with cystic fibrosis.
- Mild pulmonary exacerbations are usually managed with an intravenous combination of ticarcillin/clavulanic acid and tobramycin.

Answers on page 135

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Cystic Fibrosis Australia

Cystic Fibrosis Australia promotes health and support services for children, youth and adults with cystic fibrosis, and their families. With its state and territory organisations, it distributes information at national and international levels.

Brochures, books, videos and information packs are available via the website, and there is an online forum for people to share their experiences with managing cystic fibrosis. A trust funds research into cystic fibrosis, and promotional events include the national 65 Roses Day (www.65rosesday.org.au).

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