Primary care for young people with cystic fibrosis

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Cystic fibrosis (CF) is a relatively common, complex chronic condition. This article provides an overview of the common aspects of care for patients with CF and highlights the potential for general practitioners to complement the care provided by specialist CF services at each life stage.

Cystic fibrosis (CF) is a life-limiting, autosomal recessive condition that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The CFTR is an ATP-regulated chloride and bicarbonate channel normally found on the apical surface of epithelial cells. Absence or dysfunction of the CFTR protein results in abnormal epithelial ion transport. The clinical manifestations include suppurative lung disease, pancreatic exocrine insufficiency, biliary cirrhosis and increased sweat electrolyte loss (Figure).

There are about 3300 people living with CF in Australia, more than 50% of whom are adults.[1] Improved survival means that CF may now be regarded as a chronic, multisystem disease of adolescence and young adulthood. Most people with CF (95%) are diagnosed by the age of two months through newborn screening. The median life expectancy is 50.9 and 40.6 years in Canada and the USA, respectively, with men living longer than women.[2] The improvement in outcomes can be attributed to changes in clinical practice, including newborn screening, early introduction of aggressive respiratory and nutritional management, and an emphasis on multidisciplinary care at specialist CF centres.

The latest advance is the development of medications that restore CFTR function. The first of these, ivacaftor, is now used routinely for patients with gating mutations. In such patients the CFTR protein reaches the cell membrane but the channel does not open properly and chloride transport cannot occur. Although gating mutations comprise only nine alleles, affecting just 8% of patients in Australia and about 4 to 5% worldwide, the proof of concept has been established.[1,3]

In a randomised, double-blind, placebo-controlled trial of 161 subjects with at least one *G551D CFTR* mutation (the most common gating mutation), ivacaftor was associated with a mean increase in forced expiratory volume in one second (FEV_1) percent predicted, with a treatment effect of 10.6 percentage points at 24 weeks.[4] At 48 weeks, sweat chloride levels

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Key points

- **Improved survival means that cystic fibrosis (CF) may now be regarded as a chronic, multisystem disease of adolescence and young adulthood.**
- **Care for patients with CF is typically provided at specialised CF centres by multidisciplinary teams.**
- **Engagement of young people with CF with a general practitioner is particularly important to complement the care provided by specialist CF services at each life stage.**
- **Treatment considerations in patients with CF include minimising respiratory exacerbations and deteriorating pulmonary function, treating gastrointestinal manifestations such as pancreatic insufficiency and distal intestinal obstruction syndrome, monitoring nutritional status and treating CF-related diabetes.**
- **Adolescence brings an added layer of complexity to management and adolescents with CF may show poor adherence with treatments.**
- **Addressing health concerns not specific to CF, including developmental concerns, mental health and sexual health and contraceptive advice is an area that has lacked attention.**

of subjects in the treatment group had on average decreased to below the diagnostic threshold for CF, with a treatment effect of 47.9 mmol/L. Weight had increased by 2.7 kg more among the treatment group, and there had been a 55% reduction in the risk of pulmonary exacerbations. There were also significant improvements in quality of life measures.[5]

Medications for the most common *CFTR* mutation, *p.F508del*, are under development. Although the effects of the currently available (although not PBS-subsidised) combination therapy lumacaftor/ivacaftor are modest compared with those of ivacaftor in the population with the *G551D* mutation, it is likely that future developments will further improve patient outcomes.

Growing up with CF is associated with a substantial treatment burden and significant morbidity. Adolescents and young adults with CF are expected to face the same challenges and achievements as their peers without CF, including those related to education, employment, relationships and, often, parenthood, while at the same time managing their complex chronic disease. It is in this context that engagement with a general practitioner is of particular importance to the delivery of good health care to the young person with CF, with the potential to complement the care provided by specialist CF services at each life stage. The aim of this article is to describe the current model of specialist CF care in Australia, to summarise the medical problems commonly encountered by adolescents and young adults with CF and to highlight areas for engagement with a general practitioner.

Cystic fibrosis care

Care for patients with CF is typically provided at specialised CF centres by multidisciplinary teams including respiratory

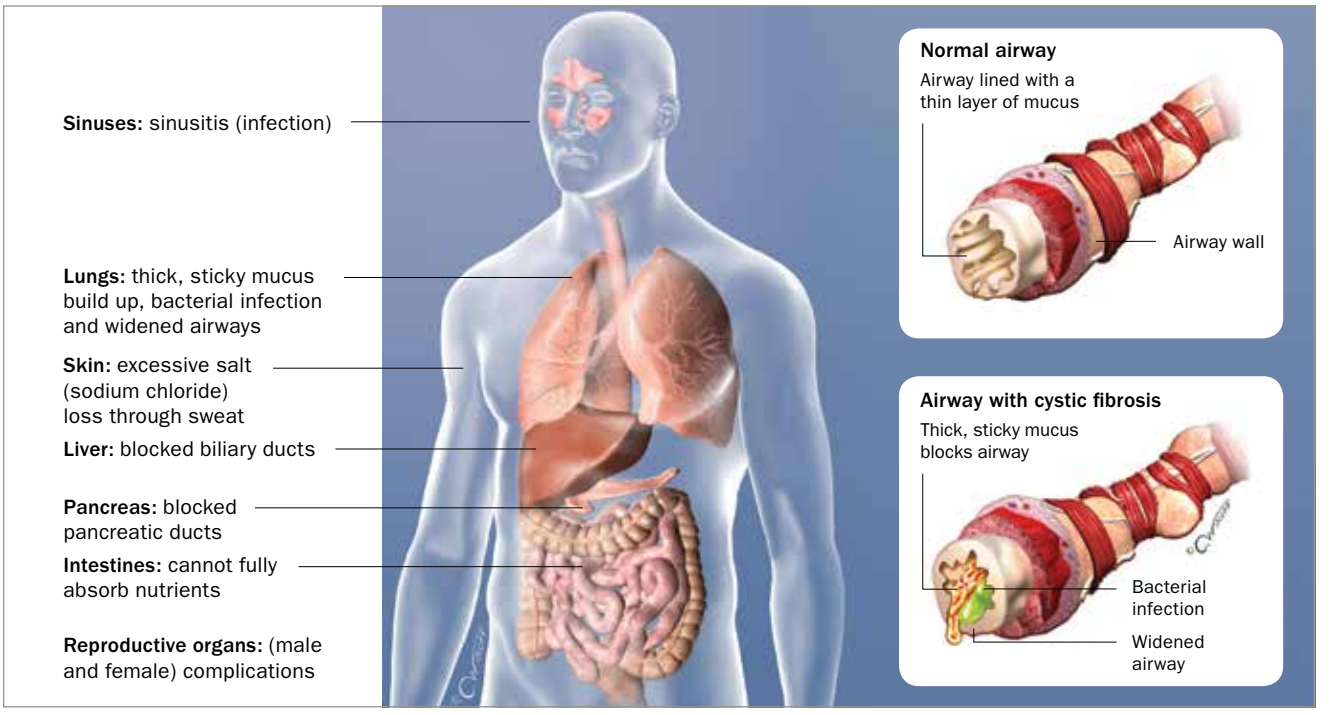

Figure. Organs affected by cystic fibrosis, including a comparison of a normal airway and an airway of a person with cystic fibrosis.

physicians or respiratory paediatricians, nurses, physiotherapists, dietitians, psychologists and social workers. From infancy, patients attend at least four outpatient appointments per year, with additional appointments as required for acute deterioration or medical subspecialist (i.e. gastroenterology, endocrinology) review. They are commonly admitted to hospital multiple times per year for about two weeks, and admissions are usually planned days to weeks in advance. Telehealth and hospital-in-the-home facilities are increasingly used to reduce patients' time away from school or work and to minimise the burden on patients and their families. Anecdotally, many families may turn to their CF multidisciplinary teams as surrogate primary care providers; however, health concerns not specific to CF (including, for example, developmental concerns, mental health and sexual health and contraceptive advice) are not routinely addressed.

Common clinical presentations of cystic fibrosis

Case scenario 1

Simon, a 12-year-old boy with CF presents with a two-week history of productive cough. He has associated viral symptoms and others in the household are unwell. He is growing normally, rarely misses school, participates in sporting activities, does not usually cough and his baseline FEV_1 is 90% predicted. He typically grows Haemophilus influenzae *on sputum culture. He has not been infected with* Pseudomonas aeruginosa *for some years.*

Although Simon is generally doing well, it is important to recognise that 80% of people with CF die as a result of respiratory failure secondary to progressive bronchiectasis in early to middle adulthood, and aggressive treatment of respiratory symptoms, as outlined below, is a cornerstone of management. The abnormal airway surface fluid creates an environment that promotes bacterial infection (with *Staphylococcus aureus, H. influenzae, P. aeruginosa*) and a vigorous inflammatory response. CF lung disease begins in infancy, and even in the absence of symptoms almost two-thirds of preschool children with CF have some degree of bronchiectasis evident on serial CT chest scans.[6] Despite this, most have normal lung function when first measured by spirometry at the age of 6 years. FEV_1 is directly related to survival, and a decline in this measure commonly accelerates during adolescence.[7]

The foundations of respiratory treatment are daily airway clearance (chest physiotherapy) and antibiotics to treat infection. Many centres use prophylactic antibiotics for the first one to two years of life, continuing them thereafter on an as-needed basis. Mucolytic therapy, such as nebulised dornase alfa and hypertonic saline, are often introduced in early childhood.

Respiratory exacerbations, defined as an increase in symptoms (e.g. productive cough, dyspnoea) from baseline, are typically associated with deterioration in pulmonary function, from which recovery is often incomplete. Patients with a normal range FEV_1 (80 to 120%) have historically been least likely to receive treatment for such exacerbations and are most likely to fail to regain their premorbid lung function.[8]

At the onset of a viral illness or of any new respiratory symptoms, patients are advised to commence antibiotics (based on their recent sputum cultures), increase their airway clearance to twice daily and contact their CF team if there is no improvement in seven to 10 days. Sputum samples should be obtained, and subsequent antibiotic selection

is guided by the results of microbiological culture. Lung function tests can be helpful to ensure patients return to their baseline level. Those who do not respond to outpatient therapy are admitted to hospital for intravenous antibiotics, intensive airway clearance and multidisciplinary assessment (known as a 'tune-up') over a period of 10 to 14 days.

Case scenario 2

Jasmine, a 15-year-old girl with CF, is brought to your practice by her parents as she has lost 2 kg over the past six months. Her body mass index is now on the 20th percentile for age. Her lung function, currently 70% predicted, has decreased by 10% during the same period. She has just started Year 9 at a new school, where her friends are not aware of her diagnosis, and tells you that she does not like taking her pancreatic enzyme replacement tablets in front of them.

Jasmine, in mid-adolescence, brings an added layer of complexity to management as she wrestles with personal identity, peer relationships and autonomy in the context of chronic illness. Declining adherence with treatment is a common manifestation of these struggles. It is important to realise that the gastrointestinal epithelium is profoundly affected by the absence of functional CFTR protein. In the pancreas, inspissated secretions lead to duct obstruction and autodigestion, resulting in exocrine pancreatic insufficiency in 85% of patients, typically by 1 year of age. The manifestations of fat malabsorption are failure to thrive and steatorrhoea and management is with oral pancreatic enzyme replacement therapy (PERT). Failure to take sufficient enzymes to match fat ingestion may cause weight loss. Adherence with PERT, particularly at school, is a common problem in adolescence.

Nutritional status is directly related to lung function, and unintentional weight loss is a sign of clinical decline. Both energy expenditure and loss are increased (due to increased metabolic requirement in the setting of chronic infection/inflammation and malabsorption, respectively). Increased caloric intake (to 125 to 150% recommended) is typically required, aiming for a body mass index greater than or equal to the 50th percentile for age.[9] This requirement may increase further with the development of suppurative lung disease, and nutritional supplementation, either orally or via overnight gastrostomy feeds, is commonly needed.

CF-related diabetes can be another cause of weight loss. CF-related diabetes is secondary to a combination of reduced insulin production (destruction of islet cells occurs over time) and peripheral insulin resistance. It typically begins in adolescence, and by adulthood 50% of the population with CF are affected.[10] The clinical presentation is often insidious, with weight loss and unexplained decline in pulmonary function. Patients are treated with low doses of long-acting insulin, with a target glycated haemoglobin (HbA_{1c}) level of less than 6%. Caloric restriction is not recommended; rather, an approach that favours matching insulin doses with measured blood sugar levels is used. Oral hypoglycaemic agents are not used. Vascular complications are now expected to become apparent in patients with CF-related diabetes as survival among people with CF has increased.

Jasmine's presentation is concerning and the cause of her weight loss is likely to be multifactorial. Considerations should include nonadherence with PERT (and potentially other CF therapies), disordered eating, concerns regarding body image, mental health and coping with her disease, worsening lung disease and the development of CF-related diabetes.

Case scenario 3

Samuel, a 16-year-old boy with CF, presents with a four-day history of cramping abdominal pain and loss of appetite. He has vomited twice. He is often constipated and experiences intermittent abdominal pain. He was diagnosed with CF as a newborn with meconium ileus, requiring bowel resection. On examination, his abdomen is distended and tender (maximally in the right lower quadrant).

Samuel is most likely to have distal intestinal obstruction syndrome (DIOS). In the gut, thick inspissated faecal matter and altered motility result in a spectrum of clinical problems, ranging from constipation to acute bowel obstruction. Fifteen percent of neonates with CF present with meconium ileus. In older children and adults, similar pathophysiology results in DIOS and patients classically present with abdominal pain, distension, vomiting and a right lower quadrant mass.[11] In Samuel's case, the differential diagnosis includes bowel obstruction secondary to adhesions from previous surgery, and intussusception (with inspissated faecal matter acting as the lead point).

Risk factors include previous episodes of DIOS, severe CF genotype with pancreatic insufficiency, poorly managed malabsorption and lack of adherence with PERT, constipation and intercurrent illness causing dehydration. Patients with suspected DIOS or unexplained abdominal pain should be referred to their CF centre for urgent assessment. In the early stages, macrogol may treat the DIOS. Preventive treatment should include the message of adherence with PERT, adequate salt and water intake (particularly during the summer months) and regular laxatives.

Case scenario 4

Annika, a 20-year-old woman with CF, presents for advice regarding contraception. Her FEV_1 is 55% predicted and has been stable for the past two years. She takes regular antibiotics and has three to four inpatient 'tune-ups' per year. She had a central venous access device inserted at the age of 16 years. She also has CF-related liver disease. She often initiates topical treatment for candidiasis. She tells you that she has never really discussed sexual health with her CF team.

With improved physical health, young people with CF are expected to have similar sexual and reproductive health milestones and behaviours as their peers without CF, including those related to the timing of puberty and first sexual activity.[12]

Women with CF are fertile and appropriate contraception is very important. There are several CF-specific factors to consider, including the risk of venous thromboembolism, which is increased by totally implantable venous access devices as well as the combined oral contraceptive pill (COCP), reduced bone density, liver disease and potential inconsistent absorption of oral medications. Although

interactions between most common antibiotics and oral contraceptive agents are not of concern, liver enzyme-inducing antibiotics (e.g. rifampicin) do reduce the effectiveness of the COCP. As is increasingly recommended for all young women, it would be appropriate to consider the early use of long-acting reversible contraceptive agents, such as a hormonal intrauterine device.

Women with CF have successfully given birth to healthy babies. The risks of pregnancy are greatest in those with reduced or unstable lung function. Ideally, pregnancy should be planned, with preconception optimisation of maternal physical health and psychological and genetic counselling.[13]

The offspring of women with CF will be CF carriers and have a one in 50 risk of CF without carrier screening of the woman's partner. Pregnancies in women with CF are considered high risk and require multidisciplinary management by CF, obstetric and neonatal teams. Mothers with CF may struggle to give attention to maintaining their own health while looking after the baby. Further, the lung function of some women who fall pregnant may decline more rapidly and not fully recover to the pre-pregnancy baseline, and this may be associated with a further reduced life expectancy.

Most men (98 to 99%) with CF are infertile due to congenital bilateral absence of the vas deferens. Fertility can be confirmed by semen analysis, and biological fatherhood is possible using assisted reproductive technologies (e.g. IVF with intracytoplasmic sperm injection). Men with CF have described confusing infertility with impotence, particularly during adolescence, and not understanding the need for barrier protection from sexually transmitted infections.[12]

Genital candidiasis and stress urinary incontinence are common, often underreported but manageable complications in both women and men with CF. The latter occurs in the setting of increased coughing, may interfere with airway clearance, exercise and spirometry and has been associated with poorer mental health outcomes.[14] Management includes treatment of constipation, screening for diabetes and pelvic floor physiotherapy.

Case scenario 5

Ben is 24 years of age and concerned about his increasing stress levels. He lives with his girlfriend and has just started work as a plumber. He has moderate CF lung disease, spends 45 minutes twice daily doing nebulisers and airway clearance and has two 'tune-ups' each year.

Patients are transferred to adult CF services after they complete high school. Many (38%) go on to complete further education, and to be in married or de facto relationships. Most (67%) are employed in full-or part-time positions.[1] CF care is time consuming and some people report difficulty balancing the demands on their time.

The prevalence of anxiety and depression in young people and adults with CF, as well as in their parents and caregivers, is increased two- to threefold above community levels.[15] They are expected to engage in risk-taking activities including cigarette smoking, alcohol consumption and illicit drug use at similar rates to their peers without CF. Annual mental health screening is recommended, and transition to adult services is a key opportunity for increased primary care support.

Conclusion

A positive relationship with a regular general practitioner and closer collaboration between CF teams and the patient's general practice are likely to considerably improve the health care provided to young people with CF, and in particular, to augment the provision of general health care, including preventive health measures. RMT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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