

## 9. Cystic fibrosis

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## 9.1 Key points

### What is cystic fibrosis?

- Cystic fibrosis is a life-shortening disorder affecting electrolyte transport in epithelial cells in the lungs, pancreatic ducts, biliary ducts, gastrointestinal tract, sweat ducts and vas deferens.
- Cystic fibrosis is an autosomal recessive condition, more common in people of northern European descent.
- Cystic fibrosis affects approximately one in every 2500 births in Australia.

### Common clinical features

Cystic fibrosis has a variable clinical picture and course.

Its features include:

- Chronic suppurative lung disease.
- Failure to thrive, due primarily to pancreatic exocrine insufficiency.
- Excessive salt loss in sweat.
- Neonatal intestinal obstruction (meconium ileus).
- Infertility in males (congenital absence of the vas deferens) and reduced fertility in females.
- Liver disease.
- Diabetes mellitus.

### Management issues

- Chronic suppurative lung disease is the most serious complication of cystic fibrosis and is progressive. Treatment is focused on minimising respiratory disease with regular chest physiotherapy and antibiotics. Other treatment goals are achieving normal growth, nutrition and, in adulthood, dealing with reproductive issues.
- Optimum management occurs with a multidisciplinary team and regular attendance at specialist cystic fibrosis centres. Admission to hospital may be necessary on occasion for intensive physiotherapy and antibiotic treatment.

The median survival in Australia is currently 30 years. With early diagnosis, improved treatments and a better understanding of the disorder, average life expectancy is increasing.

### Investigations

The majority of cases are diagnosed by newborn screening; the remainder are diagnosed on the basis of clinical features with laboratory confirmation by either elevated sweat electrolytes and/or the presence of two cystic fibrosis gene alterations (mutations).

#### *Newborn screening*

See also Part J *Newborn screening*.

- Newborn screening is a free test provided for all babies. A sample of blood is collected by heelprick onto a Guthrie card 48 to 72 hours after birth.
- Newborn screening detects approximately 95% of babies with cystic fibrosis (Massie et al. 2000).
- Newborn screening is performed in three phases and may include DNA analysis and sweat testing.
- Newborn screening may detect carriers of cystic fibrosis.

## Sweat tests

- A sweat test detects raised levels of sodium and chloride, typical of cystic fibrosis and is the gold standard test for diagnosing cystic fibrosis.
- If there is clinical suspicion of cystic fibrosis, a sweat test should be arranged, even if the patient has had a normal newborn screening result.
- Sweat tests can be performed at any age, but adequate sweat volumes may not be obtained before six weeks of age.

## DNA (gene) tests

- There are >1000 gene alterations known to cause cystic fibrosis (Cystic fibrosis mutation database), although one predominates in Australia ( $\Delta F508$ ). Standard genetic testing of affected babies tests for 17 gene changes.
- DNA testing identifies the causative genetic alterations in most cases.
- Identification of the gene alterations allows carrier testing of other family members and prenatal diagnosis in subsequent pregnancies.
- A DNA screen will not detect all cases of cystic fibrosis. Sweat tests are recommended as a more definitive diagnostic test.

## Carrier testing

Referral to genetic services is recommended before carrier testing.

- Carriers of cystic fibrosis carry one altered copy of the gene causing cystic fibrosis and one normal copy. Cystic fibrosis carriers are healthy.
- Approximately one in 25 Australians are carriers of cystic fibrosis.
- Carrier testing is performed to identify couples who are both carriers of cystic fibrosis and therefore have a one in four risk of having a child with cystic fibrosis for each pregnancy.
- Ideally, carrier testing should be performed prior to pregnancy
- Carrier testing cannot detect all gene changes and therefore will fail to detect some cystic fibrosis carriers.

## Who should be offered carrier testing?

- Relatives of people with cystic fibrosis.
- Partners of people with cystic fibrosis.
- Partners of cystic fibrosis carriers.
- Close consanguineous relationships in ethnic groups where the cystic fibrosis carrier rate is high (for example, Anglo-Saxon, Jewish).
- Men with congenital absence of the vas deferens and their partners.

## Prenatal diagnosis

- Carrier couples considering pregnancy should be referred to Genetic Health Services Victoria for discussion of options such as pre-implantation diagnosis with IVF technology and prenatal diagnosis. The feasibility of pre-implantation diagnosis may need to be determined prior to pregnancy.
- Prenatal diagnosis is performed on samples taken by chorionic villus sampling, from 11 weeks gestation. Pre-and post-test genetic counselling is necessary (National Pathology Accreditation Council 2000), and it is strongly recommended that carrier couples are referred to the Genetic Health Services Victoria for coordination of the prenatal diagnostic procedure, counselling and support.

## 9.2 Background

### What is cystic fibrosis?

Cystic fibrosis is the result of gene changes in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which regulates chloride and sodium transport in the epithelial surfaces of the bronchi, pancreatic and biliary ducts, the gastrointestinal tract, sweat ducts and the vas deferens. The defects in electrolyte transport caused by cystic fibrosis result in thick tenacious secretions. The presence of these secretions causes airway obstruction, initiates suppurative lung disease and, in other organs, can result in *obstruction*.

Cystic fibrosis is an autosomal recessive condition. People with cystic fibrosis have two alterations in the CFTR gene. There are approximately 1000 known CFTR gene changes (Cystic fibrosis mutation database). There are approximately 600 people in Victoria with cystic fibrosis, two-thirds of these are children, one-third are adults.

### What are the common clinical features?

There is variability in clinical features and clinical course.

Clinical features may include:

- |  |      |
|--|------|
| • Chronic suppurative lung disease       | 95%  |
| • Pancreatic exocrine insufficiency      | 85%  |
| • Sweat gland salt loss                  | 100% |
| • Male infertility (absent vas deferens) | 99%  |
| • Meconium Ileus                         | 20%  |
| • Distal intestinal obstruction syndrome | 20%  |
| • Cystic fibrosis-related diabetes       | 20%  |
| • Chronic liver disease                  | 20%  |
| • Nasal polyps                           | 10%  |
| • Arthropathy                            | 10%  |
| • Osteoporosis                           | 30%  |

Some clinical features are influenced by genotype.

### Which investigations?

The sweat test is the definitive test for cystic fibrosis.

#### *Newborn screening*

The majority of babies with cystic fibrosis will be detected in the neonatal period by the Newborn Screening Program. Newborn screening for cystic fibrosis commenced in 1989.

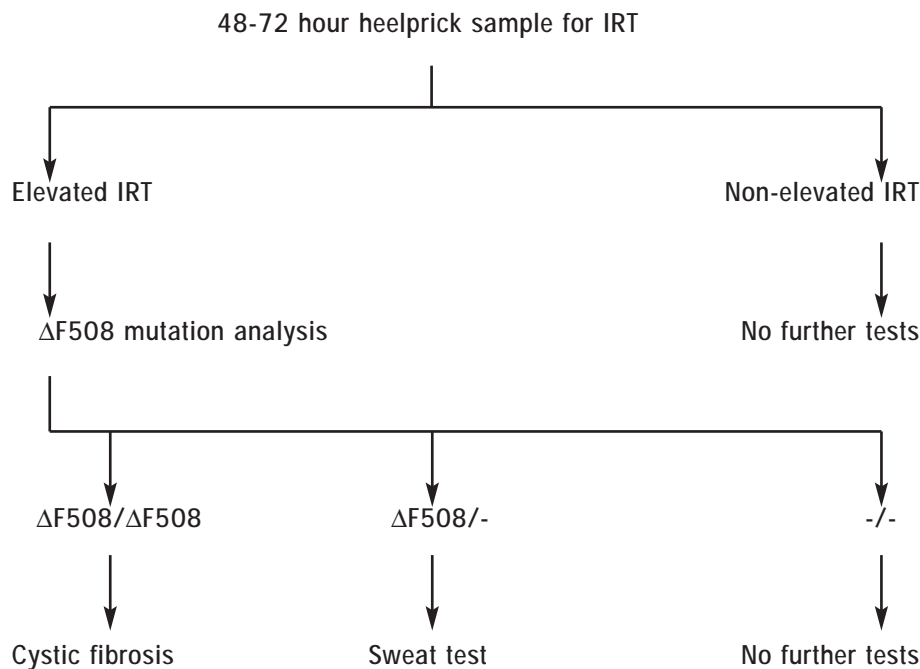
- The newborn screening protocol for cystic fibrosis is outlined in Figure 1.
- Newborn screening is performed on all babies 48–72 hours after birth. Immunoreactive Trypsinogen (IRT) is measured from a heelprick test sample (Guthrie sample). Raised IRT is an indication for DNA testing for the common CFTR gene change ( $\Delta F508$ ), which is also performed from the heelprick sample.
- The presence of two  $\Delta F508$  gene changes is diagnostic of cystic fibrosis. A repeat blood sample may be collected to confirm the diagnosis.
- If one copy of the  $\Delta F508$  gene alteration is present, the baby is considered at increased risk and a sweat test is performed. Eleven babies out of every 12 requiring a sweat test on the basis of newborn screening results *do not have cystic fibrosis*, but are simply carriers.
- If no copies of the  $\Delta F508$  gene change are present, the baby is considered to be at low risk and no further testing is performed. Babies with cystic fibrosis caused by gene alterations *other* than  $\Delta F508$  will be in this group and will be missed by newborn screening.

- The Newborn Screening Program provides a coordinated service that includes genetic counselling and sweat testing.
- If a sweat test is required, the GP will be contacted if their details are on the newborn screening card or held by the hospital that delivered the baby. GPs then have the option of informing the family themselves or allowing the genetic counsellor to do so. Feedback from families suggests they prefer to be contacted with results by someone known to them.
- **Cystic fibrosis may not be diagnosed by newborn screening for one of the following reasons:**
  - ✦ Screening sample not collected.
  - ✦ IRT is not raised.
  - ✦ Condition caused by gene changes other than  $\Delta F508$ .
  - ✦ The sweat test is negative.

GPs with queries regarding newborn screening results can call (03) 8341 6201.

See also Part J Newborn screening.

Figure 1. Newborn screening for cystic fibrosis



Source: Massie, J 2001, 'How to treat cystic fibrosis', *Australian Doctor*, 18 May

## Sweat tests

- Sweat tests detect levels of chloride and sodium in the sweat. They can be performed at any age but adequate sweat volumes may not be obtained before six weeks of age.
- If there is clinical suspicion of cystic fibrosis, a sweat test should be arranged, even if the patient has had newborn screening, as approximately 5% of cystic fibrosis cases are not detected by newborn screening (Massie et al. 2000).
- Sweat test results are usually available within 12 hours and often on the same day.
- Occasionally, sweat test results will be equivocal and a repeat will be required.
- Adults with suggestive clinical features should have a sweat test. Sweat electrolyte values in adults are often higher than children and need to be interpreted by an expert.
- Sweat test accuracy is laboratory dependent. It is recommended that a laboratory associated with a cystic fibrosis centre is used. For patients in isolated areas, this usually means travelling to a cystic fibrosis centre to get an accurate test. Discussion of the case with a cystic fibrosis physician may help.

Sweat tests are arranged by the Biochemistry Department at the Royal Children's Hospital (call (03) 9345 5906) and the Monash Medical Centre (call (03) 9594 2284).

## DNA tests

- DNA testing for cystic fibrosis is performed during newborn screening or where there is clinical suspicion.
- DNA testing during newborn screening tests only for the common DF508 gene alteration.
- More extensive DNA testing is performed where there is clinical suspicion or after a positive sweat test.
- Knowledge of ethnicity can assist gene change detection.
- Cystic fibrosis gene change screening will diagnose 85% of people with cystic fibrosis. Sweat tests are recommended as a more definitive test. Genetic testing may be considered as a starting point for diagnosis if there is limited accessibility to sweat testing. Discussion of such cases with a CF physician may be helpful.

## Treatment and management

- While there is no cure for cystic fibrosis, with early diagnosis, improved treatments and a better understanding of the disorder, average life expectancy is increasing.
- Management is undertaken by a specialist multidisciplinary team.
- GPs provide routine medical care and care of early phase pulmonary exacerbations or other complications. GPs play an important role in support and assisting in adherence to therapy.
- Cystic fibrosis suppurative lung disease is progressive. Consequently, there is increasing need for hospitalisation and intensity of care as disease progresses.

## Respiratory symptoms

- The thick mucus in the lungs initiates a cycle of airway obstruction, infection, inflammation and further obstruction, damaging the lungs. The cycle is initiated in the small airways but progresses to larger airways with time. Infants may present with recurrent wheeze and/or cough that becomes productive with time. Established suppurative lung disease is the final result in the cystic fibrosis-affected lung. Management focuses on assisting mucus clearance and treatment of chest infections.
- Daily *chest physiotherapy* is recommended.
- Under-treated bacterial infection is responsible for destruction of the airways in cystic fibrosis patients. *Antibiotics* should be started early and continued until symptoms improve. Prolonged therapy might be required in some patients. Sputum culture is important to guide antibiotic therapy.
- Antibiotics should also be used for common viral infections, as bacteria may colonise the lower airway during the viral infection. In young children, *Staphylococcus aureus* and *Haemophilus influenzae* are common infecting organisms with *Pseudomonas aeruginosa* becoming the predominant organism with time.
- *Lung transplantation* will cure the lung disease, but has its own complications such as bronchiolitis obliterans and other manifestations of graft versus host disease, and the increased risk of infection in an immunocompromised patient.

The main criteria for transplantation are poor quality of life and a likelihood of death in the next one to two years. Fewer than 50% of patients with cystic fibrosis receive a transplant and mortality is high (Liou et al. 2001). Discussion of lung transplantation raises issues of dying: GPs may have a role in supporting patients and their families as they deal with these issues.

## Growth, nutrition and bone mass

- Most patients with cystic fibrosis have pancreatic exocrine insufficiency and, if not treated, will present with steatorrhoea and failure to thrive. In these patients, pancreatic enzyme replacement is necessary prior to all meals and snacks.
- In addition, patients with cystic fibrosis have an increased basal metabolic rate requiring 120 to 150% of the recommended daily calorie intake. This requirement increases with the addition of persistent lung infections. A diet high in fat and protein is required.
- Gastrostomy may be beneficial to supplement feeds, if growth is seriously compromised according to standard growth charts. Body image is an issue for adolescents.
- Most patients require fat-soluble vitamin replacement (principally vitamins A and E). Some will require vitamin D. Serum levels should be measured annually.
- A DEXA scan should be performed during puberty to determine bone mineral density.
- Salt replacement is necessary to avoid salt depletion.

## Fertility

- Men with cystic fibrosis virtually always have congenital absence of the vas deferens and require assisted conception to have children (sperm can be aspirated from the epididymis).
- Fertility in women is linked to nutritional status and its role in ovulation.
- Lung function may deteriorate during and after pregnancy, probably because of the physical demands of child rearing and reduced time for the patient's own care.
- Respiratory failure may occur in women with cystic fibrosis and low lung function.
- Adolescents with cystic fibrosis may benefit from referral to the Centre for Adolescent Health service to explore reproductive and sexual health issues.

## Carriers of cystic fibrosis

- A carrier has inherited one altered gene for cystic fibrosis (CFTR gene) but also has one normal copy of the gene. Two alterations are required to cause the condition.
- Carriers are healthy and do *not* develop cystic fibrosis.
- One in 25 Australians of Anglo-Saxon descent are carriers of cystic fibrosis. People of other ethnic backgrounds may be carriers, but the risk may be lower.
- *Partners of carriers should have carrier testing, if pregnancy is being considered.*
- Only a couple who are both carriers for cystic fibrosis can have a child with cystic fibrosis. If both parents are carriers of cystic fibrosis, they have a one in four (25%) chance of having a child with cystic fibrosis in each pregnancy (autosomal recessive inheritance).
- Carriers have a 50% chance of passing on the altered CFTR gene to each child.
- Genetic counselling is available.

## Carrier testing

- Carrier testing is the genetic testing of a healthy individual to determine if they have one gene change in the cystic fibrosis gene. Currently there is no program in Victoria to routinely test individuals for cystic fibrosis carrier status and only those with a family history of cystic fibrosis or relatives of known carriers are tested.
- The goal of cystic fibrosis carrier testing is to identify couples who are both carriers and therefore have a high chance of having a baby with cystic fibrosis. It is important that carrier testing be performed prior to pregnancy, where possible.
- If a couple know they are both carriers prior to pregnancy, they are able to consider reproductive options, such as having prenatal diagnosis or pre-implantation diagnosis, or to prepare themselves for the possibility of having a child with cystic fibrosis.
- Routine carrier testing detects the 10 most common gene alterations. Approximately 18% of carriers will not be detected. The frequency of particular mutations varies between populations; therefore, knowledge of ethnicity assists carrier testing.
- If no gene change is found by carrier testing, the risk of being a carrier is reduced but not removed. The risk remaining after a normal carrier test will depend on their risk prior to testing. For an individual of Anglo-Saxon background with no family history of cystic fibrosis, it is reduced to one in 134.
- Results are available in three to four weeks.

## Who should be offered carrier testing?

- Relatives of an individual with cystic fibrosis (see Table 1 for risk of being a carrier).
- Partners of individuals with cystic fibrosis.
- Partners of cystic fibrosis carriers.
- Couples in close consanguineous relationships in ethnic groups where cystic fibrosis carrier rate is high (for example, Anglo-Saxon, Jewish).
- Men with infertility and congenital absence of the vas deferens and their partners.

Table 1. Risks of an unaffected individual being a carrier of cystic fibrosis prior to genetic testing

Relationship to person with cystic fibrosis	Risk of being a carrier
No relatives with cystic fibrosis	1 in 25 (4%)
Parent	Obligate carrier (100%)
Brother or sister	2 in 3 (66%)
Half-brother or half-sister	1 in 2 (50%)
Uncle or aunt	1 in 2 (50%)
Cousin	1 in 4 (25%)

### ***Requesting carrier testing***

A referral to Genetic Health Services Victoria for carrier testing should be encouraged.

**Requests for carrier testing of blood relatives of an affected individual *must* include:**

- *Either* the gene change causing cystic fibrosis in that family *or* the name of the affected individual.
- The degree of relationship to the closest affected family member.
- Ethnic background.

This ensures the correct gene changes will be tested and that the risk figures given are accurate if the testing does not detect a gene alteration.

### **Reproductive options**

- Carrier couples wishing to discuss their reproductive options should be referred to the cystic fibrosis genetic counsellor.
- Reproductive options for carrier couples include prenatal testing by chorionic villus sampling from 11 weeks gestation and pre-implantation diagnosis (PGD) with IVF technology.
- The availability of pre-implantation diagnosis may need to be determined for each couple.
- The availability of prenatal testing is best established *prior to pregnancy*.
- Prenatal diagnosis for cystic fibrosis requires pre- and post-test genetic counselling (National Pathology Accreditation Advisory Council 2000) and coordination between ultrasound services and laboratory services. A referral to the cystic fibrosis genetic counsellor should be made *as soon as the pregnancy is confirmed*.

## 9.3 Patient and further information

### Support groups

Cystic Fibrosis Victoria  
80 Dodds Street, Southbank 3006  
Call: (03) 9686 1811  
Fax: (03) 9686 3437  
Freecall: 1800 633 685  
Email: [admin@cfv.org.au](mailto:admin@cfv.org.au)  
Website: <http://www.cfv.org.au/>

### Websites

Cystic Fibrosis Victoria: <http://www.cfv.org.au/>  
This website contains many links to CF-related websites around the world.

Cystic Fibrosis Australia: <http://www.cysticfibrosisaustralia.org.au>

The Lung Foundation: <http://www.lungnet.org.au/cystic-fibrosis-health.html>

Better Health Channel: <http://www.betterhealth.vic.gov.au>

Relevant topics:

- Cystic fibrosis is a life threatening genetic disorder
- Newborn screening

### Further reading

Massie, J 2001, 'How to treat cystic fibrosis', *Australian Doctor*, 18 May

Massie, J & van Asperen, P 1997, 'Cystic fibrosis: what's new?', *Modern Medicine*, 40:88–101.

## 9.4 Where to refer

### Paediatric management

Royal Children's Hospital  
Department of Respiratory Medicine  
Royal Children's Hospital  
Flemington Road, Parkville 3052  
Call: (03) 93455844  
Fax: (03) 9349 1289

Monash Medical Centre  
Department of Respiratory Medicine  
Monash Medical Centre  
Clayton Road, Clayton 3168  
Call: (03) 9594 2900  
Fax: (03) 9594 6415

### Adolescent services

Centre for Adolescent Health  
William Buckland House  
2 Gatehouse Street, Parkville 3052  
Call: (03) 9345 5890  
Fax: (03) 9345 6502  
Website: <http://www.copas.net.au/cah>

#### Referral information

Ring 10–12 p.m. Monday to Friday for intake and appropriate appointment. GPs can refer but, where an adolescent with CF is being managed by a treating physician, the GP could discuss these issues with the physician and consider referral through the physician.

### Adult management

Alfred Hospital  
Cystic Fibrosis Centre of Excellence  
5th Floor, Department of Respiratory Medicine  
Alfred Hospital, Commercial Road, Prahan 3181  
Call: (03) 9276 3443  
Fax: (03) 9276 3601

Monash Medical Centre  
Department of Respiratory Medicine  
Monash Medical Centre  
Clayton Road, Clayton 3168  
Call: (03) 9594 2900  
Fax: (03) 9594 6415

### Prenatal diagnosis, genetic testing and counselling

Royal Children's Hospital  
Genetic Health Services Victoria  
Flemington Road, Parkville 3052  
Call: (03) 8341 6270  
Fax: (03) 8341 6390

Monash Medical Centre  
Clinical Genetics/Genetic Health Services Victoria  
Clayton Road, Clayton 3168  
Call: (03) 9594 2026  
Fax: (03) 9594 2022

### Non-metropolitan services

(Ballarat, Bendigo, Frankston, Geelong, Mildura, Sale, Shepparton, Traralgon, Warragul, Warrnambool)

Genetic Health Services Victoria  
Call: (03) 8341 6201  
Fax: (03) 8341 6390

Wodonga Genetics Clinic  
Genetic Health Services Victoria  
78 Vermont Street, Wodonga 3690  
Call/Fax: (02) 6056 0451

Royal Women's Hospital  
Genetic Health Services Victoria  
Grattan Street, Carlton 3053  
Call: (03) 9344 2121  
Fax: (03) 9344 2066

Mercy Hospital for Women  
Genetics Department  
Clarendon Street, East Melbourne 3002  
Call: (03) 9270 2394  
Fax: (03) 9270 2498

## 9.5 References

Cystic fibrosis mutation database. <http://www.genet.sickkids.on.ca/cftr/>

Liou, T, Adler, FR, Cahill, BC et al. 2001, 'Survival effect of lung transplantation among patients with cystic fibrosis', *JAMA*, 286:2683–89.

Massie, RJ, Olsen, M, Glazner, J, Robertson, CF & Francis, I. 2000, 'Newborn screening for cystic fibrosis in Victoria: 1989–1998', *Medical Journal of Australia*, 172:584–88.

National Pathology Accreditation Advisory Council 2000, *Laboratory accreditation standards for nucleic acid detection techniques*.

