CYSTIC FIBROSIS

Introduction

Cystic fibrosis (CF) is a multi-organ disease with an autosomal recessive pattern of inheritance. For a child to have CF both parents need to be carriers of a CF gene. It is most common in populations of predominantly Northern European descent where around one in 3,000 babies are born with the condition.[1] Most developed countries where CF is common, including New Zealand, have national newborn screening programmes that identify most babies with CF soon after birth. [1,2]

Cystic fibrosis is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[3] The CFTR regulates anion transport across cell membranes. When CFTR activity is reduced or absent the mucus secreting functions of the epithelial cells lining the airways, pancreatic ducts and other tissues are impaired.[3] The most significant result of this dysfunction is obstruction of the small airways by thick mucus leading to frequent infections, bronchiectasis and progressively worsening lung function. Other effects include pancreatic insufficiency leading to malabsorption of nutrients (and diabetes in some cases), and cirrhosis of the liver. Most males with CF have congenital absence of the vas deferens which makes them infertile.[4]

Life expectancy for people with CF is improving due to better treatment and it is now around forty years.[1,5] Recently, new drugs have been developed that correct the basic defect in CFTR function.[6] These drugs hold the promise of effective disease-modifying treatment and could potentially prevent lung disease if they were started as soon as the disease was identified by newborn screening.[1]

The following section reviews cystic fibrosis in children and young people using information from the newborn metabolic screening programme, New Zealand Cystic Fibrosis Registry, National Mortality Collection and National Minimum Dataset. The section concludes with a brief overview of possibilities for prevention and evidence-based health care for children and young people with CF.

Data sources and methods

Indicator

Rates of cystic fibrosis (CF) among 0–24 year olds

Definition

Hospitalisations of 0–24 year olds with cystic fibrosis per 100,000 population

Data sources

Numerator:	National Minimum Dataset
Denominator:	Statistics New Zealand Estimated Resident Population (with linear extrapolation being used to calculate denominators between Census years)

Additional information

Cystic fibrosis was the principal diagnosis or was documented as one of the first 15 diagnoses
Codes used for identifying cases are documented in Error! Reference source not found..

National trends and distribution

There was a total of 14 deaths of 0–24 year olds with cystic fibrosis (CF) as the underlying cause of death in New Zealand during 2009 to 2013, as documented within the National Mortality Collection.

CF is one of the 20 congenital metabolic disorders that babies are screened for within the New Zealand Newborn Metabolic Screening Programme (NMSP).[2] Screening tests are performed utilising blood samples obtained from the babies' heels during the first 48–72 hours of life. The NMSP screened 58,673 babies in 2014, of which 15 had cystic fibrosis detected. The 2014 incidence rate of CF was 27.1 per 100,000 live births, including one case diagnosed outside of the NMSP.

The National Cystic Fibrosis Data Registry includes over 95% of people with CF in New Zealand. Around two-thirds (n=293) of the 443 individuals registered in 2014 were registered before 24 years. Of those registered, 33 (7.4%) were aged 0–3 years at registration.[7]

The number of 0–24 year olds hospitalised with CF during 2011 to 2015 is presented in **Table 1**. It also presents the number of hospital discharges in which CF was documented as the primary diagnosis or as any diagnosis.

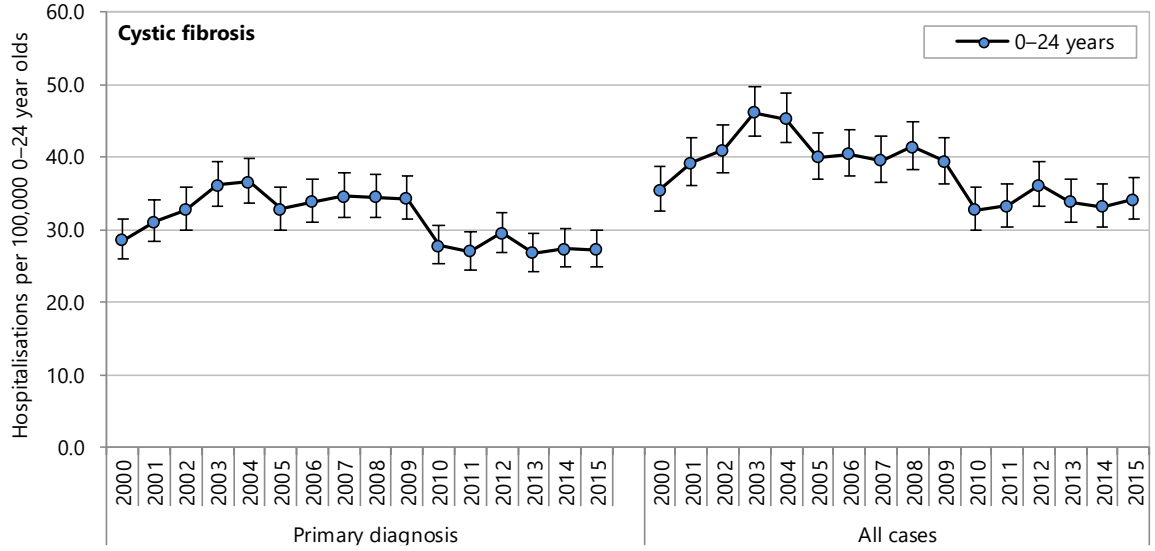
While there has been year-on-year variability in hospitalisations for CF since 2000, the hospitalisation rate has remained relatively stable over the last five years (**Figure 1**).

Table 1. Individuals aged 0–24 years hospitalised with cystic fibrosis using primary diagnosis compared to all cases, New Zealand 2011–2015

Age group	Unique individuals *(n)*	Hospitalisations *(n)*		Ratio All:Primary
		Primary diagnosis	All cases	
Cystic fibrosis				
Hospitalisation				
0–24 years	336	2,122	2,625	1.24
0–14 years	226	1,199	1,533	1.28
15–24 years	147	923	1,092	1.18

Source: National Minimum Dataset. 'All cases' corresponds to hospitalisations with cystic fibrosis listed in any of the first 15 diagnoses; The sum of the age groups may total to more than the 0–24 year old total

Figure 1. Hospitalisations for cystic fibrosis in 0–24 year olds, New Zealand 2000–2015



Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. 'All cases' corresponds to hospitalisations with cystic fibrosis listed in any of the first 15 diagnoses

Diagnosis

The majority of hospitalisations of 0–24 year olds involving cystic fibrosis had CF as the primary reason for hospitalisation. The diagnoses with the highest hospitalisation rate were CF with pulmonary or other manifestations (**Table 2**).

Table 2. Hospitalisations involving cystic fibrosis in 0–24 year olds, by primary diagnosis, New Zealand 2011– 2015

Primary diagnosis	*n*	Annual average	Rate	95% CI	%
Cystic fibrosis* in 0–24 year olds					
New Zealand					
Cystic fibrosis with pulmonary manifestations	955	191	12.43	11.67–13.25	36.4
Cystic fibrosis with intestinal manifestations	76	15	0.99	0.79–1.24	2.9
Cystic fibrosis with other manifestations	968	194	12.60	11.83–13.42	36.9
Cystic fibrosis, unspecified	123	25	1.60	1.34–1.91	4.7
Cystic fibrosis total	2,122	424	27.63	26.48–28.83	80.8
Other endocrine, nutritional and metabolic diseases	12	2	0.16	0.09–0.27	0.5
Diseases of the respiratory system	106	21	1.38	1.14–1.67	4.0
Diseases of the musculoskeletal system and connective tissue	76	15	0.99	0.79–1.24	2.9
Factors influencing health service contact	75	15	0.98	0.78–1.22	2.9
Symptoms and/or abnormal clinical findings NEC	69	14	0.90	0.71–1.14	2.6
Injury and/or poisoning	58	12	0.76	0.58–0.98	2.2
Infectious and parasitic diseases	38	8	0.49	0.36–0.68	1.4
Other diagnoses	69	14	0.90	0.71–1.14	2.6
Total	2,625	525	34.18	32.89–35.51	100.0

Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. * Cystic fibrosis in any of the first 15 diagnoses; Rate per 100,000 0–24 year olds; NEC = not elsewhere classified

Demographic distribution

Table 3 presents the demographic distribution of individuals with CF in New Zealand between 2011 and 2015. CF was significantly lower among individuals residing in areas with high deprivation scores (NZDep2013 deciles 9–10), and significantly higher among 0–4 year olds compared to 15–24 year olds. The majority of individuals with CF were of European/Other ethnicities.

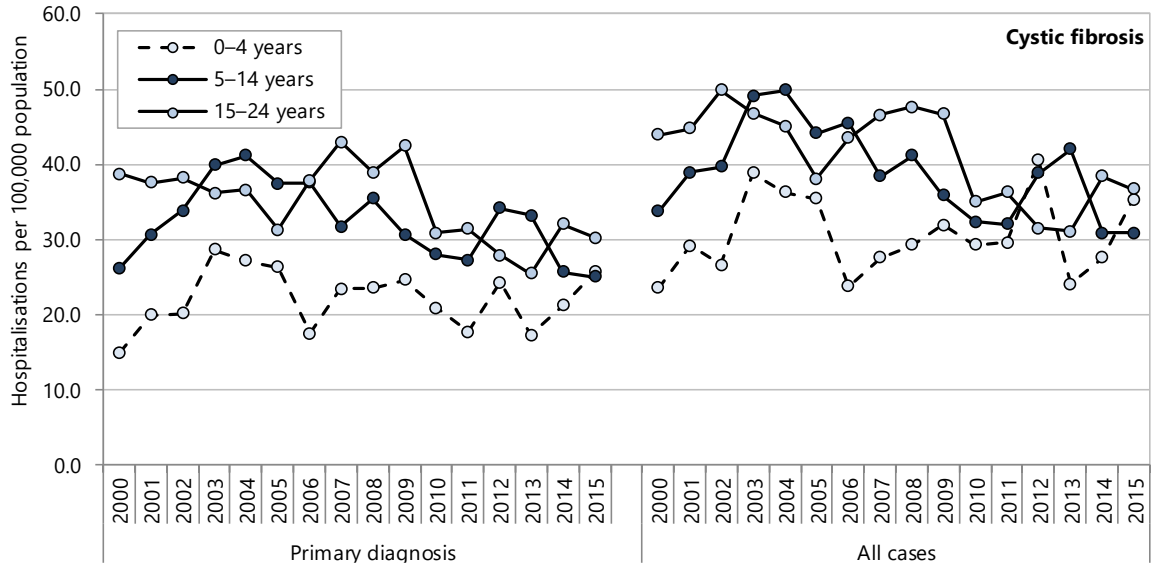
Although the age specific rate of 0–4 year olds with CF is higher than those for the other age groups, hospitalisations have generally been lower for 0–4 year olds (**Figure 2**). The hospitalisation rate for Māori has gradually increased since 2000, although is still consistently lower than the hospitalisation rate for European/Other (**Figure 3**).

Table 3. Individuals aged 0–24 years hospitalised with cystic fibrosis, by demographic factor, New Zealand 2011– 2015

Variable	Unique individuals 2011–2015 *(n)*	Rate per 100,000 population	Rate ratio	95% CI
Cystic fibrosis* in 0–24 year olds				
New Zealand				
NZ Deprivation Index quintile				
Deciles 1–2	97	6.84	1.00	
Deciles 3–4	105	7.85	1.15	0.87–1.51
Deciles 5–6	100	6.94	1.01	0.77–1.34
Deciles 7–8	97	5.97	0.87	0.66–1.16
Deciles 9–10	74	3.98	0.58	0.43–0.79
Prioritised ethnicity				
Māori	38	2.11	0.30	0.22–0.43
Pacific	5	0.71	0.10	0.04–0.25
Asian/Indian	6	0.63	0.09	0.04–0.20
MELAA	5	4.96	0.71	0.30–1.73
European/Other	285	6.94	1.00	
Gender				
Female	154	4.10	1.00	
Male	183	4.66	1.14	0.92–1.41
Age group (years)				
0–4	106	6.80	1.45	1.13–1.86
5–14	153	5.13	1.09	0.87–1.37
15–24	147	4.69	1.00	

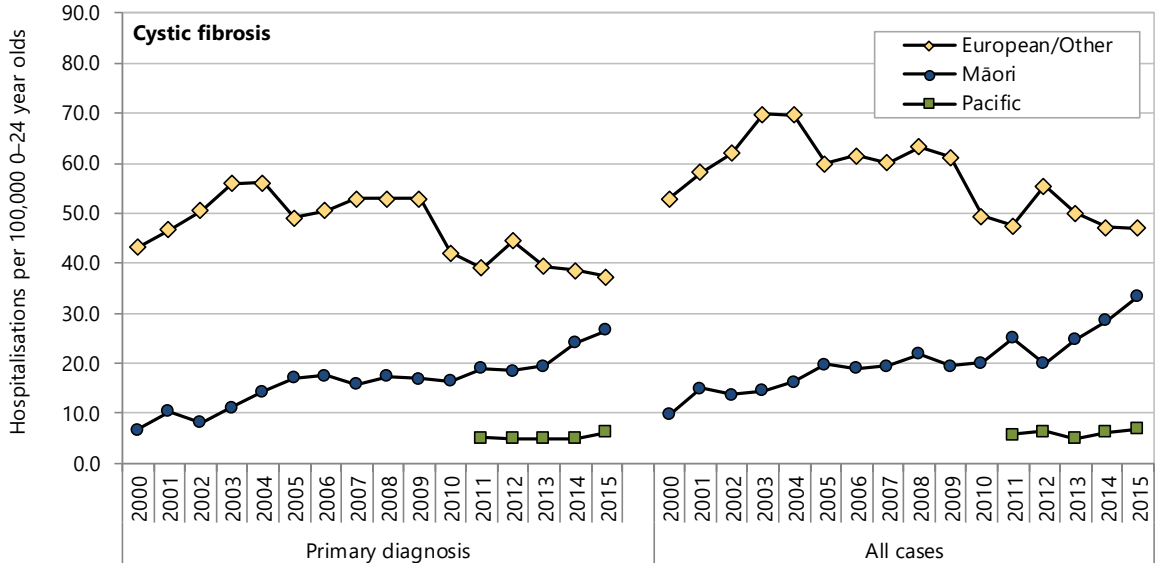
Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. Cystic fibrosis* in any of the first 15 diagnoses; Rate per 100,000 age-specific population; Rate ratios are unadjusted; Ethnicity is Level 1 prioritised; Decile is NZDep2013

Figure 2. Hospitalisations for cystic fibrosis in 0–24 year olds, by age group, New Zealand 2000–2015



Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. 'All cases' corresponds to hospitalisations with cystic fibrosis listed in any of the first 15 diagnoses

Figure 3. Hospitalisations involving cystic fibrosis in 0–24 year olds, by ethnicity, New Zealand 2000–2015



Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. 'All cases' corresponds to hospitalisations with CF listed in any of the first 15 diagnoses

Regional trends and distribution

Table 4 presents the number of individuals resident in each district health board that had a CF diagnosis during 2011 to 2015. It also presents the number of hospital discharges in which CF was documented as the primary diagnosis or any diagnosis.

The All:Primary diagnosis ratio reflects the extent to which hospitalisations of 0–24 year olds with CF occur when this condition is not the primary diagnosis and it provides an indication of the extent to which using only the primary diagnosis undercounts CF related hospitalisations. A high ratio may be associated with more thorough documentation and it may also indicate that children with CF are often hospitalised for other condition (**Table 4**).

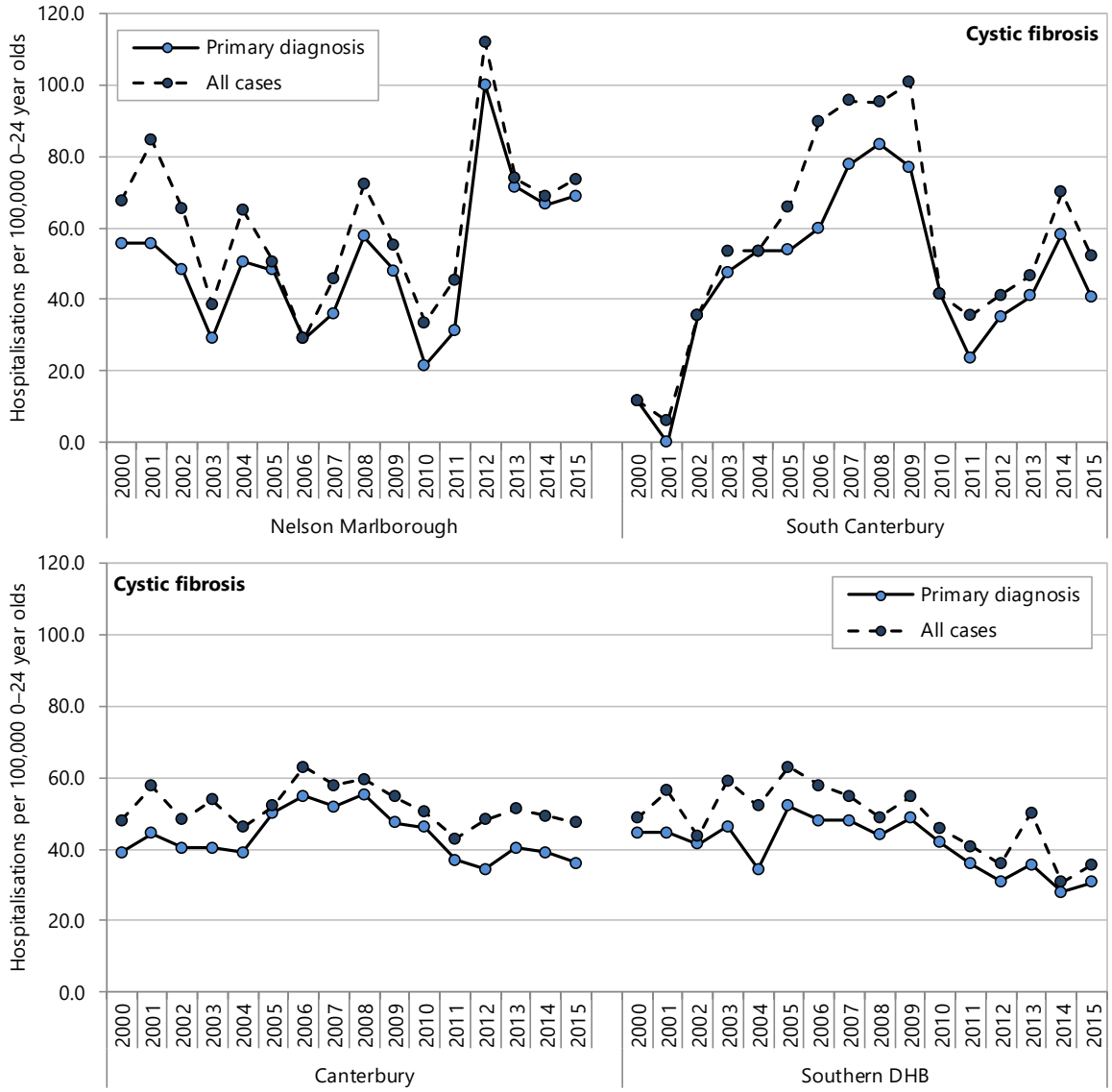
While there was year-on-year variability in the hospitalisation rate for CF within the South Island DHBs, the hospitalisation rate had generally increased since 2000 for the Nelson Marlborough and South Canterbury DHBs, decreased for Southern DHB, and remained relatively constant in Canterbury DHB (**Figure 4**). For West Coast DHB, the total number of hospitalisations since 2000 where CF was the primary diagnosis was 16 and any diagnosis was 26.

Table 4. Hospitalisations for cystic fibrosis in 0–24 year olds, South Island DHBs vs New Zealand 2011–2015

DHB	Unique individuals *(n)*	Hospitalisations *(n)*		Ratio All:Primary
		Principal diagnosis	All cases	
Cystic fibrosis in 0–24 year olds				
Nelson Marlborough	18	142	157	1.11
South Canterbury	<5	s	s	s
Canterbury	59	310	397	1.28
West Coast	<5	s	s	s
Southern	27	167	200	1.20
New Zealand	336	2,122	2,625	1.24

Source: National Minimum Dataset. 'All cases' corresponds to hospitalisations with cystic fibrosis listed in any of the first 15 diagnoses

Figure 4. Hospitalisations for cystic fibrosis in 0–24 year olds, South Island DHBs 2000–2015



Numerator: National Minimum Dataset, Denominator: Statistics NZ Estimated Resident Population. 'All cases' corresponds to hospitalisations with cystic fibrosis listed in any of the first 15 diagnoses

Evidence for good practice

Possibilities for prevention

Preconception carrier screening of couples planning a pregnancy and prenatal testing early in pregnancy are both possible and recommended by the American College of Medical Genetics,[8] the American College of Obstetricians and Gynecologists,[9] the National Institutes of Health,[10] and the Human Genetics Society of Australasia.[11] The sensitivity of carrier screening varies between ethnic groups and ranges (in the US population) from almost 90% in non-Hispanic whites to around 50% in Asian Americans.[9] In places where carrier screening has been carried out, there has been a decrease in the incidence of cystic fibrosis.[12,13]

In New Zealand, carrier screening and prenatal testing is free only for family members and partners of people with CF and relatives and partners of known carriers of CF.[11,14] In Australia, since 2006, CF carrier screening has been available to individuals and couples in Victoria as a fee-for-service programme at a cost of $150 per patient.[15] There has been some resistance to the uptake of CF screening from both the public (who lack awareness of CF) and health professionals. Some health professionals have concerns about the time needed to counsel patients about genetic testing, lack knowledge about carrier frequency and the risks of CF and are unaware that 95% of cases of CF occur without a family history of the condition.[15]

It is difficult to assess the cost-effectiveness of carrier screening and published economic evaluations of CF screening have had considerable variation in methods and results.[16] Estimating cost-effectiveness involves weighing the cost of screening against the cost savings that result from the lifetime healthcare costs averted because there are fewer people with CF (because couples who are both carriers can choose to terminate their affected foetuses or to use IVF with preimplantation genetic testing). There are new developments in genetic testing, including next-generation DNA sequencing, that make it possible to screen for many disorders at once and are likely to bring down the cost of genetic testing.[17] Therapies for CF are advancing and it is possible that in the future there may be treatments that can be given from birth to correct the defect in CFTR function and prevent some or all of the complications of CF.[18] The availability of such therapies could have several consequences: people with CF would be more likely to live longer with a good quality of life (although new drugs will probably be very expensive), and couples might be less likely to terminate a CF pregnancy if they were more hopeful of their child's prognosis, (providing they did not have to pay for their child's healthcare themselves).[18]

Evidence-based health care for children and young people with cystic fibrosis

Newborn screening leads to better nutritional outcomes for children with CF and has the potential to improve pulmonary outcomes.[19] When a couple have a baby with CF, there is a risk that any future pregnancies may also be affected by CF, so genetic counselling is indicated. The international consensus is that a person newly diagnosed with CF should have immediate and on-going access to a CF specialist centre staffed by a multidisciplinary team.[20] New Zealand does not have the population to support the types of specialist CF centres found overseas. Care for New Zealand children with CF should be provided using a shared care model. The majority of care should be based in a clinic at a hospital near their home, supplemented with at least annual reviews at a regional CF centre.[21]

To maintain the best possible lung function, people with CF (PWCF) need meticulous daily management of their lung disease. This may involve the use of airway clearance techniques taught by physiotherapists and inhaled aerosol medications together with prompt and aggressive treatment of infective exacerbations.[20] There is no good evidence to indicate which is the best way of educating PWCF to manage their disease.[22] People with CF need monitoring of their nutritional status as they are at risk of CF-related malnutrition due to pancreatic insufficiency and they (and their families) need psychosocial support to deal with the demoralisation that results from having multiple health problems.[20]

These national and international guidelines, systematic reviews, other publications and websites relevant to the prevention and management of CF are provided for further reading.

New Zealand guidelines

- Standards of Care for Cystic Fibrosis in New Zealand Group, Medical Advisory Committee of Cystic Fibrosis Association of New Zealand. 2011. Standards of Care for Cystic Fibrosis in New Zealand Cystic Fibrosis Association of New Zealand. http://www.cfnz.org.nz/wp-content/uploads/Standard-of-Care-NZ-2011.pdf

International guidelines

- Lahiri T, Hempstead SE, Brady C, et al. 2016. Clinical Practice Guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics. http://pediatrics.aappublications.org/content/137/4/e20151784.long
- Smyth AR, Bell SC, Bojcin S, et al. 2014. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis*, 13 Suppl 1, S23–42. http://www.sciencedirect.com/science/article/pii/S156919931400085X
- Conway S, Balfour-Lynn IM, De Rijcke K, et al. 2014. European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre. *Journal of Cystic Fibrosis*, 13, S3-S22. http://www.sciencedirect.com/science/article/pii/S1569199314000848
- Stern M, Bertrand DP, Bignamini E, et al. 2014. European Cystic Fibrosis Society Standards of Care: Quality management in cystic fibrosis. *Journal of Cystic Fibrosis*, 13, Supplement 1, S43-S59. http://www.sciencedirect.com/science/article/pii/S1569199314000861
- Cystic Fibrosis Trust. 2011. Standards for the clinical care of children and adults with cystic fibrosis in the UK (second edition). London: Cystic Fibrosis Trust. https://www.cysticfibrosis.org.uk/~/media/documents/the-work-we-do/care/consensus-documents/standards-for-the-clinical-care-of-children-and-adults-with-cf-dec-11.ashx?la=en

Evidence-based medicine reviews

- The Cochrane Library Reviews relating to Cystic Fibrosis http://www.cochranelibrary.com/topic/Lungs%20%26%20airways/Fibrosis%3A%20cystic%20fibrosis/?per-page=100&stage=review
- Edmondson C, Davies JC. 2016. Current and future treatment options for cystic fibrosis lung disease: latest evidence and clinical implications. *Therapeutic Advances in Chronic Disease*, 7(3), 170-83. http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27347364/
- Saiman L, Siegel JD, LiPuma JJ, et al. 2014. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infection Control & Hospital Epidemiology*, 35 Suppl 1, S1-S67. (summary at http://www.guideline.gov/content.aspx?id=48772&search=cystic+fibrosis)
- Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. 2013. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *American Journal of Respiratory and Critical Care Medicine*, 187(7), 680-9. (summary at https://www.guideline.gov/content.aspx?id=45307)

Other relevant publications

- Quon BS, Rowe SM. 2016. New and emerging targeted therapies for cystic fibrosis. *BMJ*, 352, i859. http://www.bmj.com/content/352/bmj.i859.long
- Massie J, Ioannou L, Delatycki M. 2014. Prenatal and preconception population carrier screening for cystic fibrosis in Australia: where are we up to? *The Australian & New Zealand Journal of Obstetrics & Gynaecology*, 54(6), 503-9
- PORT CFNZ National Data Registry. 2014 Registry Report. Cystic Fibrosis New Zealand. http://cfnz.org.nz/wp-content/uploads/2015/12/2014-PORT-CFNZ-Registry-Report.pdf

Websites

- National Institute for Health and Care Excellence Cystic Fibrosis https://www.nice.org.uk/guidance/conditions-and-diseases/genetic-conditions/cystic-fibrosis
- Cystic Fibrosis Association Of New Zealand Publications http://www.cfnz.org.nz/our-services/library/downloads/
- Cystic Fibrosis Trust (UK) Consensus Documents https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/consensus-documents
- European Cystic Fibrosis Society Standards of care available in open access https://www.ecfs.eu/content/ecfs-standards-care-available-open-access
- Cystic Fibrosis Foundation (US) CF Clinical care guidelines https://www.cff.org/For-Caregivers/CF-Clinical-Care-Guidelines

References

1. Elborn JS. 2016. Cystic fibrosis. *The Lancet*, 388(10059) 2519–31. http://dx.doi.org/10.1016/s0140-6736(16)00576-6
2. Ministry of Health. 2016. Newborn Metabolic Screening Programme annual report 2014 https://www.nsu.govt.nz/system/files/page/nmsp_annual_report_2014_0.pdf accessed September, 2016
3. Quon BS, Rowe SM. 2016. New and emerging targeted therapies for cystic fibrosis. *BMJ*, 352 i859. http://dx.doi.org/10.1136/bmj.i859
4. Jarzabek K, Zbucka M, Pepinski W, et al. 2004. Cystic fibrosis as a cause of infertility. *Reproductive Biology*, 4(2) 119-29.
5. Wolfenden LL, Schechter MS. 2009. Genetic and non-genetic determinants of outcomes in cystic fibrosis. *Paediatric Respiratory Reviews*, 10(1) 32-36. http://dx.doi.org/10.1016/j.prrv.2008.04.002
6. Solomon GM, Marshall SG, Ramsey BW, et al. 2015. Breakthrough therapies: Cystic fibrosis (CF) potentiators and correctors. *Pediatric Pulmonology*, 50 Suppl 40 S3-S13. http://dx.doi.org/10.1002/ppul.23240
7. PORT CFNZ National Data Registry. 2014 Registry Report. Cystic Fibrosis New Zealand. http://cfnz.org.nz/wp-content/uploads/2015/12/2014-PORT-CFNZ-Registry-Report.pdf
8. Grody WW, Cutting GR, Klinger KW, et al. 2001. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genetics in Medicine*, 3(2) 149-54. http://dx.doi.org/10.109700125817-200103000-00010

9. The American College of Obstetricians and Gynaecologists. 2011. ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis. *Obstetrics and Gynecology,* 117(4) 1028-31. http://dx.doi.org/10.1097/AOG.0b013e31821922c2
10. 1999. Genetic testing for cystic fibrosis. National Institutes of Health Consensus Development Conference Statement on genetic testing for cystic fibrosis. *Archives of Internal Medicine,* 159(14) 1529-39.
11. The Human Genetics Society of Australasia. 2013. Population-based carrier screening for cystic fibrosis. http://www.hgsa.org.au/documents/item/1282
12. Castellani C, Picci L, Tamanini A, et al. 2009. Association between carrier screening and incidence of cystic fibrosis. *JAMA,* 302(23) 2573-9. http://dx.doi.org/10.1001/jama.2009.1758
13. Lewis PA. 1999. Influence of five years of antenatal screening on the paediatric cystic fibrosis population in one region. *Archives of Disease in Childhood,* 80(5) 493.
14. Cystic Fibrosis Association of New Zealand. Genetics of cystic fibrosis. http://cfnz.org.nz/wp-content/uploads/2015/10/Genetics-of-CF-Laypersons-Guide.pdf
15. Archibald AD, Massie J, Smith MJ, et al. 2014. Population-based genetic carrier screening for cystic fibrosis in Victoria. *The Medical Journal of Australia,* 200(4) 205–06.
16. Radhakrishnan M, van Gool K, Hall J, et al. 2008. Economic evaluation of cystic fibrosis screening: a review of the literature. *Health Policy,* 85(2) 133-47. http://dx.doi.org/10.1016/j.healthpol.2007.07.007
17. Azimi M, Schmaus K, Greger V, et al. 2016. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. *Molecular Genetics & Genomic Medicine,* 4(3) 292-302. http://dx.doi.org/10.1002/mgg3.204
18. Massie J, Castellani C, Grody WW. 2014. Carrier screening for cystic fibrosis in the new era of medications that restore CFTR function. *The Lancet,* 383(9920) 923-5. http://dx.doi.org/10.1016/s0140-6736(13)61092-2
19. Southern KW, Mérelle MME, Dankert-Roelse JE, et al. 2009. Newborn screening for cystic fibrosis. *Cochrane Database of Systematic Reviews,* (1) http://dx.doi.org/10.1002/14651858.CD001402.pub2
20. Smyth AR, Bell SC, Bojcin S, et al. 2014. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. *Journal of Cystic Fibrosis : Official Journal of The European Cystic Fibrosis Society,* 13 Suppl 1 S23-42. http://dx.doi.org/10.1016/j.jcf.2014.03.010
21. Standards of Care for Cystic Fibrosis in New Zealand Group, Medical Advisory Committee of Cystic Fibrosis Association of New Zealand,. 2011. Standards of Care for Cystic Fibrosis in New Zealand Cystic Fibrosis Association of New Zealand. http://www.cfnz.org.nz/wp-content/uploads/Standard-of-Care-NZ-2011.pdf
22. Savage E, Beirne PV, Ni Chroinin M, et al. 2014. Self-management education for cystic fibrosis. *Cochrane Database of Systematic Reviews,* (9) http://dx.doi.org/10.1002/14651858.CD007641.pub3