

Periodic health examination, 1991 update: 4. Screening for cystic fibrosis

Canadian Task Force on the Periodic Health Examination

In 1979 the Canadian Task Force on the Periodic Health Examination concluded that there was fair evidence to support the recommendation that siblings of patients with cystic fibrosis (CF) be screened with a sweat test.^{1,2} In addition, it was concluded that there was fair evidence to support the recommendation that screening not be considered for the general population. At that time there were no tests available for prenatal or neonatal screening, and these manoeuvres were not considered.

Since those recommendations were published a number of new screening tests have been developed, and the gene mutation responsible for approximately 70% of CF carriers and about 50% of homozygotes has been identified; 20 other mutations together account for less than 5% of carriers. It is appropriate, therefore, that the task force re-evaluate screening for CF, using its standard methodology³ to weigh the newly available information.

SCREENING FOR CYSTIC FIBROSIS

Five population categories can be considered in evaluating screening: all newborns; the general popu-

lation at risk for carrier status; pregnant women either with or without a family history of CF; siblings of affected children; and other relatives of affected children at risk for carrier status.

The situation with CF may be unlike that for phenylketonuria (PKU) or congenital hypothyroidism, in which initiation of treatment after the onset of symptoms is clearly too late, because irreversible brain damage has occurred. The degree to which diagnosis of CF in the neonatal period is associated with improved outcome is currently unknown, as are the risks and costs of a universal screening program.

Since approximately 5% of white people are carriers, counselling couples with a 25% risk of having an affected child could further decrease the incidence of disease.

Burden of suffering

The incidence of CF in the United States has been reported as being between 1/1500 and 1/2000 live births among whites and 1/17 000 live births among blacks.⁴ In a more recent Canadian study the incidence was found to be 1/2927 live births; there

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may have been a decrease due to earlier diagnosis and genetic counselling.⁵ The disease is transmitted in an autosomal recessive manner, and it is estimated that about 5% of the general population carry the gene.⁴

The triad of chronic obstructive pulmonary disease, pancreatic exocrine deficiency and abnormally high sweat electrolyte concentrations is present in most patients. Many of the clinical and pathological findings are thought to be attributable to a generalized defect in mucus secretion due to an abnormality in the chloride channel. The genetic defect is believed to produce an abnormal protein as a component of the chloride channel gate at the cell surface.

There are abnormalities in all the exocrine glands, with three types of involvement: obstruction of the lumen by viscid material (pancreas, intestinal glands, intrahepatic bile ducts, gallbladder and submaxillary glands), production of an excess of histologically normal secretions (tracheobronchial glands) and production of secretions with excess electrolyte concentrations (sweat, parotid and small salivary glands).

In 1985 the median age at the time of death was 24 years, whereas in 1950 survival past infancy was unusual.⁶ Clinically, pulmonary complications usually dominate the course of the disease, although manifestations may not appear until weeks, months or years of age. Bronchiectasis is present in most patients by the end of the second year of life. Lung infections due to *Staphylococcus aureus* and *Pseudomonas aeruginosa* are extremely common and cause additional lung damage. In patients with advanced lung disease frequent complications include pneumothorax, hemoptysis and cor pulmonale. Chronic nasal congestion due to hyperactive mucus-secreting glands, nasal polyps and sinus disease are common.

Gastrointestinal manifestations result from loss of pancreatic enzyme activity and consequent intestinal malabsorption, primarily of fats and proteins. Significant loss of exocrine pancreatic activity is seen in about 80% of patients. Malabsorption with consequent malnutrition can lead to poor weight gain, lack of subcutaneous fat and muscle tissue, and delayed puberty. In about 7% of newborns with CF, meconium ileus (intestinal obstruction due to inspissated meconium) may necessitate surgery.

Other complications include late intestinal obstruction, gastroesophageal reflux, vitamin and mineral deficiencies, hypoproteinemia and edema, salt loss, biliary cirrhosis, portal hypertension, male infertility and reduced female fertility.

The psychologic impact on the child and the family can be significant, especially in severe cases that progress rapidly in spite of treatment. In one study young adults with cystic fibrosis were found to

have age-adequate psychologic functioning, including coping style and self-concept;⁷ since the mean age of the 73 subjects was approximately 25 years, it is obvious that these patients did not have the severest form of the disease. Another study, of parents of children with various chronic diseases, showed that parents of children with CF experienced extensive stress but less than expected.⁸ In a study of adolescents with CF, including patients with significant lung impairment, most of the subjects were found to cope surprisingly well;⁹ a major source of the adolescents' stress was their concern as to how their illness was adversely affecting other family members. Among 40 adults with CF some were observed to cope more successfully than others despite comparable degrees of physical disability; the "noncopers" had twice as many hospital admissions as the copers, even though their ventilatory function was better, and had worse vocational records, less family support, less awareness of the sexual problems associated with CF and less general knowledge about the disease.¹⁰

Social class appears to be an important factor in the longevity of children with CF: the higher the social class, the higher the age at death, even where there is universal health insurance, as in England and Wales.¹¹ One interpretation of this observation is that the diagnosis of CF has a significant impact on the child and the family: repeated hospitalization and painful procedures; frequent treatment at home each day, which draws attention away from siblings who do not have CF; thinness, shortness and delayed puberty, which cause the child to be different from peers; inability to compete at sports; and frequent absence from school, which may make schoolwork more difficult. It is possible that families of higher social class are better able to cope with the many stresses and activities necessary in complying with a difficult treatment regimen. Better compliance may be the factor leading to enhanced survival in the higher social classes.

The financial burden to taxpayers in countries with universal health insurance and to individuals with private insurance plans is considerable. Each year nearly 40% of those with CF are hospitalized for at least 1 week. These episodes and the cost of outpatient medical care have an effect on the health care delivery system that is out of proportion to the number of patients with CF.¹²

Manoeuvre

The gold standard against which CF screening tests are measured is the sweat chloride test. Although elevated sweat electrolyte levels may be found occasionally in other conditions, such as adrenal insufficiency and ectodermal dysplasia, these

conditions are readily differentiated clinically from CF. There would be no need for other screening tests if sufficient sweat could be obtained from newborns, but even with stimulating localized sweating by administering pilocarpine into the skin it is often impossible to collect sufficient sweat in the first few weeks of life. The sweat test is also time-consuming and expensive for routine mass screening.

As a result, newborn screening programs have relied on other tests. The measurement properties of some of these have recently been reviewed.¹³ One of the earliest was based on the knowledge that a considerable majority of infants with CF have pancreatic insufficiency at birth; as a result the albumin content of their stool is higher than normal. The "BM meconium test" had been used on nearly 1 million infants by 1985: although 126 cases of CF had been detected with this technique, 69 known cases were missed.

An advantage to any newborn screening test would be to combine it with the two tests already widely done by means of a dried blood spot on filter paper, namely the congenital hypothyroidism and PKU tests. The immunoreactive trypsin (IRT) test can be performed in this manner and thus is inexpensive as part of a mass screening program. In one study in which it was possible to calculate the measurement properties of the IRT test the sensitivity of the test was found to be 90% but the positive predictive value only 7%. A false-positive rate of 93% could and likely does generate considerable anxiety, which may be long-lasting.¹⁴ A low positive predictive value was also seen in another study, in which only 11 (1%) of 904 infants with a positive IRT test result were found to have CF.¹⁵

In an attempt to diagnose CF prenatally, amniotic fluid alkaline phosphatase isoenzymes were studied: they were abnormal in 9 of 10 proven cases of CF, but the predictive value of a positive test result was only 50%.¹⁶ If termination of pregnancy is one possible outcome, the positive predictive value should be much higher.

Because of the problems with the measurement properties of CF screening tests the recent identification of the genetic mutation responsible for about 70% of CF carriers (ΔF_{508})¹⁷ has generated considerable excitement.¹⁸ Initially the discoverers of the CF gene were quite optimistic that the mutation(s) responsible for the other 30% of CF carriers would soon be found: "Mutation analysis introduces the possibility of population-based screening programs for carriers".¹⁹ The initial enthusiasm has been dampened somewhat. At the Mar. 6, 1990, US National Institutes of Health (NIH) Workshop on Population Screening for the Cystic Fibrosis Gene, attended by world leaders in this area of research, the following statement was released.

Currently, DNA analysis can identify a single mutation in the cystic fibrosis gene that is present in 70 to 75 percent of carriers of European ancestry. Many additional mutations producing cystic fibrosis, currently about 20, have been identified. The identification of multiple individually rare mutations rather than a small number of common mutations will make carrier testing more difficult. The inability to detect all carriers creates complexities for the use of carrier testing at this time. . . . At present, newborn screening primarily to detect carriers is inappropriate, as are screening programs directed at children below reproductive age.²⁰

In spite of the unexpected problem of many rare mutations as opposed to a small number of common mutations and the lower frequency (30% to 50%) of ΔF_{508} in some ethnic populations²¹ there is still great potential in this area. Screening the relatives of people with CF has excellent sensitivity, since the specific mutation involved can be identified.²¹ However, this screening approach has not been evaluated.

With the polymerase chain reaction, mutations in the CF gene can be detected with the use of minute quantities of blood.^{22,23} Automation will make possible neonatal or heterozygote screening by means of the dried blood spot on filter paper already used in other screening programs.²⁴

Wilfond and Fost²¹ estimated that in the United States mass screening would cost as much as \$2.2 million for each birth of an infant with CF avoided, assuming individual test costs of \$200. Test costs would probably drop as volume increased: in the United States, where only 3000 CF tests per year were ordered, each test cost \$300, but in Britain, with a volume of 50 000 samples per year, each test cost only \$2.²⁵

Effectiveness of early intervention

Before any screening program is implemented there should be good evidence that people identified in the presymptomatic phase do better than those in whom a diagnosis is made because of symptoms. To be certain that disease severity or other confounders are similar in screened and unscreened subjects and that it is the time of identification of the disease, rather than other factors, that is associated with an improved outcome, random allocation into screened and unscreened groups or at least allocation into presymptomatic and symptomatic treatment groups is necessary. Such a randomized controlled trial of screening or early treatment has not been done.

Several cohort studies of screened and unscreened subjects have suggested that early diagnosis does make a difference. In one study,²⁶ done in the Netherlands, 88% of screened children but only 60% of unscreened children were still alive at age 11 years. The difference between the two groups had a *p*

value of 0.045 with a one-sided Fisher's exact test; about 20 variables were tested. The screening method was determination of the albumin content of meconium; the number of false-negative test results was large. Although screening was done between 1973 and 1979, only patients surviving until 1980 were included in the follow-up. Before 1980, 4 of 22 screened and 5 of 24 unscreened children had died.

In an earlier study by the same group, screened children were found to have better clinical scores at age 8 years than did unscreened children with CF, but the differences in chest x-ray films, heights and weights were not statistically significant.²⁷ The only selection factor for screening was the willingness of the hospital, maternity ward or regional maternity service to cooperate in the screening and follow-up program. This volunteer bias makes interpretation of the results difficult.

A group of Australian workers compared hospital admissions of 40 children identified at birth by screening with the dried-blood-spot IRT test and 56 children born in the 3 years before screening began.²⁸ Unscreened patients without meconium ileus had spent a mean of 27.25 days in hospital because of CF-related illness in the first 2 years of life, whereas screened patients had spent a mean of 3.9 days. The authors noted that the control and screened groups may not have been comparable, that there may have been changes in hospital admission policies before and after screening began and that there may have been significant changes in outpatient therapy. However, they contended that none of these possible explanations for their findings was valid and that it was the screening and early treatment that made the difference. They acknowledged that there are concerns about studies involving nonsimultaneous cohorts but felt that ethical considerations precluded a proper randomized controlled trial of screening.

In another Australian study, involving 23 unscreened children born between 1980 and 1983 and 28 children born between 1983 and 1985 and screened at birth with the IRT test, the screened children were found to have had fewer chest infections and to have gained more weight during the first 2 years of life.²⁹ The difference in mean weight between the screened and unscreened groups was statistically significant at 6 months (7.0 v. 6.3 kg, $p = 0.001$) but not at 12 and 24 months. Hospital admissions were not significantly more frequent in the unscreened group. The authors acknowledged that the two groups may not have been comparable: the screened group may have included mildly affected children who might have done well even without therapy, and the unscreened group may have included only those with disease severe enough to have been diagnosed in the first 2 years of life (mean age at diagnosis 0.6 years). They also acknowledged the

absence of adequate studies on the psychosocial implications of neonatal screening for CF.

Finally, there is some evidence that nutritional deficiencies due to malabsorption predate the onset of symptoms.³⁰ By implication, early diagnosis and the oral administration of pancreatic enzymes as well as careful attention to nutrition could prevent these deficiencies. In a study of the 20 infants with CF identified via the Colorado Immunoreactive Trypsin Screening Program in 1983, diagnosis was confirmed by the sweat test at a mean age of 5.5 weeks. The mean birth weight and the weight at 5.5 weeks were both close to the 50th percentile, but in most infants the triceps skinfold measurement was below the 50th percentile at 5.5 weeks. In addition, 5 of the 20 babies already had a low serum albumin level. The clinical significance of these findings is unclear.

Treatment of CF

The treatment of CF is complex, costly and time-consuming. Most children with CF in the developed world are seen in CF clinics, often subsidized by charitable foundations. These clinics are often multidisciplinary, involving physicians, nurses, social workers, nutritionists and physiotherapists. There have been no randomized controlled trials comparing outcomes of children with CF treated in multidisciplinary clinics and those treated by physicians alone.

Treatment is directed at improving nutrition through the use of replacement pancreatic enzymes and vitamins, as well as a high-energy, high-protein and liberal-fat diet. For those not responding to this approach, enteral supplementation by nightly nasogastric, gastrostomy or jejunostomy infusion of high-energy diets has been used.

Pulmonary treatment includes antibiotic therapy, either maintained continuously or for exacerbations, and chest physiotherapy consisting of postural drainage, percussion, vibration and assisted coughing. Depending on the degree of pulmonary involvement, treatment is carried out up to several times daily. Alternate-day corticosteroid administration is being evaluated.

Which components of this complex regimen are responsible for the striking increase in longevity over the last 30 years⁶ is unknown, but it is likely that improved antibiotic and nutritional therapy is mainly responsible. Again, it is still not clear that initiation of this regimen in the presymptomatic phase is beneficial.

Although there have been no randomized controlled trials in which one group of patients had no treatment, it is very unlikely that the increase in survival is due to the identification in recent years of

mild cases that would not previously have been identified. Only a small percentage of patients have such mild symptoms that the diagnosis is first made in adulthood.⁴

On the other hand, there have been a number of randomized controlled trials involving individual components of treatment, principally antibiotic and nutritional therapy, in which a newer treatment has been compared with the previously accepted treatment. Some of these trials have shown progressive improvement in outcome, with either better quality of life because of quicker resolution of pneumonia or improved pulmonary function (oral v. intravenous antibiotic therapy directed against difficult organisms),³¹⁻³³ or better nutritional status.³⁴⁻³⁶ One study in which intravenous antibiotic therapy was compared with placebo therapy for acute respiratory exacerbations showed that for mild to moderate episodes antibiotic therapy added nothing to the benefits derived from nutritional support and bronchodilator and oxygen therapy as needed.³⁷ The sample was too small to detect any difference of less than 30% between the groups, assuming an α value of 0.05 and a β value of 0.2. Although there is a consensus that antibiotic therapy does make a difference during exacerbations, a call for controlled studies evaluating efficacy in a blinded fashion has recently been made.³⁸ A recent review of therapy with inhaled antibiotics concluded that, until additional well-controlled trials are completed, routine aerosol administration of antibiotics to patients with CF is not warranted because of the cost, the potential side effects and the propensity for organisms to become resistant to antibiotics.³⁹

With regard to treatment of the nutritional deficiency secondary to pancreatic insufficiency, randomized controlled trials comparing different forms of pancreatic enzyme replacements have shown significant decreases in symptoms and improvements in fat absorption and weight with newer enzyme formulations.^{34,35} Supplementary enteral feeding has also been studied: children with pulmonary exacerbations were randomly allocated to a regular ward diet *ad libitum* or to the same diet plus nocturnal nasogastric feeding that supplied approximately 1200 kcal (5000 kJ). Although the mean weight and forced expiratory volume in 1 second were not significantly different in the two groups, there was a significant difference in weight in favour of the supplemented group among those who were malnourished at the beginning of therapy.³⁶

The long-term clinical benefit of physiotherapy for CF is not conclusive. In one quasi-experimental study in which eight children with CF were used as their own controls, chest physiotherapy did not lead to immediate improvement in pulmonary function but did appear to prevent deterioration.⁴⁰ In a

randomized controlled trial chest physiotherapy did not reduce the number of hospitalizations or hospital days but did result in less deterioration in the forced expiratory flow.⁴¹

Recently a small randomized double-blind study of an inhaled sodium-channel blocker, amiloride, which is thought to inhibit the excessive absorption of sodium and liquid from mucus, showed less deterioration of pulmonary function and less sputum viscosity during the amiloride phase.⁴²

Recommendations of other groups or agencies

The American Society of Human Genetics reached consensus that carrier testing should be offered to couples in which either partner has a close relative with CF.⁴³ At the time (Nov. 13, 1989) it was felt to be premature to undertake population screening or carrier testing of pregnant women. Such screening would miss about 30% of carriers. The statement did not address the issue of newborn screening.

The statement from the NIH Workshop on Population Screening for the Cystic Fibrosis Gene²⁰ concluded that, unlike carrier testing through DNA analysis in the general population, carrier testing in families in which the disease has occurred is nearly 100% informative. Therefore, carrier testing should be offered to all individuals and couples with a family history of CF. This statement also did not address the issue of newborn screening.

The Research Advisory and Medical Advisory Committee of the Cystic Fibrosis Research Trust in Britain has invited pilot projects on CF heterozygote screening based in general practitioners' offices as well as in hospital clinics,⁴⁴ as is the practice with screening for neural tube defects, for which the expected detection rate is also approximately 70%.

The Canadian Cystic Fibrosis Foundation and the Canadian College of Medical Geneticists do not have an official position on CF screening encompassing the new technology. Both agencies were asked to review this manuscript.

Recommendations of the task force (Table 1)

Recommendations with regard to screening by DNA analysis are based on very new information and are therefore tentative.

1. There is fair evidence not to perform universal newborn screening for CF by DNA analysis or other tests, based on the poor positive predictive value of the sweat, IRT and "BM meconium" tests and the fact that the recently discovered genetic mutation (ΔF_{508}) characterizes only about 50% of people homozygous for CF and

Table 1: Summary of manoeuvre, effectiveness of preventive intervention, level of evidence and recommendation for screening for cystic fibrosis (CF)

Manoeuvre	Effectiveness	Level of evidence*	Recommendation*
Sweat test, immunoreactive trypsin and "BM meconium" tests	Positive results in newborns have poor predictive value, and the benefits of treatment before 4 to 6 weeks of age have not been established.	Cohort studies ¹³⁻¹⁵ (II-2)	Fair evidence not to perform universal newborn screening (D)
Sweat test at 4 to 6 weeks of age	Early diagnosis may benefit treatment outcome.	Cohort studies ²⁶⁻³⁰ (II-2)	Fair evidence to test siblings of children with CF for the diagnosis of CF (B)
DNA analysis in newborns for case-finding or subsequently to determine carrier status	ΔF_{508} characterizes only about 50% of homozygotes and about 70% of carriers, and the benefits of treatment before 4 to 6 weeks of age have not been established.	Cohort studies ^{17, 21} (II-2)	Fair evidence not to perform universal screening (D)
DNA analysis matching mutation with that in child who has CF	Test characteristics are superior (sensitivity may approach 100%) in the high-risk population since the mutation is known.	Expert opinion ²¹	Fair evidence to screen siblings of children with CF for carrier status (B)

*For descriptions of the levels of evidence and classification of recommendations see Appendix I in part 1 of the 1989 update (*Can Med Assoc J* 1989; 141: 206).

about 70% of carriers (grade D recommendation).

2. Similarly, there is fair evidence not to screen the general population for heterozygote status (grade D recommendation).

3. Siblings of children with CF should have a sweat test after 4 to 6 weeks of age (grade B recommendation).

4. First-degree relatives of children with CF should be screened by DNA analysis for carrier status (grade B recommendation).

Research priorities

1. Continuation of studies of DNA analysis for those mutations responsible for the 30% of carriers who lack the recently discovered mutation.

2. Continuation of studies designed to make screening for CF less costly, such as the use of dried blood spot specimens and polymerase chain reactions.

3. Randomized controlled trials of neonatal screening to see if earlier diagnosis makes a difference, once the technology for mass screening is available and the measurement properties of the DNA analysis are acceptable.

4. Cost-benefit and psychosocial studies of neonatal and general population screening.

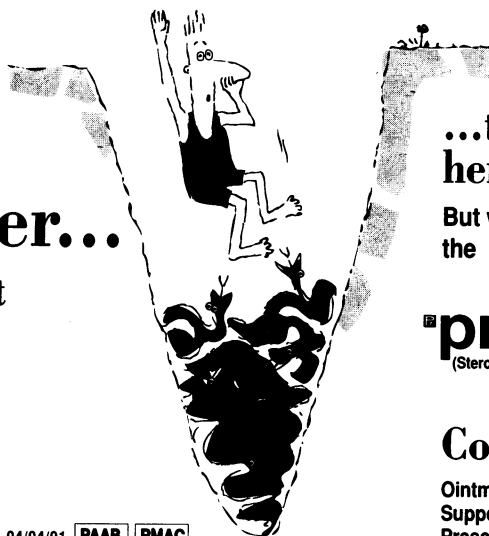
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