



HUMAN GENETICS PROGRAMME
DIVISION OF NONCOMMUNICABLE DISEASES

Manama, Bahrain, 18-19 November 1995

**IMPLEMENTATION OF CYSTIC FIBROSIS SERVICES
IN
DEVELOPING COUNTRIES**

Report of a Joint WHO/International Cystic Fibrosis (Mucoviscidosis) Association Meeting

Contents

	<u>Page</u>
1. Introduction	2
2. Cystic Fibrosis in Developed Countries	2
3. Cystic Fibrosis in Developing Countries	2
4. Prerequisites for Establishing a Cystic Fibrosis Service	3
5. Contributing Agencies	4
6. Implementation of a Cystic Fibrosis Service	5
7. Obstacles to Development of Cystic Fibrosis Services	8
8. Strategies for Progress	9
9. Role of WHO, ICF(M)A & other Agencies in Developing Countries	10
10. Conclusions & Recommendations	11
11. List of Participants	12
12. Acknowledgements	13
13. References	13

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1. INTRODUCTION

Previous joint meetings between WHO and the International Cystic Fibrosis (Mucoviscidosis) Association (ICF(M)A) have considered the geographical distribution of cystic fibrosis (CF), its control, population screening, and current and prospective treatment¹⁻³. Although CF is a serious genetic disease which is widespread throughout the world, there are significant variations in incidence with relative sparing of the African and Oriental races. Although recognition of CF and provision of appropriate clinical services are well developed in Western Europe, the USA and Australasia, there are large populations in whom the disease is infrequently recognized and inadequately treated, with consequent avoidable death and suffering in infancy, childhood and adult life.

The meeting reported here was convened in order to address these problems, and to define strategies for the implementation and development of cystic fibrosis services in developing countries. In this context, the term "developing country" is used in a medical, not a socio-economic sense. It refers to those countries where CF is known to exist, and thought to be much more common than is appreciated by either the medical profession or the general public, and where cystic fibrosis services are either non-existent or in the early stages of development. Similarly, the "developed" countries in a CF sense are those in which cystic fibrosis is usually rapidly diagnosed and appropriately treated.

2. CYSTIC FIBROSIS IN DEVELOPED COUNTRIES

Cystic fibrosis was first recognized about 60 years ago in Europe and the USA. In the early descriptions of the disease, life-expectancy was generally limited to less than 2 years. Diagnosis depended on identifying a combination of malabsorption of pancreatic origin and chronic pulmonary infection, and family histories demonstrated that the inheritance pattern was autosomal recessive. With the development of the sweat test in the 1950's, diagnosis became easier and more accurate, and was made with increasing frequency. It is now recognized to be the most common serious single gene disorder in most Caucasian populations.

With treatment delivered from special centres, and attention to all the major features of the disease (respiratory, nutritional, digestive, etc.), the prognosis in many countries has improved so that the mean actuarial life expectancy is calculated at approximately 30 years. As these calculations are based on historical evidence, projections for young children with CF alive today suggest that they may live for 40 years or more, even without the development of new modalities of treatment. However, since the gene defect in CF was identified in 1989 there has been unprecedented progress in our understanding of the causative mechanisms of the disease and new approaches to development of definitive gene therapy or pharmacological treatment. Such treatments are expected to be available within the life-time of most current patients, with a corresponding anticipated improvement in outlook.

3. CYSTIC FIBROSIS IN DEVELOPING COUNTRIES

The participants in the meeting were invited to provide completed questionnaires covering the overall conditions and peculiarities of the countries represented regarding the availability of CF care. The following common problems among developing countries were identified:

- under diagnosis of CF
- reduced life-expectancy among those diagnosed to have CF
- the clinical picture may vary from the "classical" description of CF in some populations
- poor availability of necessary drugs
- lack of CF centres or basic research

Against this background, the objectives of a basic CF service in developing countries should be to improve diagnosis, improve survival, define the clinical picture of CF in the local population, and to explore possibilities for improving the supply of medications.

Health services and socio-economic development varied considerably among the countries represented. The question of the relative contributions of public and private health care to a CF service was not discussed, but the general principle of access to appropriate care for all individuals with CF was assumed.

4. PREREQUISITES FOR ESTABLISHING A CYSTIC FIBROSIS SERVICE

4.1 Case-finding

Simple tools must be available for identifying affected patients. The essential diagnostic test is the sweat test, in which sweating is induced by the local application (iontophoresis) of pilocarpine, collected under standardized conditions and analyzed for its content of sodium chloride. It must be carried out meticulously by trained and experienced personnel. Several commercial adaptations have been developed for use outside special laboratories, but they should be regarded as screening tests and, when positive, the patient should be referred to a centre able to carry out a definitive sweat test before the diagnosis is confirmed.

Neonatal screening offers another route to diagnosis and may be of particular value in providing an estimate of the burden of CF in a population where it is under-diagnosed. There are 2 methods: the measurement of immuno-reactive trypsin (IRT) in dried blood spots, and the measurement of albumin in meconium using a test strip (BM test). The latter is much cheaper but less reliable, and has a false-negative rate of about 15%. Nevertheless, in populations such as most of Latin America, where it is estimated that 90% of patients die without a diagnosis having been made, it offers the possibility of greatly improved diagnosis and increase awareness of CF at relatively low cost. Both the IRT and BM tests are strictly screening tests, and the diagnosis cannot be made until a definitive sweat test or genetic analysis has been performed.

4.2 Medical staff

One or 2 dedicated physicians with a major interest in cystic fibrosis provide the starting point for a diagnostic and clinical service. Such individuals may have had their interest aroused while training in or visiting a unit elsewhere. It is essential that they are highly motivated and willing to give leadership. It is helpful but not essential if they work in the capital or a large city, with access to the resources of a major hospital.

4.3 Training facilities

As the care of cystic fibrosis involves a team of professionals, other members of the team also

require training and need to develop experience. Skills must be passed on to others, particularly nurses and physiotherapists, and provision must be made for their training.

4.4 Support groups

A national lay organization involving families, friends and other volunteers should be established early, so that the service can be developed as a partnership between professional and lay persons.

4.5 Education

Parents are the primary care-givers and they must be taught as much as possible about CF if they are to be the most effective. They also need careful genetic counselling. Other lay persons having regular contact with the child, such as a school teacher, will need basic information so that they can appreciate the importance of regular medication, dietary needs and the possibility that the child may have recurrent bouts of illness.

4.6 Evaluation

It is important to build into the service from the beginning some form of regular evaluation and audit, so that the outcome of the service can be monitored.

5. **CONTRIBUTING AGENCIES**

5.1 National agencies

Hospitals: Cystic fibrosis services are at least initially mainly hospital-based, although in some situations participation by community health services can be very valuable. The hospital or hospitals providing the location for this service need to be supportive.

Medical schools: If awareness of CF is to increase among the medical professions, it is important that medical schools play their part by including it in the undergraduate curriculum.

CF Associations: The value of a lay organization has been referred to above. Such organizations can be very helpful in raising public and professional awareness of the disease.

CF physicians: In addition to any involvement with the national lay CF association, clinicians dealing with the disease in a single country often find it helpful if they meet together from time to time to share experience and collaborate in future developments.

5.2 International organizations:

World Health Organization (WHO)

International Cystic Fibrosis (Mucoviscidosis) Association (ICF(M)A)

International Physiotherapy Group for Cystic Fibrosis (IPG/CF)

European Working Group for Cystic Fibrosis (EWGCF)

Latin American Working Group for Cystic Fibrosis (LAWGCF)

The industry

The role of the above-mentioned organizations is discussed in point 9 below.

6. IMPLEMENTATION OF A CYSTIC FIBROSIS SERVICE

6.1 Improving awareness

It is first necessary to identify some cases of CF and to concentrate clinical experience for their diagnosis and management. The primary responsibility for improving the awareness of CF will rest with the medical leadership referred to under 4.2, together with support from the national CF association. Initially it is wise to concentrate on obtaining the interest and support of the medical profession. Case reports and papers can be presented at local and national medical conferences. Leaders of the medical school and the health services should be invited to these conferences, and perhaps to regional or international CF meetings. Speakers from outside the country can be invited to national conferences, and suitable speakers may be identified through WHO, the ICF(M)A and the IPG/CF, while pharmaceutical companies may be willing to help with the expenses involved.

Subsequently, or perhaps at the same time, attempts should be made to inform the public health authorities and the general public about CF, but this is more likely to succeed when a consensus has been reached within the medical profession.

6.2 Estimate the incidence

Due to poor ascertainment and poor survival, the prevalence of CF in a community will be no guide to its true incidence. It is helpful for health authorities to know the scale of the problem if they are to make provision of CF care. For this reason, in addition to ensuring that all CF cases are well-documented and notified to a central registry, consideration should be given to some form of population screening, preferably neonatal.

6.3 Increase knowledge of CF

It is not enough to simply inform professionals and others that CF exists in a community. They should be given information about the nature of CF, its diagnosis, management, severity and prognosis. This may be achieved through presentations at meetings, conferences and in national medical journals.

Professional: Medical conferences can be used not only to improve the awareness of CF but also to develop the knowledge of the disease among paediatricians, physicians and others. Literature, including that produced by WHO, the ICF(M)A and the IPG/CF, and by the pharmaceutical industry, may be used to good effect. It is important that CF should be included in the medical school curriculum so that the next generation of doctors will know how to recognize and deal with it.

Lay: It is essential that parents and other volunteers within the wider CF community have as complete and up-to-date knowledge of CF as possible. Some of the simpler literature designed

for professionals is suitable for educated lay persons. A manual for parents and families of CF patients is in preparation by WHO/ICF(M)A and other similar information packages can be obtained from industries. Local parent groups appreciate and derive great support from informative talks arranged for them.

Public: It requires determination to educate the general public about medical matters. Much depends on the underlying level of general education, but in most countries there is a poor understanding of basic genetics. In the long-term, the most rewarding approach will probably be to ensure that human genetics is taught in schools, where CF provides an excellent example of an autosomal recessive disorder. Newspapers, fund-raising events, radio and television all provide opportunities for disseminating information.

6.4 Reliable diagnosis

The importance of establishing a reliable sweat test has been referred to above (4.1). In addition, diagnostic radiology, and laboratory facilities for sputum culture and pulmonary function tests are important for assisting in initial diagnosis and diagnosing complications. If available, a genetic reference laboratory capable of identifying CF mutations is a valuable asset.

6.5 Treatment centres

CF team: The members of the CF team can be divided into core members who have a continuing role, and fringe members who may contribute from time to time. The core team must include:

- pulmonary and/or gastrointestinal physician (usually a paediatrician) who will function as team leader
- a second general paediatrician, who may be senior or junior
- a nurse who is not necessarily specialized but should be trained by the team
- a physiotherapist whose main function would be to train and update patients and parents in the techniques of chest physiotherapy
- dietician

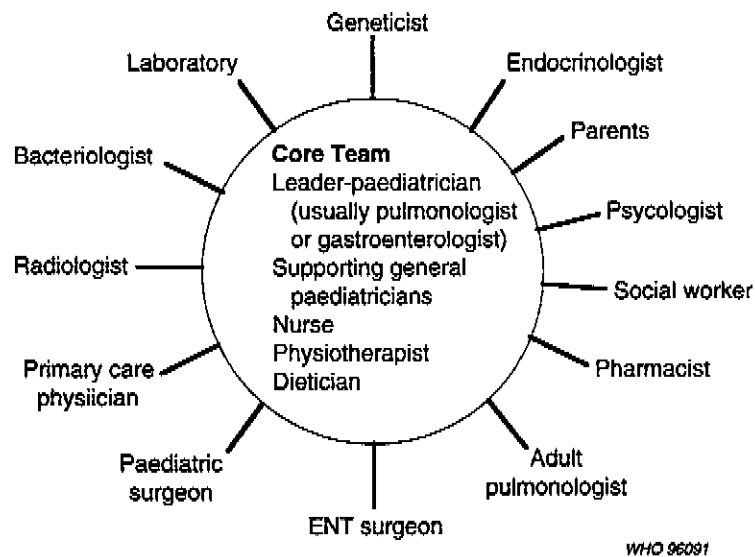
The fringe members include:

- adult physician, usually a pulmonologist
- bacteriologist
- geneticist
- psychologist and/or social worker
- endocrinologist
- ear, nose and throat (ENT) surgeon
- paediatric surgeon
- pharmacist
- primary care physician
- radiologist
- laboratory staff

The parents of an affected child, and the older patients themselves, are full members of the team and their committed involvement is essential to the success of any therapy.

The team should meet regularly and monitor results, including patient and team performance.

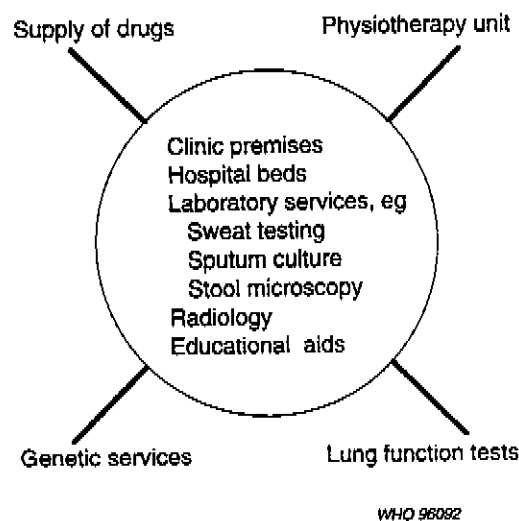
Fig. 1 Core and Fringe Teams



Facilities: Therapeutic facilities must include the following:

- physiotherapy - simple equipment may be needed
- nutritional support, using local resources
- pharmaceutical supplies of pancreatic enzymes and basic antibiotics, including anti-pseudomonas agents
- educational facilities for professionals and lay persons
- laboratory resources for sweat testing, bacteriology, stool microscopy for fat

Fig. 2 Facilities for Management of CF



The frequency with which a patient should be reviewed depends on the clinical condition, but on average should be about every 6-12 weeks. In infants, this interval should not exceed 1 month.

6.6 Registry

It is important to establish and maintain a CF registry, but this should be kept simple. Essential data will include: name, date of birth, sex, age at diagnosis, date of death. Other very useful information includes mode of presentation, mode of death, and, when available, genotype. Additional desirable data include information on height and weight at time of diagnosis and at annual intervals, lung function and bacteriological data.

6.7 Local research and audit

Participation in simple local research projects and in evaluation of performance engenders a team spirit and helps morale. It is also of potential international importance in populations where the clinical picture of CF differs from the classical picture seen elsewhere, and may be correlated with differences in gene mutations.

7. **OBSTACLES TO DEVELOPMENT OF CYSTIC FIBROSIS SERVICES**

Even when awareness of CF has been enhanced, provision of CF services must be seen in the context of the general health needs of a population and there may be substantial remaining difficulties for the development of an adequate service. Some of these problems have been identified as follows:

7.1 Public health priorities

These may be different from those of the families and the professionals concerned with CF. This is more likely when CF is perceived as a rare disease.

7.2 Existing medical services

In existing medical services, there are usually financial constraints and it is often difficult to add a completely new service to the budget.

7.3 Dependence on the "developed" CF nations

There may be a real and perceived dependence on the "developed" CF nations for support, and a corresponding delay in becoming self-sufficient. As more and more countries join the international CF family, it will be increasingly difficult to give each of them even rudimentary support, and priorities for aid will take into account the potential as well as the existing services available locally.

7.4 Health services

Health services themselves are variable between and sometimes even within countries. It is a general principle that patients should not be penalized because they happen to be born and live in areas where there are no CF services or medical insurance, but there will always be a conflict

between access and quality of care.

7.5 Diagnosis of CF

The diagnosis of CF is often missed or delayed in populations with a high prevalence of malnutrition, diarrhoea, and lung diseases. It may therefore take some time before clinicians dealing with these everyday problems learn to identify the children who are atypical or resistant to conventional treatment.

7.6 Lack of other models for management

There is often a lack of other models (for example, on the control of thalassaemia or haemophilia) in countries for the management of chronic, debilitating disorders of childhood and adolescence. The provision of a long-term supportive service may therefore involve acceptance of new concepts.

7.7 Population distribution

The population distribution may make access to diagnosis and treatment difficult for a large proportion of affected families.

7.8 Supply of necessary drugs

The free supply of necessary drugs, particularly pancreatic enzymes, may be unreliable for a variety of reasons, including a rigid adherence to an essential drugs list, and a relatively small target population which reduces profitability for importers.

8. STRATEGIES FOR PROGRESS

There are no easy solutions to many of the problems which have been outlined above. Some of them, such as financial limitations, are common to developed and developing countries, and have not been completely resolved even in the most affluent societies. In general, they will be overcome only by persisting with the strategies used for the implementation of the service (see point 6). They may be summarized as follows:

8.1 Education

The professions, particularly the medical profession, must be educated about CF. The public needs basic genetic education on which knowledge of CF can be superimposed. Schools and the mass media may be of great help.

8.2 CF centres

Centres for CF diagnosis and care must be developed. Diagnostic resources should be created at strategic locations throughout a country. Medical staff and those in allied professions must be trained. The use of local resources should be maximized, particularly for nutritional treatment, and physiotherapy should be adapted to those forms which are acceptable to the local population, using programmed exercise as a major component. High-cost imported antibiotics and equipment should be avoided whenever possible.

8.3 Publicity

It is essential to remain in contact with public health authorities. They should be informed about national and international developments, particularly therapeutic developments. A partnership must be maintained between the lay organizations and the professionals.

8.4 Documentation

A CF registry must be developed and maintained. Outcome measures should be monitored, including patient survival, patient well-being (often demonstrated as weight gain) and the number of respiratory episodes. Surveys may be expensive and time-consuming, but local genotype studies may be useful to define the expression of CF in the local population.

8.5 Fund-raising

However generous the support of health authorities, there is always a need for funds for new developments, publicity, family support and other activities. Raising funds should be predominantly the task of the CF lay organization, with support from professionals when needed.

9. **ROLE OF WHO, ICF(M)A & OTHER AGENCIES IN DEVELOPING COUNTRIES**

9.1 The World Health Organization (WHO)

WHO should organize meetings and workshops at an international level. With advice from the ICF(M)A and others, it can identify experts able to advise particular countries and groups on development of services. Through its publications, it helps to make national governments and health services aware of the existence of CF and the need for services.

9.2 The International Cystic Fibrosis (Mucoviscidosis) Association (ICF(M)A)

The ICF(M)A provides a forum for national CF organizations to get together, to share experiences and give mutual support. Through its Scientific/Medical Advisory Council, it has a small research and development budget, which may be used to support visits of experts to developing countries, and also to support visits of young professionals to established centres in order to gain experience and training. In addition, it provides funding for training courses for physiotherapists. Both the ICF(M)A and WHO have produced literature suitable for dissemination to professional and lay people. Every 4 years, the ICF(M)A supports an international congress on CF which brings together interested professionals from all parts of the world.

9.3 The International Physiotherapy Group for Cystic Fibrosis (IPG/CF)

With support from the ICF(M)A, the IPG/CF organizes occasional training courses for physiotherapists. These courses demonstrate the range of techniques available, and help physiotherapists decide upon the most appropriate methods for their own population. The IPG/CF holds annual meetings and has a world-wide membership. It has recently produced a small handbook which can be obtained upon request from the IPG/CF.

9.4 The European Working Group on Cystic Fibrosis (EWGCF)
The Latin American Working Group on Cystic Fibrosis (LAWGCF)

Regional CF organizations exist in Europe and Latin America. Each of these holds a regional/international meeting every year, except when there is an ICF(M)A International CF Congress. Attendance at these meetings is excellent, and the presentations range from the latest developments in basic science in genetic research to new forms of treatment. Both organizations work closely with the ICF(M)A and will help to identify individuals and centres which are willing to take part in training programmes for professionals from developing countries.

9.5 The industry

The industry may help the development of CF services in several ways. Firstly, various companies produce a wide range of scientific publications on CF, including interactive computer programmes. The industry also has an interest in defining the incidence of CF through epidemiological studies, and maybe willing to contribute towards the maintenance of a CF register. Ethical constraints would not allow them access to the register itself, but there is no objection to their knowing how many CF patients might exist in a particular country. Companies are also a traditional source of support for congresses, conferences and local meetings. This may extend to funding visiting speakers from outside the country. They may also be willing to support short-term training of medical and allied personnel. Some produce suitable literature for the information of patients and families.

10. CONCLUSIONS AND RECOMMENDATIONS

Knowledge of CF is poor in many countries where it represents a significant health burden. In those countries, many children with CF are unrecognized and may die before diagnosis. Patients who are diagnosed are often treated inadequately or inappropriately. Life expectancy, even among those patients who are diagnosed, is consequently far below that which would be attainable with adequate treatment. Services for diagnosis, particularly sweat testing, are poorly developed. Services for treatment are also poorly developed. Support services for families affected by CF are usually non-existent.

The following recommendations are made:

1. WHO and the ICF(M)A should continue to collaborate, and should focus their efforts particularly on the needs of "developing" countries.
2. The resources of both Organizations should be used to improve knowledge of CF, particularly in the medical and associated professions in those countries. They should also draw the attention of the health authorities in those countries to the problem of CF.
3. WHO and the ICF(M)A should use their resources to improve the training of professionals involved in the diagnosis and management of CF. The methods used can include training fellowships, visiting professorships, partnership and twinning arrangements between established and emerging CF centres, training courses, and assisted attendance of key personnel at international CF conferences. The two Organizations should continue to prepare and disseminate educational materials and guidelines produced by themselves or in

collaboration with others (such as the IPG/CF).

4. At least one specialist CF clinic should be set up in each country with a population affected by CF. Each centre should be led by a trained clinician, who will be responsible for ensuring the provision of a reliable service for diagnosis, and an adequate service for treatment. The CF centre should also act as the initial focus for setting up a national cystic fibrosis association, with lay and professional involvement.
5. Regular contact should be established between CF centres both within countries and within regions. Such regional groupings are already well established in Western Europe and Latin America. A similar regional grouping should be established in the Eastern Mediterranean region.
6. Consideration should be given to setting up limited neonatal screening projects as a means of establishing the incidence of CF and identifying affected infants in "developing" countries.
7. National and regional genetic laboratories should be encouraged to identify the precise genetic mutations for CF most commonly found in their populations, in order to help clinicians recognize the variations in clinical features which they may encounter.
8. National registers of CF patients should be established in order to identify and predict the need for services and to monitor survival trends. WHO should collate and publish the summarized data from all countries providing such reports.
9. National and international organizations should work in partnership with the industry, which may help by supporting educational and epidemiological activities.

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12. ACKNOWLEDGEMENTS

The participants of the meeting should like to express their sincere thanks to Dr Ibrahim Yacoub, Assistant Under-Secretary for Primary Care and Public Health, Ministry of Health, Manama, Bahrain for kindly accepting to open the meeting, and to Dr Abdul Jabber Al-Abassi, Chairman, Paediatric Department, Ministry of Health, Manama, Bahrain; Mr Ismail Akbari, Chief, International Health Relations, Ministry of Health, Manama, Bahrain; and, Mr Helmut Dassel, Director, Segment Pancreas, Knoll AG, Ludwigshafen, Germany for their expert advice and support throughout the meeting.

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