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Editorial

"Maintaining the Horizontal Line": early intervention and prevention of CF lung disease

The pulmonary disease of Cystic Fibrosis (CF) is characterized by periods of well-being with minimal symptoms and functional stability, interspersed with acute episodes of clinical deterioration ("exacerbation") caused by blazing endobronchial inflammation and bacterial growth, or slower, smoldering episodes ("sub-acute" or slow "exacerbation") of clinical and decline (Fig. 1).

Functionally, this cycle manifests itself by drops in lung function from which the patient may either recover completely with therapy ("return to the baseline"). Or be left with a permanent loss ("lower baseline"). This cycle which results in progressive airways obstruction, parenchymal destruction, disability and eventual demise, can only be reverted, eventually, by a successful lung transplantation (Fig. 2).

Medical interventions must be timely and aggressive, if they are to arrest, delay or prevent the ineffable downward spiral of deterioration. Prevention of irreversible damage is the *si ne qua non* of CF management. The concept of *early intervention* has become the "mantra" of clinicians caring for individuals with CF. The constellation of therapies and hygienic measures encompassed in such interventions requires clear definition, guidelines for implementation, and eventual measurement of outcomes to prove its efficacy.

Therapeutic programs must be adapted to specific geographical, social and political environments. The therapy of CF is intrinsically expensive and complex, and will become more so as new drugs are discovered. Poverty, ignorance, geographic barriers among others factors, hamper access to CF care. Lastly, therapeutic schemes must be individualized—since no two patients with CF are identical—but always within the framework of care guidelines such as the ones offered in this issue of The Journal of Cystic Fibrosis. Further, therapeutic schemes must be evaluated over time by means of data gathering in national and international registries, and periodic measurement of clinical outcomes.

The earliest form of intervention, the most drastic (and one that for many people represent a perverse approach to the problem) is simply the avoidance of births of individuals homozygous for CFTR mutations, or even individuals carrying any known CFTR mutation. Pre-natal testing is currently routinely offered to expectant mothers in the US. Those found to carry known mutations of CFTR have their husbands tested and—if they are also found to be carriers—chorionic villous sampling or amniocentesis are recommended. In cases of donor eggs and sperm, the situation becomes obviously more complicated, however, donor screening is becoming prevalent. Decisions based on discovery of mutated copies of CFTR in a fetus vary greatly and run the gamut of human behavior, as described in this European Consensus. These attitudes are based on religious, social and emotional factors. Many parents of children with CF choose not to undergo pre-natal testing, or do so only to prepare themselves to care for a potential affected child, without intention of terminating the pregnancy. Pre-natal testing has already resulted in decreased rates of CF births in some communities, however. To avoid a birth of an affected offspring, some couples resort to methods such as such as artificial insemination, in vitro fertilization and embryonic biopsy, and others. The ultimate impact of all these interventions is still to be measured.

Gene transfer into affected embryos and fetuses, as a form of early intervention and possible cure, is still in its experimental phase; it is unclear to date if gene transfer at all will be a successful therapeutic avenue; its prenatal use adds complexity to this option, both from technical and philosophical view points.

The impact of neonatal screening on the ultimate course of the disease, as described in the accompanying document, is still unclear. Long-term, longitudinal blind studies on the impact of neonatal screening have become impossible, as these programs are being instituted across the board. Long-term epidemiological studies and eventual multivariate analysis may cast some light, years from now, as to the ultimate effect of neonatal screening on outcome. It is clear, nevertheless, that neonatal screening may be important in helping to "maintain the horizontal" insofar early identification of patients results in improved nutrition, one of the risk factors associated with deterioration of lung disease. The effect on Pseudomonas infection is not evident, suggesting that this risk factor may be more tightly linked to the type of mutation carried by the affected individual.

The basic abnormality of CFTR renders the epithelium prone to up-regulation of inflammation and favors bacterial adherence. Newer investigational therapies such as protein

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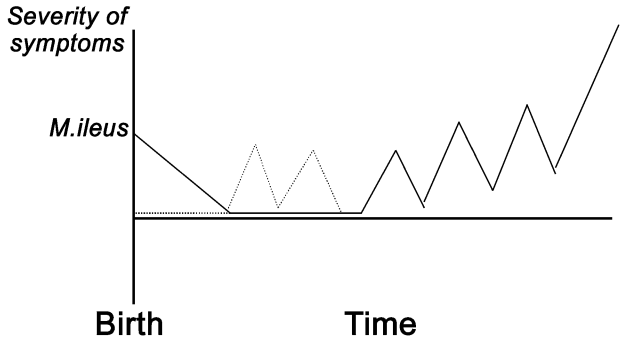

Fig. 1. Diagrammatic representation of clinical course over time in Cystic Fibrosis. Meconium ileum is the earliest event. Affected individuals can be largely symptomatic or mildly symptomatic for variable periods of time (solid line) or start becoming increasingly symptomatic earlier in life (dotted line) and then suffer increasingly severe, frequent, and permanent signs and symptoms of pulmonary disease until death.

repair and alternative activation of ion channels appear to hold promise in the ultimate control of the pathophysiologic mechanisms that cause lung damage. To date, however, clinicians do not count with commercially available weapons of the kind, and must concentrate their efforts in containing the risk factors known to be associated with a downward course, and containing the cycle of infection–inflammation known to result in eventual lung destruction. Genotype-phenotype correlations are notoriously unpredictable when it applies to CF lung disease; although type I and II mutations are known to be associated with worse lung disease, meconium ileus, etc, any CF clinician can report, for instance, on patients who are homozygous for the delta Γ508 mutation, who have reached adulthood with minimal lung disease and dysfunction. The effect of modifier genes and other factors remains still a fertile ground for investigation and a largely unknown field.

Thus, the management of CF, and early intervention and prevention programs must center on known clinical factors about which clinicians can exercise some control, for which therapeutic approaches, albeit imperfect, are available.

The identification of risks factors for deterioration has been the product of multivariate analyses of large databases. These studies have highlighted the importance of the ongoing acquisition of epidemiological data at regular intervals into patient registries, whether these are regional, national or even international. The variability of the disease and the insertion of therapeutic agents over time demand that large amounts of data are collected and analyzed over long periods of time to assess efficacy and changes in clinical outcomes.

Some of the most important risk factors for deterioration and poor survival include the acquisition of *P. aeruginosa*, especially the mucoid form [1] (Fig. 3) and, later, multiresistant organisms, malnutrition, and pulmonary function over time .Other factors include complications such as diabetes and hepatic dysfunction among others.

The European community of CF caregivers has gained distinction for its aggressive approach to the biology, detection and management of *P. aeruginosa* infection and the attendant inflammation in CF. The consensus document in this issue addresses this aspect of the disease in detail and in a scholarly manner. The evidence to date indicates that eradication of *P. aeruginosa* upon new acquisition should be attempted as a means to delay permanent colonization and infection. The issue that upon which there seems not to be universal agreement is the degree of aggressiveness with which the search for the microorganism should be undertaken, e.g. the use of bronchoscopy and bronchial lavages. The need to gain a better understanding of the infection status of patients is tempered by the logistics and cost of submitting patients to repeated invasive procedures. Should genotype enter into the indication for such procedures, as *P. aeruginosa* is more likely to be present in individuals with types I and II mutations? Further investigation appears warranted.

I should like to highlight the problematic nature of early detection of inflammatory activity, which seems to occur even in the absence of apparent infection. The lack of adequate biological markers of inflammation leaves the clinician bereft of means of detection of nascent or increasing inflammatory activity, before the patients acknowledge symptoms. Clinicians are rendered incapable of intercepting the course at its onset or shortly thereafter. We are left to obtain surrogate markers, such as clinical manifestations and measurement of pulmonary function.

Pulmonary function is the single most important objective outcome criterion in the assessment of patient health and the efficacy of interventions. The most frequently used parameters are the spirometric measurements of flows at all lung volumes and flow rates; little attention has been paid to the value of measurement of residual value and RV/TLC (residual volume over total lung capacity over time) due perhaps to the fact that these measurements require a

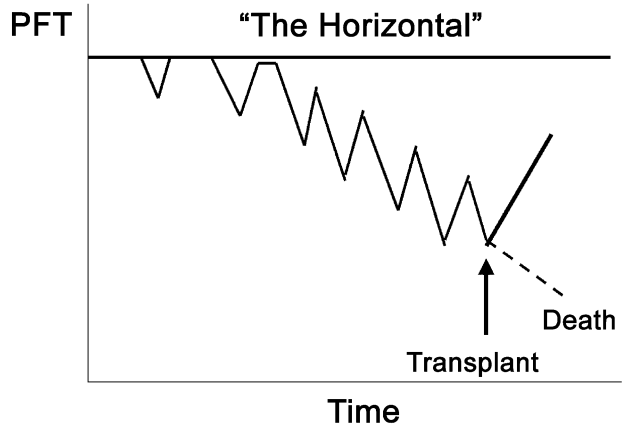

Fig. 2. Diagrammatic representation of pulmonary function (PFT) over time. Exacerbations of lung disease result in drops in PFT, which are recoverable to “baseline” “The Horizontal” represents an ideal state of stability and normality. Clinical exacerbations and progression of lung disease lower the baseline progressively, until death or successful lung transplantation is achieved.

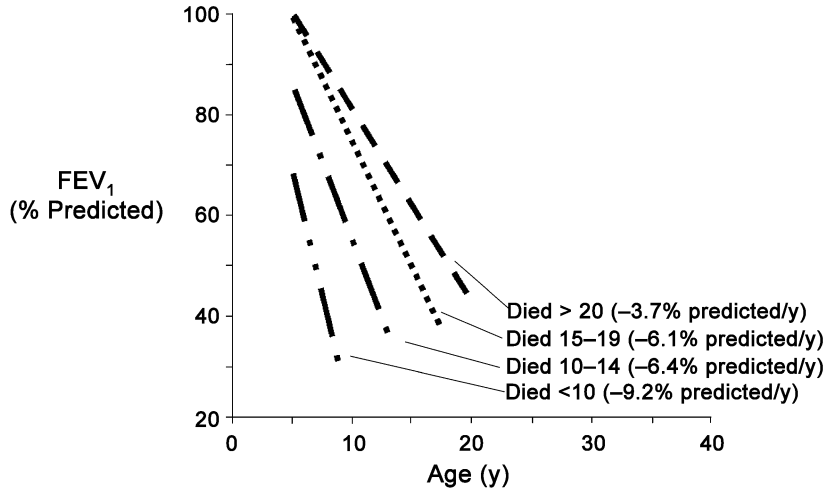

Fig. 3. Survival by age against slope of decrease of flow rates. Steeper decreases result in decreased survival rate (adapted from Corey et al., J Pediatr 1997; 131:809–814, with permission).

complete laboratory and are more costly and complex to obtain than spirometry data. The slope of deterioration over time is more important as a prognostic factor than isolated measurements [2,3]. Slow deterioration over time, or low, steady values are less alarming than sudden or accelerated loss of pulmonary function, which heralds uncontrolled disease (Fig. 4) The aim of early and aggressive intervention when confronted with any loss of lung function is to "restore the horizontal" and then "maintain the horizontal", that is, bring the patient's lung function to an optimum baseline and maintain it, as a means to improve survival and quality of life.

Periodic and regular measurements of PFT are an important aid to early intervention and prevention of lung disease. Similarly to a diabetic individual who measures his blood glucose daily, or a labile hypertensive person who measures his blood pressure, I would submit that daily spirometry should be incorporated in the regiment of individuals with CF. Hand-held spirometers are already part of the daily monitoring regimen of patients after lung transplantation; we have used such devices in difficult to con troll asthmatics, for instance. Newer technology, which allows for distance monitoring with the use of tele-spirometry should improve response time by clinicians to significant changes in patient's status. This would be especially useful in individuals who enjoy good lung function, as their symptoms may not become apparent to them until significant obstruction—as measured by flow rates and timed volumes—is present.

The development of national and international registries is essential to the understanding of the impact of biological phenomenon on large populations. Registry items often stem from consensus documents and guidelines like this one and become and important source of assessment of widespread interventions and practice patterns. The mainte-

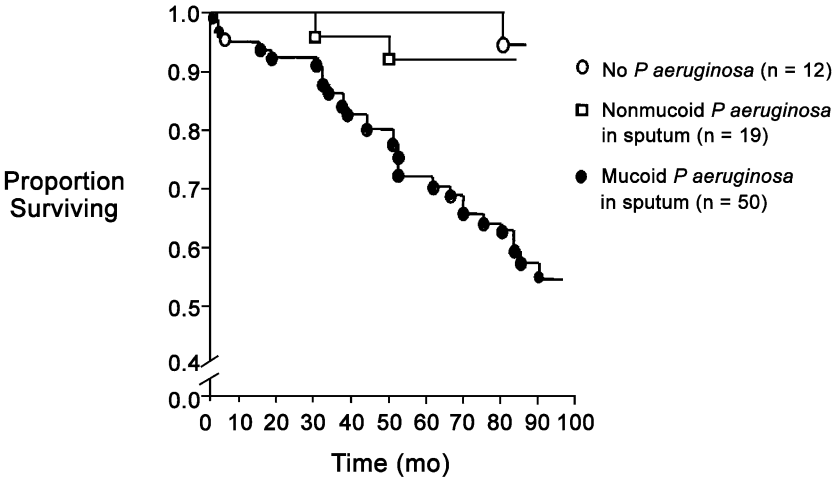

Fig. 4. Graphic representing the impact of *Pseudomonas aeruginosa* infection on survival of patients with CF (adapted from Henry, R.L. et al., Pediatr Pulmonol 1992;12:158–161; with permission from the publisher).

nance of these databases requires ongoing economic support and attention.

The document in this issue of the Journal of Cystic Fibrosis is an important hallmark for the European CF community. The value of establishing guidelines via consensus cannot be underestimated, especially when absolute truths based on accurate scientific data are lacking. These documents are not ''recipes'' for management, or attempts at regulating or legislating therapy without giving physicians the right to exercise their individual judgment (as some corridor conversations would suggest). The recommendations contained therein are based on the best available knowledge, and where this is incomplete, the best judgment and combined wisdom of a group of experienced clinicians and scientists. I had the privilege of chairing the first such consensus conference in the US fifteen years ago, that resulted in the US CF Foundation Guidelines for Patient Services, Evaluation and Monitoring in CF Centers [4]. To quote from the original document: ''The aim of this guideline is to promote a uniform level of care and teaching services at CF centers and to provide a general framework for good patient care. The relevance to specific situations will depend on the individual variation and clinical course and professional judgment.''

In sum, the basic philosophical tenet of management of CF, in the absence of definitive methods of control (i.e. cure) are the prevention of deterioration by modification or elimination risk factors and the earliest possible interruption of injurious processes. In the absence of biological markers of early inflammatory activity and lung damage we are forced to carefully follow clinical substitutes. Ongoing surveillance of clinical status—a clinical ''radar''—would help to provide signals indicating the need for therapeutic intervention.

Finally, the issue of adherence by patients to therapeutic regimens brings all considerations to a very practical crossroad. Patient adherence to daily routines is the least understood and controllable of all variables affecting outcome. Neither the best therapeutic guidelines, enhanced drug delivery systems, nor the most compulsive of caregivers can prevent the damaging impact of behaviors that are essentially self-damaging. The mounting complexities of CF care and drug regimens runs counter to the desires of people affected with CF to lead a normal life. This ongoing struggle between ''living right and doing what is right'' is a sobering reminder that until a real cure or effective control of CF is achieved, which can be administered in an expeditious manner (and what a tall order this is!!), we will be constantly humbled by human nature itself.

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