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EDITORIAL

Improving standards of clinical care in cystic fibrosis

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For the clinician involved in the care of cystic fibrosis patients, the last decade has been an exciting period. The discovery of the gene coding for the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) protein [1] gave a novel impulse to CF care and research. The function of the CFTR protein was first described as a simple chloride channel. Soon evidence accumulated that the chloride channel regulates other ion channel functions [2]. The knowledge about epithelial salt and water movement across respiratory membranes greatly improved. Novel functions of the CFTR protein continue to be discovered such as a possible role in bacterial phagocytosis [3].

To a certain extent, the basic defect in CF is understood [4]. There are more than 800 known mutations in the gene that can lead to the production of an abnormal protein and hence abnormal ion transport across epithelial membranes. The abnormal composition of airway secretions can predispose patients to airway obstruction and infection with *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus*. The relentless neutrophil-driven lung infection and inflammation that follows culminates in organ destruction and death.

The hope for a quick cure by gene therapy proved unrealistic. But the search for the basic defect and the efforts to circumvent the hurdles in gene therapy brought new insights into cell physiology and possibilities of novel therapies. All these new therapies have one thing in common that is they are likely to stop the pathophysiological process at an earlier level, before chronic infection sets in. The most basic approach would still be a correction of the defect by gene therapy. But other possibilities abound. The classification of mutations into functional groups is helpful to situate possible therapies [5]. For full function, the CFTR gene has to be translated, in sufficient amounts, into a full length protein. The protein has to travel to the cell membrane, be activated in the appropriate way, permit sufficient chloride efflux and interact normally with other ion channels. Class one mutations, usually nonsense mutations, may be overcome by drugs that read through these premature stop codons [6]. In class two mutations, including the most frequent mutation DF508, the CFTR protein is structurally abnormal and is degraded by the cell′s quality control system. Chemical chaperones could assist the abnormal protein to escape from degradation and "to make it to the cell membrane" as a functional chloride channel [7]. Class three mutations interfere with the activation of the CFTR chloride channel. Compounds such as the protein phosphatase inhibitor genistein may influence the gating of the CFTR channel [8]. Improving chloride channel conductance would be the goal for class four mutations, usually mutations in the protein′s transmembrane domain. Restoring the efficiency of splice mutations to normal would be the goal for class five mutations, in which insufficient amounts of functional CFTR protein are being produced. Inhibiting the excessive sodium reabsorption by amiloride may be seen as a therapy aimed at compensating for some of the control function of CFTR on other ion channel functions [9].

A spin off from unravelling the link between abnormal secretions and chronic infections are the discovery of defensins [10] and the manufacturing of synthetic defensins for future therapy.

This boom of information has led to innumerable papers and several new, well structured textbooks that assist the clinician in keeping up to date with current knowledge [11–14]. The hope for a cure has strengthened clinical interest in managing the patient optimally; only patients in a fairly good condition will optimally benefit from new therapies. There has already been a vast improvement in patient survival, without using the knowledge about the basic defect but by better follow-up, more intensive treatment and attention to all aspects of this multi-system disease [15]. A central issue that remains is the correct treatment of lung infection because relentless pulmonary infection will be the cause of respiratory insufficiency and death in the majority of patients.

Although knowledge has greatly improved, critical information is missing. How exactly to bridge the gap between altered chloride secretion and pulmonary infection? Why is *Pseudomonas* lung infection so typical for CF patients? Is it a matter of dehydrated mucus incapable of maintaining normal airway clearance? Is there an increased salt content in the secretions inhibiting the normal defensins? Do CF patients carry specific *P. aeruginosa* binding sites on their cell membranes? Is some preliminary lung damage required before chronic *Pseudomonas* infection sets in? Is there a primary overactive inflammatory status in CF lung tissue? Whilst scientists try to close the gap in knowledge, clinicians focus on optimal management of chronic lung infection. Many trials have studied aspects of antibiotic therapy for *P. aeruginosa* lung infection in CF. But in different countries different definitions for chronic colonization are used, different treatment protocols for

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lung infection are investigated and different protocols for overall patient follow-up and management prevail. The results from one group therefore, often don′t match the results from another group. When deciding on the optimal therapy for each individual patient, the clinician is often left with a difficult choice.

The European consensus on antibiotic therapy against *P. aeruginosa* [16] presented in this issue of the *European Respiratory Journal* is warmly welcomed. A group of experts in the field was convened, where available information about this complex topic was discussed and classified, the result of which has become a very useful document. Following a brief introduction, the available information concerning *P. aeruginosa* lung infection in CF patients is discussed in several clinical headings: assessment of chronic lung infection in CF patients, antibiotic resistance of *P. aeruginosa*, pharmacokinetics and penetration of antibiotics into sputum, therapy by intravenous, oral and nebulized route, antibiotic treatment strategies and a summation of the future studies needed. The authors have selected their discussion points carefully so that the final document contains a large amount of information but still remains rather concise and easy to read. At the end of the document the authors have added 24 important questions and answers (Q&A). The answers of the panel will definitely stimulate a lot of healthy discussion between CF clinicians. It is advisable to read the overall document, and not to be too hasty in disagreeing with the panel, before going through this stimulating Q&A section.

This paper will undoubtedly become a much discussed classic. The several unanswered and controversial issues will stimulate research in the field. Unequivocal answers are available to a minority of questions. Too many studies concern too small a number of patients to be conclusive. Especially comparative trials with different antibiotic regimens which suffer from negative results, including those in the authors′ study [17, 18]. The public health authorities and the industry need to fund larger scale, multicentre trials. The difficulties inherent to multicentre trials in a multi-organ disease will have to be overcome. Only studies involving larger groups of patients will disclose relevant differences in outcome between comparative antibiotic treatment strategies in CF patients. The recent large scale studies on mucolytic therapy using rDNAse [19] and on intermittent inhaled tobramycin therapy [20] lead to clear conclusions and are prime examples of the types of studies needed. It is important that sufficient funding goes to clinical research with immediate relevance for patient wellbeing. A balance needs to be found between investments with an immediate return and those that will pay-off with time.

The document is very much a report from clinicians to clinicians. It is "down to earth" and discusses the practical issues important in the day-to-day patient care: which nebulizers to use, how to obtain isotonic aerosol solutions, what combination of drugs to use, intravenous therapy in the hospital or at home, and the side effects from therapy to watch out for. The consensus report limits itself to the management of *P. aeruginosa* infection. The whole realm of "new" bacteria encountered in the last decade of CF care including *Burkholderia cepacia*, *Alcaligenes xylosoxidans*, *Stenotrophomonas maltophilia*, *Acinetobacter Iwoffii*, untypable *Pseudomonas* species and others is left untouched [21, 22]. Several important questions arise. Are these new bacteria the result of the improving skills of bacteriologists? Have they always been there or are they a side-effect of the aggressive treatment of *P. aeruginosa* lung infection? After all, wasn′t *Staphylococcus aureus* the major pathogen responsible for lung disease in the era before antibiotic therapy? Should colonization and infection with these pathogens be treated the same way as *P. aeruginosa* infection? The committee has limited their first consensus on *P. aeruginosa* lung infection and has come up with a clear statement. On the other hand, by doing so we are left "without consensus or expert′s thoughts" for the treatment of up to half the patients. Although *P. aeruginosa* may still be the major villain, it is time to launch a large study addressing this issue since the number of patients colonized with these pathogens is increasing.

Even with good definitions some confusion exists. The definition of chronic *P. aeruginosa* infection proposed by the consensus report is: at least 3 positive cultures at least one month apart over a 6 month period. But when reporting 80% success rates in the prevention of chronic *P. aeruginosa* infection, 7 yrs after initial colonization, by early and intensive treatment of first or intermittent *Pseudomonas* colonization, the slightly different Danish definition of chronic colonization is used: a patient with a positive culture in 6 consecutive months [23]. The answer to Q21 "Regular maintenance therapy or treatment on demand: what is recommended?" is somewhat unclear. It is stated that patients suffering from chronic *P. aeruginosa* infection should be treated with antibiotics with specific activitiy against *P. aeruginosa* either 3–4 times a yr intravenously or by appropriate aerosol administration using either colistin or tobramycin throughout the year. In the full document it states that these therapies can be combined and this is often done. The answer also slightly contradicts the comments to Q8 "How are optimal airway concentrations of antibiotics obtained (during maintenance therapy)?", by inhaled antibiotic therapy with and without intravenous antibiotic therapy. Also the answer to Q15 "Is administration of nebulized antibiotics clinically effective" contains the statement "All patients chronically infected with mucoid *P. aeruginosa* should be offered this treatment (nebulized antibiotics) irrespective of lung function". In the review a balanced summary of the available literature is given. In the Q&A section a specific statement is sometimes chosen as the answer, for example, the discussion on pharmacokinetics mainly quotes the older literature stressing the differences in renal clearance but the answer to Q10 "Do pharmacokinetics of antibiotics in CF patients differ from that in nonCF individuals?" leans towards the more recent view that any alteration in pharmacokinetics is more likely a "calculation error" in patients with a different body composition. Few readers will agree with every statement, but most clinicians will consent to the general tenor of the consensus and read it with great interest.

New areas and future developments are not touched upon since the consensus is based on current evidence. A new consensus will be necessary in the future, as fresh data emerges about: the drug dosages to be used, the influence of macrolides on biofilm formation, bacterial resistance mechanisms and ways of interfering with it, the role of synthetic defensins. If the link between CF and the chronic

Pseudomonas lung infection is finally understood, the effectiveness of using hygienic measures to decontaminate common environmental reservoirs of *Pseudomonas aeruginosa* such as sinks, toilets and showers will probably become clear.

To conclude, this consensus on antibiotic treatment against *Pseudomonas aeruginosa* is an important document that will stimulate discussion about the topic, incite cystic fibrosis clinic directors to create or review their current treatment protocols and thus improve standards of patient care. It will hopefully initiate new large scale multicentre clinical trials and thus necessitate a follow-up statement in the future.

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