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Topical Reviews

A ten year review of Colomycin

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The changing face of cystic fibrosis management

There are few conditions where treatment and outlook have improved so steadily and impressively, over so long a period, as cystic fibrosis (CF). Since the first clear description of the disease by Dorothy Andersen in 1938 (1), there has been a steady improvement in prognosis, particularly marked over the past 10 to 15 years. The outlook has improved from almost inevitable death in early childhood to the present median survival of over 30 years (2) and a predicted survival of over 40 years (3,4). An infant with CF born today, diagnosed before chronic pulmonary infection is established, should, with modern treatment, have few, if any, chronic respiratory symptoms for many years, avoiding chronic respiratory infection and the inevitable associated decline in pulmonary function (5,6).

Although in many countries the outlook remained poor until the mid 1970s, some clinicians realized that chronic pulmonary infection and the inevitable respiratory failure which followed were not inevitable and could be delayed or minimized (7,8,9,10).

In 1974, Crozier, who started the Toronto clinic, in an article *Cystic fibrosis: a not so fatal disease* advised that 'there should be regular detailed assessment of the patient with attempts to return to normal as far as possible' (8). Over recent years his advice has been a guiding principle of management employed by an increasing number of clinicians (11).

ESTABLISHMENT OF CF CENTRES

The remarkable scientific advances of the 1980s, from the demonstration of chloride impermeability of the sweat gland (12) to the identification of the CF gene in 1989 (13,14,15) have not, as yet, had a significant influence on treatment. The improved outlook has been due entirely to better conventional treatment that has been developed at CF centres. The development of CF centres, where medical, paramedical, nursing and laboratory staff gain experience in management of the disease, has been central to the progress made (16,17).

The more effective treatment of *Pseudomonas aeruginosa* infection has been central to the increased survival, and is repeatedly stressed by the authors of this review. Nebulized Colomycin (Pharmax, Bexley, U.K.) (colistin), both to eradicate early *P. aeruginosa* infection either alone (18) or with oral ciprofloxacin (19,20) and to stabilize chronic infection (21), has been a central component of the modern treatment package in most European clinics.

The improved condition and survival of people with CF has undoubtedly paralleled the increased use of antibiotics and improved nutrition achieved by aggressive nutritional support and the more effective acid resistant enzymes. It is important to stress that all these improvements have been introduced and evaluated at CF centres where the staff has the opportunity of treating large numbers of patients.

GROWTH OF SHARED CARE

The essential requirement for a CF centre is an adequate number of patients—usually a minimum of 50 on full care at the clinic. Constantly being faced with the diverse problems presented by large numbers of CF patients causes the CF centre staff to explore ways in which treatment of various aspects of the disease can be improved. In addition, the most efficient and acceptable methods of giving new treatments can be developed and tested if there are

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adequate patient numbers—for example nebulized antibiotics, intravenous antibiotics, regular 3 monthly i.v. (intravenous) antibiotics and enteral nutrition, to mention only a few of the significant components of modern care.

When the details of monitoring and treatment have been established, much of the treatment can often be given by those with fewer CF patients working in smaller general hospitals. There is a move towards this so-called 'shared care' in the U.K. for children although it is important that all CF patients are known to and periodically reviewed by the staff of a large specialist CF centre. Adults with CF are advised to attend specialist CF centres in view of the increasingly complex treatment they require.

MORE AGGRESSIVE TREATMENT OF INFECTIONS DELAYS THE ONSET OF CHRONIC INFECTION AND PROLONGS LIFE

Previous studies showed that patients attending CF centres in the U.S.A. where there was more frequent follow-up and more frequent use of i.v. antibiotics had a much better survival rate (22). The introduction of a policy of 3-monthly i.v. antibiotics for patients chronically infected with *P. aeruginosa* at the Copenhagen CF centre significantly reduced the mortality of their patients (4). Also, the reduction in the total number of chronically infected patients has obviously had a major favourable effect on survival (20).

Thus, the timing and intensity of treatment will determine the fate of the CF patient. Prevention or early treatment to eradicate *P. aeruginosa* infection is probably the most important single measure that will improve the long term prognosis, by preventing the patient moving from a stable state to one of variable—but relentless—decline in pulmonary function (23). When chronic infection becomes established, aggressive treatment with regular 3-monthly courses of i.v. antibiotics and with suppressive nebulized antibiotics appears to be the best available treatment option at present.

Colomycin is an interesting drug in the context of CF, having been resurrected in the 1980s as *P. aeruginosa* proved an increasing problem in children with CF. Many were in excellent condition and without chronic infection, *Staphylococcus aureus* having been successfully avoided or treated (24), only to deteriorate following the onset of *P. aeruginosa* infection. The drug's activity against *P. aeruginosa*, the very rare occurrence of resistance and the ability to deliver it by nebulizer resulted in its introduction and increasing use both to eradicate early *P. aeruginosa* and to stabilize those who had acquired chronic infection. The problems of resistance to other anti-pseudomonal antibiotics for the treatment of exacerbations has lead to an increasing use of Colomycin by the intravenous route (25,26).

In this article the various aspects of the use of the Colomycin are reviewed by experienced microbiologists and clinicians who have been involved in the increasing and successful use of the drug in the treatment of CF.

A radical change in therapy: C. Koch

P. aeruginosa has, over recent decades, become the most frequent pathogen in the lower respiratory tract of patients with CF. Chronic *P. aeruginosa* infection is now responsible for the large majority of excess morbidity and mortality in these patients since once established the organism cannot be eradicated from the lower respiratory tract (27). Chronic *P. aeruginosa* infection is, however, preceded by a period of intermittent colonization which averages 12 months (28). This prompted us to consider whether very early treatment at the onset of intermittent colonization might prevent —or least postpone—progression to chronic infection.

In 1986, therefore, we initiated a controlled trial of the efficacy of 3 weeks of treatment with inhaled Colomycin 10^6 IU twice daily and oral ciprofloxacin 250–750 mg (according to body weight), administered whenever *P. aeruginosa* was isolated from lower respiratory tract secretions at the routine monthly visits to the clinic, in patients not chronically infected (19). The choice of antibiotics was based upon studies showing the clinical effect of these antibiotics in early (18) and in chronically infected patients (18,21,29). The study was designed as an open parallel trial where 26 patients were randomized to treatment or no treatment, and the outcome measure (endpoint) was progression to chronic colonization/infection: this was defined as presence of *P. aeruginosa* in monthly routine specimens for 6 consecutive months, or a shorter period accompanied by emergence of precipitating serum antibodies against *P. aeruginosa* (30). During the trial period of 27 months, seven out of 12 untreated patients (58%) became chronically colonized/infected with *P. aeruginosa* as compared with two of the 14 treated patients (14%) ($P < 0{\cdot}05$) (19). Following these promising results a modification of this strategy was introduced in our routine treatment and this has been followed by a marked reduction in the prevalence of chronic *P. aeruginosa* infection in our patients (31).

It must be emphasized that the design of this early study was quite simple and also easily applicable to our patients. All patients are seen on a strict monthly basis and all visits include sampling of lower respiratory secretions. The patients/parents were familiar with our aggressive antimicrobial treatment ('intermittent prophylaxis' with prescription of antibiotics whenever pathogens were isolated, even when asymptomatic, and were also familiar with inhalation therapy (inhalation of β_2-agonists and other drugs). Furthermore, regular quantitation of anti-pseudomonal antibodies has been a routine measure since the 1960s (30).

The task that now lies ahead is to improve this early treatment in order to protect all—not only 80%—of the patients. We must be aware of the side effects such as the acquisition of other and potentially more aggressive Gram-negative organisms such as *Burkholderia cepacia*.

Furthermore we need to consider whether the principle of very early aggressive treatment might be applied to other Gram-negative organisms which may chronically infect the lower respiratory tract (i.e. *B. cepacia, Achromobacter xyloxidans* and others).

Recent studies have indicated that there may be pharmacological means of correcting the cellular dysfunction(s) that lead to colonization of the respiratory tract in CF with pathogenic microorganisms (32). We would predict that only partial correction, but in combination with our principle of close microbiological surveillance coupled with early aggressive antimicrobial treatment, might lead to complete protection of the patients against chronic bronchopulmonary infections in the future. Lifelong absence of this devastating complication will dramatically improve quality of life and long-term survival in patients with cystic fibrosis.

What makes Colomycin different? P. A. Lambert

The polymyxins are a group of lipopeptide antibiotics isolated from spore-forming soil bacterium, *Bacillus polymyxa* (33). Five major, chemically distinct members of the group were recognized and designated as polymyxin A, B, C, D and E. Colistin (Colomycin) was isolated in 1950 from a related strain, *Bacillus colistinus*. It is identical to polymyxin E, and has the characteristic polymyxin structure comprising a cyclic heptapeptide joined to a tripeptide chain with a single fatty acid substituent. For parenteral and aerosol therapy colistin is used in the form of the sodium salt of the negatively-charged derivative, colistin sulphomethate, which is hydrolysed to the active, positively charged colistin base after administration (34).

Colomycin is most notable for its activity towards *P. aeruginosa*. Its spectrum of activity also includes *Escherichia coli, Enterobacter, Salmonella, Shigella* and *Klebsiella* spp but *Proteus* spp, *B. cepacia, Bacteroides fragilis* and many *Serratia marcescens* strains are resistant to this drug (35). Gram-positive bacteria are generally less sensitive than those that are Gram-negative. This unusual spectrum of activity results from its unique physical mechanism of action which occurs in two stages: disruption of the permeability barrier of the outer membrane followed by penetration of the cytoplasmic membrane and destruction of its integrity (36). The active form of the drug, the positively charged colistin base, binds to the lipopolysaccharide (LPS) component of the outer membrane of the sensitive Gram-negative bacteria. The binding involves interaction between the peptide ring of the colistin and phosphate groups present on the lipid A and core region of LPS. Colomycin displaces magnesium ions from the phosphate groups, resulting in distortion of the outer membrane structure and loss of the permeability barrier. *P. aeruginosa* is particularly sensitive to Colomycin because its LPS has a high phosphate content and associated magnesium ions. Loss of the permeability barrier of the outer membrane allows colistin to penetrate the cell wall to the underlying cytoplasmic membrane, which is the ultimate target for the lethal action of the antibiotic. Insertion of colistin molecules between the phospholipid and protein components of cell membranes results in loss of membrane integrity, leakage of cytoplasmic constituents and cell death. Colomycin therefore exerts a rapid, lethal action upon sensitive bacteria.

The self-promoted uptake mechanism of Colomycin is quite different from the uptake pathways used by other anti-pseudomonal antibiotics. The quinolones and β-lactams must cross the permeability barrier of the outer cytoplasmic membrane to reach their enzyme targets in the cytoplasm and cytoplasmic membrane respectively. They do not damage the outer membrane to promote their own uptake and must rely upon passive diffusion through porin channels to cross the cell envelope. Resistance to these agents can result from alterations in porin composition and through the action of efflux pumps (37). Clinical resistance of *P. aeruginosa* to Colomycin by these or other mechanisms is very rare. The aminoglycosides do exert some damage on the outer membrane, and, to some extent promote their own uptake. However, unlike Colomycin, they require an active transport process involving respiratory activity to cross the cytoplasmic membrane and reach their ribosomal target site. Aminoglycosides are therefore susceptible to resistance through absence of the transport system (e.g. in anaerobes) and through extrusion by efflux pumps.

In lung infections associated with CF *P. aeruginosa* exists in the form of microcolonies or adherent biofilms comprising cells surrounded by a layer of alginate polysaccharide attached to lung epithelial cells. Failure of antibiotics to eradicate the organism in this intractable mode of growth is due to the reduced growth rate of cells and restricted penetration of antibiotics (38). The alginate layer effectively protects the cells from phagocytic attack whilst LPS released from the bacteria generates a frustrated macrophage response which exacerbates the inflammatory conditions within the lungs. The therapeutic benefit of colistin in CF could result from its ability to kill slow-growing and non-growing cells in the microcolonies. Furthermore, binding of LPS released from the cells might also contribute to the treatment through neutralization of its inflammatory action (39).

Colomycin—a constant in an increasingly resistant world of microorganisms: N. Høiby

When nebulized Colomycin was introduced in the Danish CF Centre the decision was based on preliminary very promising results from Littlewood *et al.* (18). Daily inhalation therapy with Colomycin was employed to further improve the 'maintenance therapy = chronic suppressive therapy' in CF patients with chronic *P. aeruginosa* infection (21). A few years earlier the centre had experienced an epidemic caused by a multi-resistant strain (40) with a high level of chromosomal β-lactamase production and a high level of resistance to tobramycin (41). To avoid further problems of resistance, Colomycin

was chosen—long-term clinical experience had shown that resistant *P. aeruginosa* did not occur in hospitals although this drug had been used for many years, and in spite of the fact that resistance can be easily induced *in vitro* (42,43). Another reason for choosing Colomycin was its narrow spectrum, which would probably induce only minor changes in the normal flora of the mouth, the throat and the gut. The prodrug nature of Colomycin would probably further protect the normal flora, since the drug requires hydrolytic activation leading to release of formaldehyde and bisulphite. This is probably why selection of colistin-resistant microorganisms such as *Burkholderia* spp. has not been observed in the Danish CF Centre (44). Another potential beneficial property of Colomycin is its ability to neutralize bacterial lipopolysaccharides and their biological effects and thereby functioning as an anti-endotoxin reagent (45,46).

Colomycin inhalation has now been used for daily maintenance therapy in a group of approximately 120 Danish CF patients with chronic *P. aeruginosa* lung infection since 1987. During this period Colomycin resistant strains have only been observed in 14 patients (MIC 100–400 $\mu g\,ml^{-1}$) whereas strains infecting other CF patients remained sensitive (geometric mean of MIC 2.4 $\mu g\,ml^{-1}$). The following successful policy was employed several times to get rid of such strains: the use of nebulized Colomycin was stopped in each of these patients specifically, and generally in the ward for chronically *P. aeruginosa* infected CF patients for a period of 6 months. This small problem of resistance to Colomycin is remarkable in a CF centre where aggressive antibiotic treatment has been used for 30 years and where selective pressure of colistin is so intensive that resistance to aminoglycosides, β-lactam antibiotics and fluoroquinolones is common (40,41,47,4). Resistance to Colomycin, therefore, seems to develop more slowly than resistance to tobramycin (48).

When 3-week courses of Colomycin inhalation in combination with oral ciprofloxacin were introduced in 1991 to eradicate initial *P. aeruginosa* colonization (19), resistance was not a matter of concern, since the number of *P. aeruginosa* in the lungs was presumed to be low during early colonization, which is generally only accompanied by few discrete symptoms, if any (49). This assumption has been supported by monthly bacteriological data from all CF patients in the Danish CF Centre to date (31,20), since the 20% treatment failures have not been associated with resistance to the two drugs used but to switch to chronic infection characterised by the mucoid phenotype.

In conclusion, Colomycin has fulfilled the expectations as to high efficacy and low resistance after more than 10 years of use in the Danish CF Centre.

Impact of Colomycin on management of adult CF patients: J. S. Elborn

The improved survival of patients with CF over the past three decades has resulted in an increasing number of patients being cared for in Adult CF Clinics (2). One component of treatment contributing to this improved survival has been aggressive antibiotic treatment of pulmonary infection, particularly in patients with chronic *P. aeruginosa* infection (9).

The three major strategies to reduce lung injury are: eradication of early *P. aeruginosa* infection with inhaled and oral antibiotics at the time of first isolation; prompt and aggressive i.v. antibiotic treatment of acute exacerbations of pulmonary infections; and long-term inhaled suppressive therapy for patients who are chronically infected with *P. aeruginosa*. Colomycin has an important role in each of these.

It is clear that early infection with *P. aeruginosa* can be eradicated by nebulized Colomycin and oral ciprofloxacin (19,20). This treatment is increasingly used in patients attending the Adult CF Clinic as more adolescents are free of *P. aeruginosa* when transferred to adult care. Intravenous anti-pseudomonal antibiotics may also be valuable in this situation but the combination of a nebulized and oral drug has the advantage of allowing the adult patient to remain at home and continue with normal activities (50). Treating early infection and postponing chronic infection with *P. aeruginosa* is important in reducing morbidity and is likely to increase survival (5,6).

The treatment of pulmonary exacerbations in patients chronically infected with *P. aeruginosa* is a second major challenge in the management of adults with CF (51). Some centres treat such patients with regular 3-monthly courses of i.v. antibiotics though this approach is not conclusively proven to be superior to treating exacerbations promptly when required (51,52). Treatment of exacerbations usually involves a β-lactam based antibiotic and an aminoglycoside. There is evidence of increasing resistance of *P. aeruginosa* against many of the β-lactam and aminoglycoside antibiotics (53). This is most likely to be due to antibiotic pressure. Colomycin, a polymyxin antibiotic, is a different class from commonly used i.v. antibiotics and has been shown to be of value in combination with other anti-pseudomonal antibiotics in treating acute exacerbations (25). Polymyxin antibiotics can be nephrotoxic, but studies to date have shown that Colomycin has only a minimal effect on renal function (25). Although most clinicians would not use Colomycin as a first line i.v. antibiotic, it is a valuable addition to the range of i.v. antibiotics currently available.

The major use of Colomycin in adults in the U.K. and Europe is as an aerosol for chronic suppressive therapy for patients chronically infected with *P. aeruginosa* (21,54). Once chronically infected, all patients should be encouraged to use regular inhaled Colomycin (21,55), although it can be difficult to persuade patients with relatively normal lung function who feel well and have few pulmonary exacerbations to take regular nebulized treatment. Compliance with Colomycin treatment is challenging to many patients as it requires significant time for preparation and nebulization twice daily. Some patients experience tightness of the chest with the inhalations and some may have a significant drop in FEV_1 (56). This can usually be overcome by the use of a bronchodilator prior to treatment.

Many adult physicians follow the approach promoted by the Copenhagen Clinic of 3 months treatment with Colomycin and ciprofloxacin for early *P. aeruginosa* infection (20). Although there is limited evidence in terms of medium and long-term outcome for this approach to treatment, some studies do indicate improvement or stabilization of lung function (21,54). Nebulized tobramycin has also been shown to be of value as a chronic suppressive treatment in patients with CF (57), although *P. aeruginosa* resistance to tobramycin increases in some patients (48). *In vitro* resistance of *P. aeruginosa* to Colomycin is extremely rare, which is advantageous for a drug used for chronic suppressive treatment of *P. aeruginosa*, which frequently becomes resistant to other β-lactam and aminoglycoside antibiotics.

Colomycin remains a valuable antibiotic in the treatment of adult patients with cystic fibrosis. It has value as treatment for early *P. aeruginosa* infections, for acute exacerbations and chronic suppressive therapy. In general, the drug is well tolerated and is likely to remain a useful treatment for the foreseeable future.

The use of intravenous Colomycin: S. P. Conway

Patients with CF are living longer with a mean age at death in the U.K. now over 30 years of age (2). Today's children with CF are confidently expected to enjoy a near normal lifespan (4). There are many reasons for this revolution in CF care but our success is founded on optimal application of three treatment modalities: i.v. antibiotics, chest physiotherapy, and nutritional support. There are three main reasons why we are using more of the former. Although not accepted by all doctors, and although based on comparison with a retrospective control group, the Copenhagen data—showing improved survival in patients with chronic *P. aeruginosa* infection who receive elective 3-monthly courses of intravenous anti-pseudomonal antibiotic therapy—has stimulated many centres to copy the Danish lead (9). Although a large number of patients remain in good health, many others need frequent i.v. antibiotic treatments just to maintain stability. A small proportion of patients on the transplant waiting list are on a continuous programme of rotating antibiotics. The inevitable consequence of increased antibiotic use is increased bacterial resistance and an increase in patient hypersensitivity reactions (53). No new anti-pseudomonal antibiotics have been marketed since meropenem in 1995. *P. aeruginosa* resistance to Colomycin is very unusual (47,58,59) and hypersensitivity reactions are rare. It was time to revisit this potentially useful drug.

Colomycin suffers from its reputation as a neurotoxic and nephrotoxic drug. How much of this is real and how much mythical? What do the toxicity data show? Fears of increased serum creatinine and blood urea levels, acute renal failure, acute tubular necrosis, paraesthesiae, muscle weakness, dizziness, confusion, and respiratory insufficiency secondary to neuromuscular blockade stem from reports dating back 30 years or more (60–65). Such reports of Colomycin induced adverse reactions were also variable (63,65–67), did not refer to patients with CF, and reversed when Colomycin treatment was stopped, even when large doses had been used (60–62). Some patients had complex underlying illness and the attribution of adverse clinical events to Colomycin was probably not scientifically exact (60).

Recent studies in patients with CF have confirmed the safety of intravenous Colomycin. Southern *et al.* reported on 62 courses in 22 patients without any neuro- or nephrotoxic adverse effects (58). Bosso *et al.* documented only one case of reversible renal toxicity and six minor neurological events that did not necessitate withdrawal of Colomycin in 21 treatment courses (68). In a large prospective study of 71 treatment courses in our centre we saw a significant rise in mean serum urea levels, but this value remained within the normal laboratory range [$< 7{\cdot}1\,\mathrm{mmol\,l^{-1}}$]. Four patients had abnormally high levels at the end of treatment but showed values only marginally above the normal upper limit, ranging from 7.3 to $7.6\,\mathrm{mmol\,l^{-1}}$. There was no change in mean serum creatinine levels. We found no evidence of accumulated Colomycin toxicity. The four patients were observed over a further 6 to 17 i.v. courses and no significant rise in serum urea or creatinine was seen. Mean admission and discharge levels for all 53 study patients over an average of seven further treatments was 4.0 and $4.7\,\mathrm{mmol\,l^{-1}}$ for urea and 71 and $69\,\mu\mathrm{mol\,l^{-1}}$ for creatinine. Although in response to direct questioning most patients reported some experience of dizziness, numbness, tingling, unsteadiness or muscle weakness, except in one case all these symptoms were minor and well tolerated. Moreover we found no clinically significant non-neurological events (25). A subsequent retrospective study of intravenous Colomycin use in adult patients with CF in Liverpool has confirmed its good safety profile (26).

Colomycin is effective in the treatment of CF respiratory exacerbations. All the patients in our study showed resolution of their acute infective exacerbation and increases in respiratory function test results (25). Those patients who received Colomycin and a second anti-pseudomonal antibiotic showed the greater improvement when compared to patients prescribed Colomycin alone, the FEV_1 rising by 18.5% *vs.* 9%. Other antibiotics used were aztreonam, azlocillin, piperacillin, ceftazidime, imipenem and ciprofloxacin. It was not possible to correlate the greater improvement seen with combined therapy with any particular additional antibiotic because of small patient numbers. Comparison with statistics from our own general clinical databank showed Colomycin alone resulted in gains in respiratory function similar to conventional combined antibiotic therapy, and that Colomycin in combination with another antibiotic resulted in even greater improvement suggesting a synergistic effect. The Liverpool retrospective study, using Colomycin in combination with other intravenous antibiotic wherever possible, also showed improvement in all cases with significant increases in percentage predicted FEV_1 (26).

Colomycin is a valuable and safe antibiotic in CF care. We would recommend it as a second-line drug for patients with multi-resistant *P. aeruginosa*. Because of its increasing use, occasional Colomycin resistance has been seen. We should therefore use it with care for the development of widespread resistance would significantly limit our therapeutic options.

The impact of Colomycin on the management of cystic fibrosis—the paediatrician's viewpoint: R. Dinwiddie

The primary pathogenic process in the lungs affected by CF is one of early colonization and infection with various pathogenic organisms. This initiates an intense inflammatory response which persists throughout life. Early infection with organisms such as *S. aureus* and *Haemophilus influenzae* are major triggers of the inflammation, which is a central feature of the long-term lung damage (69).

Once the lungs are infected, other organisms such as *P. aeruginosa* are able to gain a foothold and contribute to the pathogenic process.

Over a period of time this organism becomes a major pathogen leading to lung damage. Any measure which can inhibit or eradicate this process is central to prevention of the progressive pulmonary damage which represents a major challenge to the paediatrician advising on the child's treatment.

The lungs of the CF infant are normal at birth but, in the absence of treatment soon become infected (69). With oral antibiotics, either given continuously or when cultures are positive, chronic infection with *S. aureus* and *H. influenzae* can be avoided, but *P. aeruginosa* sooner or later grows from the respiratory cultures. Prior to the use of nebulized Colomycin and the availability of oral ciprofloxacin in the mid 1980s, early colonization with *P. aeruginosa* was treated with i.v. anti-pseudomonal antibiotics only if the infection was symptomatic—unfortunately, with this policy, chronic infection usually followed.

The early treatment of *P. aeruginosa* with nebulized Colomycin and oral ciprofloxacin (19,20) has become an important and successful component of paediatric management which significantly reduces morbidity, reducing or avoiding chronic infection in over 80% of patients. If the organism persists after this it may be necessary to continue this regime for 3 months. This can significantly delay the recurrence of *P. aeruginosa* for up to 18 months (20).

When *P. aeruginosa* infection is persistent, then a 2-week course of i.v. antibiotics is indicated (50). Long-term administration of nebulized Colomycin is then recommended with further courses of I.V. antibiotics either at 3-monthly intervals or when respiratory symptoms and signs indicate clinical deterioration. It is important to culture respiratory secretions at 4–8 week intervals to identify organisms and monitor their sensitivity.

Nebulized Colomycin has been used in our paediatric CF clinic for a considerable number of years and the overall emergence of resistance has been low. In fact, resistance of *P. aeruginosa* to Colomycin is so rare that such a report should always raise the possibility of the supposed *P. aeruginosa* being *B. cepacia* or some other organism.

The use of increasingly frequent courses of i.v. antibiotics over a period of several years does eventually lead to the emergence of resistant organisms. Since Colomycin appears to maintain its efficacy over a long period, in recent times it has been used increasingly as an intravenous agent. More recent favourable clinical experience in children (58) and studies in adults with CF (25,26) have allayed previous concerns about systemic toxicity.

Thus, in paediatric practice, Colomycin has proved to be an effective agent for the treatment of early *P. aeruginosa* colonization/infection in combination with oral ciprofloxacin, significantly delaying or preventing the onset of chronic infection. Longer term it is a useful suppressive agent in children who are already chronically infected with *P. aeruginosa*. It has also proved a useful and safe addition to the range of agents available for intravenous use when resistance to the more commonly used anti-pseudomonal antibiotics becomes a problem.

The impact of Colomycin on the management of cystic fibrosis—the nurse manager's viewpoint: F. Duncan-skingle

Colomycin for nebulization came into use in the 1980s: patients who had been taking two nebulized antibiotics, in an effort to avoid antibiotic resistance, were now able to have monotherapy. It was a drug rarely used intravenously, and there was also a reduced risk of resistant organisms. A positive advantage for patients was the taste, which was infinitely more palatable than some of the previous antibiotics used. Some of the drugs tasted unpleasant, but patients persevered, convinced of the advantage to their health. It can be difficult, or impossible, to discontinue nebulized antibiotics with some patients: they are convinced that it is the nebulized antibiotic that is keeping them well and out of hospital. Many patients will increase the prescribed dose from twice a day to three times, especially if they are unwell, in a bid to keep out of hospital, and many times they will succeed. People with CF are always hopeful that they will reduce their admissions into hospital, and also try to avoid i.v. antibiotics at home.

If the person with CF is busy at work, or going on holiday, they may neglect their treatment, including nebulized antibiotics, arguing lack of time. If they then become ill, they are convinced of the positive indication for the use of nebulized antibiotics. As one patient states 'missing my nebulized Colomycin has an immediate effect. However I can overcome this, by only missing one or two doses. Otherwise it increases the amount of time and effort needed to get back to my starting point'.

From a nursing perspective nebulized antibiotics are easy to administer. The patient (or parent if a child) usually finds the reconstitution of the antibiotic, and the use of the nebulizer and compressor for administration, easy to learn.

Most patients tolerate nebulized antibiotics well. The biggest chore for patients is the washing and drying of the equipment every time it is used. This is essential to ensure that no harmful pathogens are harboured in the wet nebulizer.

Patients have a 'test dose' of the prescribed nebulized antibiotic, and respiratory function tests performed before and after the first nebulized dose. This is to ensure that there is no bronchial constriction, which can cause discomfort and distress to the patient. If there is any tightening in the chest it may be relieved by the use of bronchodilators with the antibiotic.

In addition to its use in delaying chronic colonization with *P. aeruginosa*, another important use for nebulized Colomycin is in the pre- and postoperative management of patients undergoing lung transplantation (70). It is usually prescribed for a period of 6 months via a face-mask, to clear the upper airways of Pseudomonas. There is some thought that it should be given for longer, even for life. Patients with multi-resistant *P. aeruginosa* awaiting transplant commonly convert to sensitive strains when treated with nebulized Colomycin (70).

There is no doubt that nebulized Colomycin has played a vital part in reducing the decline of respiratory function and therefore the number of hospital admissions for people with CF (21). Hospitalization is costly and can be depressing for young people; it also interferes with their lifestyle, and increases the risk of cross infection. In summary, nebulized Colomycin is effective treatment for early infection with *P. aeruginosa* (20), can maintain respiratory function in chronically infected patients, and reduce the incidence of infection after transplantation. It is easy to reconstitute and well tolerated by most patients.

The next ten years—future challenges: J. M. Littlewood

Over the past 20 years, advances in the understanding of the pathogenesis and treatment of have resulted in impressive improvements in the health, quality and length of life of people who have cystic fibrosis. There is no reason why improvements should not continue over the next 10 years. In the worst scenario, even if new pharmacological or gene replacement strategies to improve CFTR function do not become generally available, treatment to prevent and/or eradicate early respiratory infection with *S. aureus, P. aeruginosa* and whatever other organisms emerge as important pathogens, should permit most people with CF to remain free of chronic respiratory infection and the associated progressive decline in respiratory function for many years.

The realization that early respiratory infection, particularly with *P. aeruginosa*, can be treated and eradicated and that chronic chest infection is not inevitable, is a relatively recent but now well-established concept in many CF centres—but surprisingly not all.

If all infants with CF are to be diagnosed before the chronic infection is established and nutrition compromised, very early diagnosis by neonatal screening is essential. Unfortunately, where neonatal screening is not routine, some infants still suffer irreversible pulmonary damage before the diagnosis is eventually made. The early recognition of the infant who has CF and the careful monitoring, effective treatment and eradication of respiratory pathogens will remain a central component of CF management. Nebulized antibiotics active against *P. aeruginosa*, delivered directly to the patient's airways, are now established as a major component of such treatment. Colomycin, delivered directly to the airways, has proved particularly valuable in both the early eradication and later stabilization of *P. aeruginosa* infection. The rarity of bacterial resistance and the fact the drug is not a first line choice for i.v. treatment (although useful in patients with resistant organisms) is an added advantage.

To achieve the best results, all patients must continue to have the advantage of adequate regular contact with the professional team at a major specialist CF centre. At specialist CF centres the staff continually strive to improve existing treatments and evaluate their results; no present day treatment is regarded as 'established' and beyond improvement. They recognize and deal with the constant changes required in management as new pathogens emerge: at times, it must be said, as a result of very successful present treatments, for example the increasing prevalence of *Stenotrophomonas maltophilia* and *Aspergillus fumigatus* as *P. aeruginosa* is successfully eradicated. If new hoped-for novel treatments to correct or improve CFTR function are introduced within the next decade, as is likely, the conventional antibiotic treatments should be considerably more effective but will still be required to some extent.

Over the past decade, Colomycin has re-emerged as the first choice antibiotic for nebulized treatment of both early and chronic *P. aeruginosa* in people with CF. It is also a valuable addition to the i.v. antibiotics used when the organism becomes resistant to the more frequently used drugs. Its particular characteristics, as described in this review, suggests that it will continue to have an important role in the treatment of people with CF during the next decade.

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