

Review

# Drug induced complications; can we do more?

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## Abstract

Drug induced complications are becoming increasingly common in CF. In this review we discuss some of the key issues relating to drug side effects in an ageing population of patients with CF. Strategies to reduce drug complications are also discussed.

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## 1. Introduction

Cystic fibrosis (CF) is a multisystem disease characterized by chronic endobronchial infection and progressive obstructive lung disease. While there is still no cure, recent advances have

significantly increased average life expectancy with patients born at the start of the 21st century having an estimated median survival of 50 years. These dramatic changes in survival have occurred over decades and result from a proactive multidisciplinary approach to treatment combined with early antibiotic therapy. Treatment is now aimed at protecting specific organ damage, reducing early bacterial colonisation, preventing pulmonary exacerbations and inhibiting airway inflammation so that lung function can be maintained.

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In order to remain well, patients need to take a cocktail of medication which is onerous and leads to poor adherence. The problem is compounded by the fact that individuals can remain relatively asymptomatic despite significant decline in organ function. Symptoms are often a poor marker of disease severity, and other factors such as lung function, *Pseudomonas aeruginosa* status, liver function, exercise tolerance, CF related diabetes (CFRD) and chest radiology need to be monitored. It is vital that patients appreciate the real benefits of treatments which they perceive as having no immediate impact on their health. Prevention of disease progression remains key to further improvements in outcome.

With increased patient survival and the advent of a generation of older patients with CF, health care professionals are faced with new complications such as diabetic vasculopathies, cardiovascular disease and renal failure. This will be particularly relevant to those living into old age and those who undergo transplantation.

Clinicians often feel powerless to halt the progressive nature of chronic disease and this can result in overprescribing of medication which is often not evidence based and can result in significant and severe adverse events. Optimising treatment requires the potential benefits of a specific treatment to be balanced against long term adverse effects and quality of life rather than increasing medication in the hope that improvements will occur.

In this short review we discuss some of the key issues relating to drug side effects in an ageing population of patients with CF and challenge the logic behind some of the standard drug regimens in use today.

## 2. Mechanisms, clinical manifestation and impact

### 2.1. Pancreatic enzymes

The introduction of acid-resistant pH sensitive microsphere pancreatic enzymes resulted in a significant improvement in

overall health and nutritional status. Unfortunately between October 1993 and November 1994, 13 children with CF on high strength pancreatic enzymes developed large bowel strictures relating to a combination of newer preparations of enzymes and high dosing schedules. The first cases of fibrosing colonopathy (Fig. 1) were reported by Smyth et al. who described four cases of ascending colon stricture with histopathological changes of post-ischaemic ulceration repair and mucosal and submucosal fibrosis, pathological features which had not been previously known to occur in CF [1]. The only common change in the management of these children was a switch from conventional enteric-coated pancreatic enzymes to high-strength products 12–15 months before presentation. This was a serious and avoidable complication highlighting the importance of drug surveillance. Initially it was believed that fibrosing colonopathy was due to high doses of pancreatic enzymes. However, Creon 25,000 was never implicated and it is now believed that it results from the use of methacrylic acid copolymer in the enteric coating. This coating was also present in some low strength enzymes and in other drugs, such as mesalazine, where similar complications have been reported [2]. It is now recommended that patients should usually have a maximum enzyme dose of 10,000 IU lipase per kg day and certain preparations such as Pancrease HL, Nutrizyme 22 and Panzytrat 25,000 should be avoided in children aged 15 years or less [3].

### 2.2. Early treatment of abnormal glucose metabolism

The prevalence of cystic fibrosis related diabetes (CFRD) increases with age and is now one of the most common non-respiratory complications. There remains much controversy about both the diagnosis of CFRD and the early detection of abnormal glucose metabolism. Early diagnosis and intervention are key as CFRD has a negative impact on lung function, weight and survival. Complications such as retinopathy, nephropathy, microalbuminuria and neuropathy are commonly seen [4].

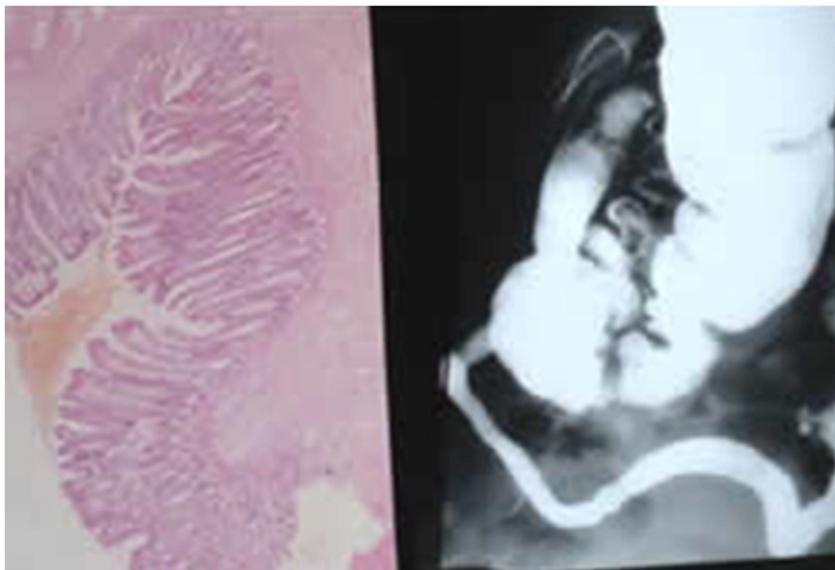


Fig. 1. Barium enema and histology of the colon showing fibrosing colonopathy (The History of Cystic Fibrosis).

There is evidence to suggest that the pre-diabetic state may contribute directly to clinical decline and that continuous glucose monitoring shows pathological glucose excursion in both patients with impaired and normal glucose tolerance. In response to these findings there is a growing trend to treat patients with insulin in the early pre-diabetic stages of disease [5,6]. Clinical trials are needed to clarify the risk benefit of such a move as early intervention can result in early stigmatisation, increased burden of treatment and has the potential for inducing hypoglycaemia and affecting cognition, an area which our group is presently investigating [7]. Conversely there is a need to improve diabetic control and reduce the risk of complications such as chronic renal failure.

There is a lack of evidence to support the routine use of oral hypoglycaemic agents in the treatment of CFRD and insulin is the only recommended treatment. [8–10]. Despite growing evidence pointing to an association between early hyperglycaemia and a negative clinical outcome, it is our view that there is insufficient data to support the routine use of early insulin therapy in the pre diabetic stage of CF. We do however use insulin in selected cases where weight loss remains a problem and subcutaneous continuous glucose monitoring shows mild elevation in glucose. An alternative might be to assess the “CF diet”, based on a high calorie intake which may include large quantities of refined sugars. Perhaps the time has come to revise dietary guidelines in recognition that most patients with CF will eventually develop insulin deficiency with or without CFRD.

### 2.3. Corticosteroids

Corticosteroids can induce hyperglycaemia and insulin resistance in patients with and without CFRD. Even low dose regimens in healthy individuals can impair glucose tolerance and interfere with the metabolic actions of insulin on liver and adipose tissue [11]. Despite the adverse effects associated with steroids, they remain an important part of the arsenal used in the treatment of conditions such as atopy, airway inflammation, gout, arthritis, drug allergy, prophylaxis for bisphosphonate infusions and allergic bronchopulmonary aspergillosis (ABPA). Oral steroids are usually prescribed for short periods of time to avoid side effects, although some patients require frequent and prolonged courses. As well as impacting on the control of CFRD, steroids are responsible for a significant number of adverse effects including recurrent oral and genital candidiasis, fragile skin, behavioural changes, peptic ulceration, growth retardation, cataracts and osteoporosis (Fig. 2) [12,13]. New regimens for the treatment of ABPA may help reduce steroid induced complications although further clinical trials are needed to ensure both their safety and their efficacy. One option could be to use monthly pulses of high-dose intravenous methylprednisolone which has been reported to induce fewer side effects [14]. Alternatively monoclonal anti-IgE antibody therapy (omalizumab) could be considered for the management of ABPA in individuals who have become steroid dependent and/or require frequent prolonged courses of treatment [15,16]. Most available data is based on case reports and randomised controlled trials are needed to assess the effectiveness of such therapies before they become routine. The urgent quest to identify alternatives to steroids



Fig. 2. MRI scan showing vertebral fractures (L3, L4, L5) in a patient with osteoporosis.

needs to be considered in the context of ensuring that any benefit is not negated by unforeseen complications.

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and are effective in the prevention of CF and steroid induced osteoporosis [17,18]. Complications which are commonly associated with intravenous preparations include severe bone pain, flu-like symptoms, muscle aches and gastrointestinal symptoms. Pre-dosing with oral steroids can significantly reduce the prevalence and severity of non-gastrointestinal symptoms. It is key to ensure good dental hygiene as there is a potential risk of bisphosphonate associated osteonecrosis of the jaw.

Over 40% of patients with CF are prescribed inhaled corticosteroids (ICS) based on either the presence of reversible airway bronchoconstriction or on the rationale that treatment may reduce airway inflammation and decline in lung function [19]. In practice many patients are prescribed treatment for symptoms of wheeze which is also common in acute bacterial infection and often resolves with intravenous antibiotics. Because of the difficulty of measuring the clinical benefits of ICS objectively “treatment may be continued unnecessarily”. There are several studies demonstrating that ICS in children with CF is associated with a slower decline in lung function [19]. In contrast ICS therapy has been reported to be associated with significant complications including reduced growth, adrenal suppression and a potential increase in the risk of pulmonary exacerbations [12,19–21]. Reassuringly, withdrawal of ICS in non-atopic individuals does not appear to be associated with an earlier onset of acute pulmonary exacerbations [22]. While these results cannot predict the long term efficacy of treatment, they provide supporting evidence that a trial of ICS withdrawal may be appropriate and safe. Patients on concomitant itraconazole are particularly at risk of developing Cushing’s syndrome and adrenal insufficiency due to the drugs inhibition of cytochrome P450 enzymes [23,24].

## 2.4. Nutrition therapy

Seminal work by Crozier radically changed the nutritional status of patients by demonstrating the importance of a normal or high fat intake in combination with pancreatic enzymes [25]. This was contrasted with the prevailing clinical view that advocated fat-restriction. Today over 10% of patients with CF are classified as overweight or obese [26]. Although these patients often have mutations associated with milder CF phenotype and may be pancreatic sufficient they do display higher levels of LDL cholesterol and fasting insulin levels compared with normal or underweight patients with CF [27]. We have recently demonstrated similarly abnormal lipid profiles in patients with and without CFRD and post solid organ transplant (Fig. 3). In addition to diet, drugs such as corticosteroids, oral contraception and anti-rejection medication can adversely affect lipid profiles.

Poor nutrition in patients with CF is associated with poor clinical outcome and early intervention remains essential for normal growth and development to be achieved. However, the impact of nasogastric and enterostomy feeding on adipose tissue deposition needs further investigation. Being heavier does not equate to being fitter and feeding regimens may inadvertently affect the pathophysiology of both CFRD and cardiovascular disease by altering the deposition of adipose tissue. Deposition in the viscera is associated with a higher cardiovascular (CVD) risk in contrast to subcutaneous deposition which may act as a buffer for excess dietary energy [28].

Studies have already shown increased arterial stiffness in patients with CF, an indicator of premature ageing and perhaps a predictor of things to come [29]. Inflammation is another key factor which may predispose patients with CF to developing atherosclerosis later in life [30,31]. Markers of inflammation, such as high sensitivity CRP, strongly predict the development of cardiovascular disease [32]. This hypothesis is supported by increased cardiovascular complications in patient cohorts with chronic inflammation such as rheumatoid

arthritis [31]. Although there are few cases of ischaemic heart disease in the literature, CF itself, as well as CFRD, could be an independent risk factor for the future development of CVD especially in the light of increased longevity and in patients undergoing transplantation (Fig. 4).

### 2.4.1. Intravenous antibiotics

Intravenous antibiotics are used to treat acute pulmonary exacerbations, as part of eradication therapy or to help control chronic infection. At present prompt and appropriate management of pulmonary exacerbations is the cornerstone of effective CF management. There are no high quality randomised controlled studies supporting the use of routine intravenous antibiotics in patient with CF. Pedersen et al. showed an increase from a five year survival of 54% to a 10 year survival of 90% from the onset of chronic *P. aeruginosa* infection with three monthly elective intravenous antibiotics irrespective of their clinical condition [33]. Since this early study treatment has progressed with improved nutrition, the introduction of dornase alpha and nebulised antibiotics. Unfortunately the only randomised controlled trial seeking to address this issue was underpowered and no differences were observed between those receiving elective versus symptomatic treatment [34].

### 2.4.2. Choice of antibiotic for exacerbation

Most centres continue to use combination intravenous antibiotics for exacerbations which include the addition of either an aminoglycoside or colistin with a beta lactam antibiotic. Both aminoglycosides and colistin are nephrotoxic. Risk of such complications is dependent on dose, duration and frequency of administration [35,36]. The potential benefits of combination therapy include synergy and reduction of bacterial resistance. However, the evidence for such strategies is inconclusive and the practice has substantial potential for causing long term harm especially as patients are living longer and the risk of

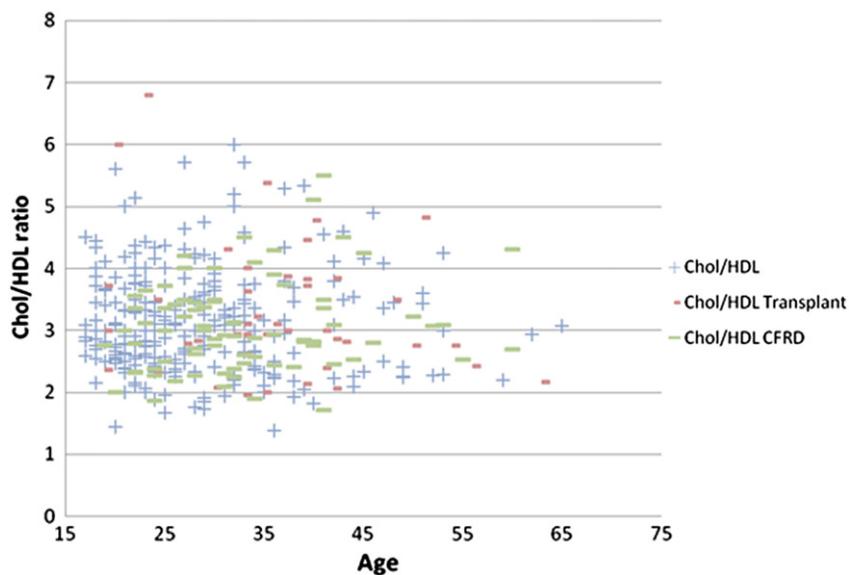


Fig. 3. Age and cholesterol/HDL ratio in 410 patients attending the Leeds Regional CF unit.

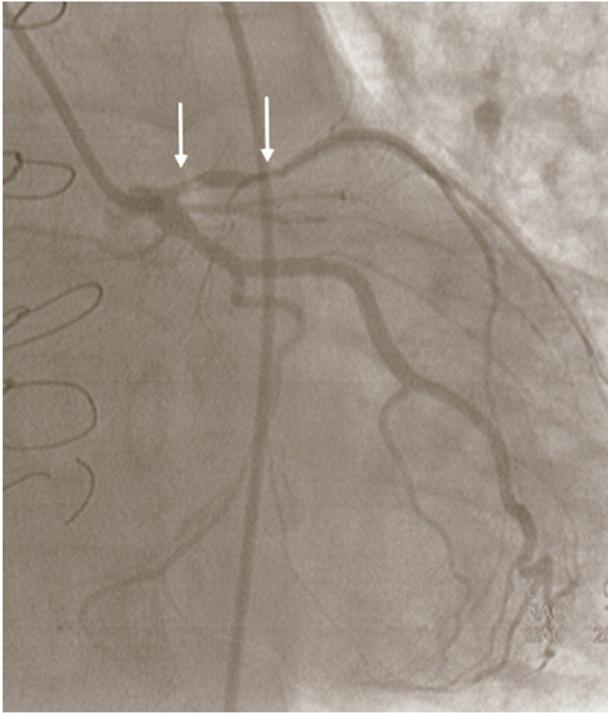


Fig. 4. Cardiac allograft vasculopathy in a 17 year old patient post-heart lung transplant.

serious adverse events from a lifetime of frequent antibiotic treatment is significantly increased [37,38].

Whilst combination intravenous therapy is standard practice there is little evidence to support its role over monotherapy. This reflects the lack of high quality randomised controlled trials [37]. Indeed monotherapy has some attractive features such as reduced toxicity and cost. An alternative regimen is to combine an inhaled and intravenous antibiotic for the treatment of exacerbations to reduce potential side effects and directly target *P. aeruginosa* in the endobronchial space. This has the added advantage of achieving a higher concentration of the drug within the airways. Further randomised controlled trials are needed to assess the relative benefit of such treatment especially in younger patients with more limited respiratory disease.

#### 2.4.3. Duration and dose of treatment

Reduced aminoglycoside toxicity can be achieved by using tobramycin rather than gentamicin on a once daily regimen [39]. Other potential solutions include reducing the length of treatment and adjusting and monitoring drug doses more effectively [40]. Standard treatment is for 14 days although there are no randomised controlled trials comparing treatment duration. Shorter courses are advantageous in terms of reduced toxicity, hypersensitivity and cost. Collaco et al. demonstrated that most lung function recovery was reached within a week of treatment and that a plateau was reached at 8–10 days [41]. It is not known whether reducing treatment duration would lead to a shorter time to next exacerbation or a more accelerated decline in lung function. It is clear, however, that pulmonary exacerbations result in progressive irrecoverable loss in lung function with a quarter of patients failing to recover their lung function within three months of an exacerbation [42].

In addition to duration of treatment, patients often receive higher doses than the general population relating to increased volume of distribution and more rapid drug elimination. Treatment doses are also aimed at ensuring that adequate levels penetrate the infected lung. This can be a problem as some drugs, such as the aminoglycosides, have very poor penetration into bronchial secretions [43] whilst endobronchial beta-lactam levels are less than 15% of plasma levels [44].

#### 2.4.4. Nebulised antibiotics

The use of nebulised antibiotics is critical in ensuring clinical stability in patients with CF. Appropriate use of nebulised antibiotics significantly reduces the risk of pulmonary exacerbation and cause fewer side effects than intravenous therapy [45].

Historically, a continuous regimen has been used with colistin and intermittent use with tobramycin and aztreonam. Benefits of intermittent therapy include reduced treatment burden and toxicity although some patients report that they feel worse during their month off treatment. Whilst tobramycin is generally well tolerated it can be associated with tinnitus and nephrotoxicity [46,47]. Other potential benefits of intermittent therapy include reduced bacterial resistance and better patient adherence. Unfortunately studies to date are inconclusive; no significant differences were seen in the only head-to-head comparison of intermittent tobramycin (300 mg twice daily) versus tobramycin 80 mg twice daily given continuously [48]. However, the results are difficult to compare given the different doses.

Several novel antipseudomonal antibiotic preparations are in development including nebulised amikacin, levofloxacin, ciprofloxacin, and fosfomycin/tobramycin as well as dry powder preparations of tobramycin and colistin. It is intriguing to note that the introduction of new nebulised antibiotics in patients who have been on alternative agents is often associated with additional benefit. Examples include the introduction of nebulised tobramycin and aztreonam in patients previously exposed to colistin and tobramycin respectively [49,50]. We hypothesise that one potential approach could be to rotate the various groups of nebulised antibiotics as part of a drug holiday thereby reducing potential bacterial resistance and increasing effectiveness of therapy. Clinical trials would be needed to be undertaken to address this hypothesis before such a regimen could be considered. Dry powder inhalers are convenient and effective and favoured over nebulised drugs by many patients for their ease and speed of administration [51].

#### 2.4.5. Aminoglycosides and ototoxicity

Aminoglycosides are commonly used in combination with other agents in the treatment of pulmonary exacerbations. Unfortunately aminoglycosides are associated with the development of auditory and vestibular toxicity and in Leeds we are seeing a growing number of patients with significant hearing loss necessitating hearing aids (Fig. 5). Studies suggest that risk is not simply related to exposure but is also linked to mitochondrial mutations such as m.1555A > G [52,53]. However, most patients develop toxicity following exposure to frequent and or high doses of aminoglycosides. This is likely to get worse as life expectancy increases. One agent used in the treatment

of *Mycobacterium abscessus* is intravenous and nebulised amikacin. This drug appears to have a predilection to causing auditory and vestibular toxicity although this may be due to the intensity and frequency of treatment [54,55]. Routine monitoring of renal clearance, through levels and regular (high tone) hearing tests should be undertaken. In patient who develop complications, alternative antibiotics should be prescribed.

#### 2.4.6. Drug hypersensitivity

Hypersensitivity reactions to antibiotics are up to three times more common in patients with CF compared with the general population [56–58]. Whilst hypersensitivity reactions to other classes of drugs occur the majority of reactions encountered are attributed to beta-lactams (Fig. 6). Drug reactions to antibiotics make it increasingly difficult to treat infective exacerbations of CF effectively. It has a major impact within the hospital both due to prolonged hospital stays and the use of expensive alternative antibiotics. A number of patients have been turned down for lung transplantation as a direct result of multiple drug allergies.

Our experience in Leeds is comparable with the published data [59,60]. A retrospective review in 2011 identified 302 beta-lactam reactions in 375 patients (Unpublished data). Only 6% were immediate reactions due to either anaphylaxis or urticaria; several

of these were skin prick positive suggesting an IgE mediated process. The vast majority presented as non-immediate rashes, fixed drug eruptions, arthralgia, and drug fever. Ceftazidime was the commonest culprit antibiotic followed by piperacillin. Many patients had more than one beta-lactam hypersensitivity reaction with 20% having had a single beta-lactam reaction and 30% having multiple beta-lactam reactions. Not unexpectedly we found that sicker patients who require more treatment have an increased risk of developing hypersensitivity reactions. Significant risk factors in review included female gender, intravenous antibiotic use, *P. aeruginosa* status, CF related arthritis, higher IgG3 levels, and lower IgG4 levels. There was a non-significant trend towards lower FEV<sub>1</sub> and lower bone density.

Antibiotics are delivered intravenously at high doses, for prolonged periods, and on a repeated basis. It is likely that these alone are sufficient to drive sensitization and hence sensitivity. The intravenous route appears particularly immunogenic and very little hypersensitivity is seen with oral or inhaled therapy. We have recently published a case series the results of which suggest that even with proven hypersensitivity to intravenous aztreonam, patients were able to tolerate inhaled aztreonam without adverse effects [59]. This is similar to our experiences with colistin; many patients tolerate the nebulized form when they have adverse effects with the drug intravenously.

The dose and duration of antibiotic therapy is also important. The binding of piperacillin to albumin is concentration and time-dependent; patients with CF usually receive 14 days of intravenous treatment. *In-vitro* 13 out of 59 lysine residues on albumin were modified. *In-vivo* only four lysine residues were identified as being modified in patient's plasma (Lys<sup>190</sup>, Lys<sup>195</sup>, Lys<sup>432</sup>, and Lys<sup>541</sup>) [61]. These haptens were shown to stimulate T-cells from hypersensitive patients and are the likely trigger of the immune system. Certainly, the longer the patient receives treatment the more likely it is that sensitisation will develop. Flucloxacillin modifies the same lysine residues on albumin as piperacillin; a reduction in piperacillin binding and the piperacillin–albumin conjugate-specific T-cell response was seen when flucloxacillin competed for binding sites. Potentially this means that co-administering a competitor for binding sites could prevent sensitisation in the first instance or even reduce the risk of hypersensitivity in a patient with known sensitivity. We are now undertaking a prospective study designed to elucidate further the aetiology and risk factors for the development of drug hypersensitivity.

We found skin testing to have a low sensitivity with only 14% of patients hypersensitive to piperacillin having a positive intradermal test [61]. However, our retrospective studies found positive *in-vitro* T-cell responses in patients hypersensitive to sulfamethoxazole [60,62], piperacillin [61,63], meropenem and aztreonam (unpublished data). This demonstrates that for the non-immediate reactions that are commonly seen T-cells are involved in the pathogenesis. The persistence of memory T-cells is potentially life long, certainly they have been found to be present with high numbers several years after the last exposure [63,64]. In our studies positive piperacillin-specific lymphocyte responses have been seen up to 12 years after the original reaction in the absence of antigen. This suggests that piperacillin hypersensitive



Fig. 5. Hearing aid in a patient who developed deafness following repeated intravenous aminoglycoside therapy.

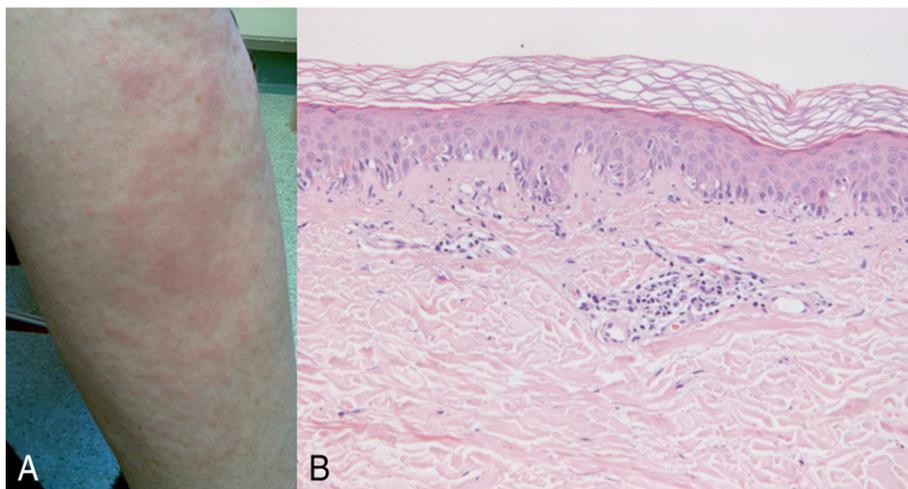


Fig. 6. A) Rash. B) Skin biopsy showing an interface dermatitis reaction associated with vacuolar degeneration of the epidermal basal layer and numerous individually necrotic keratinocytes. There is mild spongiosis and superficial dermal perivascular dermatitis reaction, which is mainly lymphocytic in character but includes a few neutrophils. Immunostains confirm the lymphocytic infiltrate as being almost entirely T-cell in character, with a CD3+, CD45RO + phenotype. Both CD4+ and CD8+ subsets are present.

patients should only be re-exposed to the offending drug with caution. Fortunately the T-cell responses in patients with CF are highly drug-specific; T-cell clones are stimulated with the chemical entity the patient was exposed to at the time of the reaction, but not closely related drugs or other drugs commonly used in patients with CF (Unpublished data). This is in keeping with the limited cross-reactivity seen clinically.

Whilst alternative regimens can be devised for most patients there are some multiple allergic patients for whom all options have been exhausted. In this difficult group desensitization represents the safest method of reintroducing the drug to the patient. Desensitization results in a temporary state of immune tolerance to the offending drug by gradual increasing a suboptimal dose prior to the full therapeutic dose. In Leeds desensitization is performed using a standard 7-step rapid intravenous protocol on a normal medical ward [65]. Whilst desensitization is an established procedure in patients with immediate reactions [66,67] there is limited evidence to support desensitization in non-immediate reactions [68,69]. We reviewed 275 desensitization procedures in 42 patients with a range of non-immediate reactions to six commonly used antibiotics [65]. The same desensitization regimen was used as in that for immediate reactions. Individual patient success ranged from 55% with tazocin through to 88% with tobramycin. In the 25 patients who failed desensitization the reactions were milder than their original reactions and the majority occurred within 48 h of starting treatment. Prophylactic anti-histamines and steroids did not reduce the risk of reaction. At present little is known about the mechanisms of desensitization for non-immediate reactions. Further studies are on-going in which patients with confirmed hypersensitivity are being desensitized to assess immune modulation.

#### 2.4.7. Other complications of intravenous antibiotics

The frequent use of antibiotics can be associated with a host of complications, many of which go unreported. One such example is oral and genital candidiasis which although a common

problem among patients with CF is often dealt with privately and not conveyed to medical professionals. The long term use of high dose antibiotics, steroids, oral contraception, urinary incontinence and CF related diabetes make patients with CF particularly susceptible to such infections. A questionnaire based survey of 101 consecutive inpatients and outpatients reported symptoms of either oral and or genital *Candida* in 70% of cases with a significant number of individuals finding their condition distressing [70].

Antibiotic disruption of the intestinal microbiota may also cause susceptibility to *Clostridium difficile* a spore-forming Gram-positive bacillus. The prevalence of *C. difficile* is an emerging problem especially in those patients undergoing transplantation. While some patient may remain asymptomatic, others can develop life threatening colitis [71]. The composition of commensal gut flora also has important and specific metabolic and protective functions. For example *Oxalobacter formigenes* (OF) is a Gram-negative, anaerobic bacterium whose main carbon and energy sources are derived from oxalate metabolism [72]. Unfortunately OF is sensitive to many commonly used antibiotics and its absence from the gut is associated with a predisposition to the development of calcium oxalate renal stones.

#### 2.4.8. Drug delivery

The route of drug administration can be responsible for a host of complications. Examples include the bacterial and fungal contamination of nebuliser and venous access devices the latter being responsible for 80% of significant blood stream infections [73–75]. Venous access devices are also responsible for an increasing prevalence of venous thrombosis and this can lead to significant pulmonary embolus (Fig. 7) [76].

#### 2.4.9. Antibiotics and microbial resistance

Over the past decade long term, low dose macrolide antibiotics have been shown to be an effective adjunct in the treatment of CF lung disease. Their use has been supported by several high quality

randomised placebo controlled trials which showed that treatment was beneficial and safe [77–79]. There is however growing evidence that clinicians should perhaps take a more selective approach to prescribing these agents. The prevalence of *Staphylococcus aureus* and *Haemophilus influenzae* macrolide resistance has increased and recent data suggests that these resistant genes are transferrable between bacteria [80,81].

The long term use of macrolides may predispose patients to colonisation by non-tuberculous mycobacteria (NTM) especially *M. abscessus*. In the mouse model, azithromycin appears to inhibit intracellular killing of mycobacteria within macrophages and resulted in chronic infection with NTM [82]. The increased prevalence of NTM is of significant worry as colonisation/infection can result in increased treatment burden and premature decline in health status. In Leeds the number of patients culturing NTM has remained relatively stable since 2009 although the prevalence of *M. abscessus* appears to be increasing (Fig. 8). It remains unclear how long we should prescribe a macrolide for. Many units continue life-long treatment or until side effects develop. However this is not supported by clinical trial data which have lasted no more than 1.5 year and where the maximum level of efficacy appears to occur at six months and declines to almost zero at 1.5 year. Long term trials are needed to address these issues and to ensure real long term benefit.

Multiple antibiotic-resistant *P. aeruginosa* is now also frequently encountered in clinical practice and its acquisition is also strongly associated with antibiotic use [83]. Whilst resistant *P. aeruginosa* does not appear to lead to increased respiratory decline other resistant organisms, such as Methicillin-resistant *S. aureus* (MRSA), have been demonstrated to lead to increased mortality. Dasenbrook and colleagues have shown both increased mortality and a more rapid decline in lung function in patients chronically colonised by MRSA [84,85]. If MRSA is transient



Fig. 7. Large pulmonary embolus within the right lower lobe pulmonary artery extending to upper lobe pulmonary artery. Associated with thrombus formation at the tip of a P.A.S. port line.

then the relative risk returns to baseline, stressing the importance of early identification and prompt eradication. It has been speculated that patients with MRSA colonisation may have been worse at baseline with more frequent antibiotics and hospital visits [86]. Of concern is data suggesting that many strains identified in patients with CF are not only community acquired but also can be very aggressive with expression of Panton–Valentine leukocidin (PVL) toxin [87,88].

It is not just bacterial resistance that is an increasing problem in CF; recently it has been reported that *Aspergillus fumigatus* resistance to itraconazole occurs in 8% of isolates from patients with CF [89]. This resistance was strongly related to previous exposure and many isolates were also resistant to voriconazole and posaconazole. Unfortunately resistance does lead to treatment failure in patients [90]. It remains unclear when anti-fungal medication should be prescribed in patients; this is especially the case when *A. fumigatus* is cultured from over half of patients with CF [91]. In ABPA, which occurs in 15% of patients, there have been no randomised controlled trials of the role of anti-fungal medication [92]. It is essential we characterise patients better and use anti-fungal medication appropriately given the risks of resistance as well as significant side effects such as liver toxicity.

## 2.5. Future perspectives

Cystic fibrosis remains a very complicated multisystem disease. Despite optimism of potentially effective new treatments such as gene therapy and drug modulators, irreversible organ damage is likely to remain a long term challenge. Conventional therapy includes complex drug regimens aimed at protecting the lungs from recurrent pulmonary infections, airway inflammation and permanent lung damage. Unfortunately drug complications and side effects remain relatively common and a minority of patients are being denied transplantation because of multiple drug allergy, renal failure, liver disease and osteoporosis. Even those accepted will be affected by today's treatment. Whatever the future holds, adult CF physicians will need to be both specialists and generalists if they are to address current and likely future challenges.

Despite using intravenous antibiotics for decades, some obvious questions remain unanswered. How long should the duration of treatment be? What is the best dose regimen? Should treatment be elective or as required? Is treatment aimed at intrapulmonary

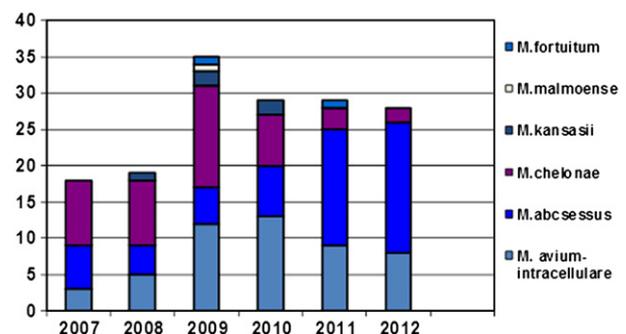


Fig. 8. Annual prevalence of NTM among adult and paediatric patients attending the Leeds unit.

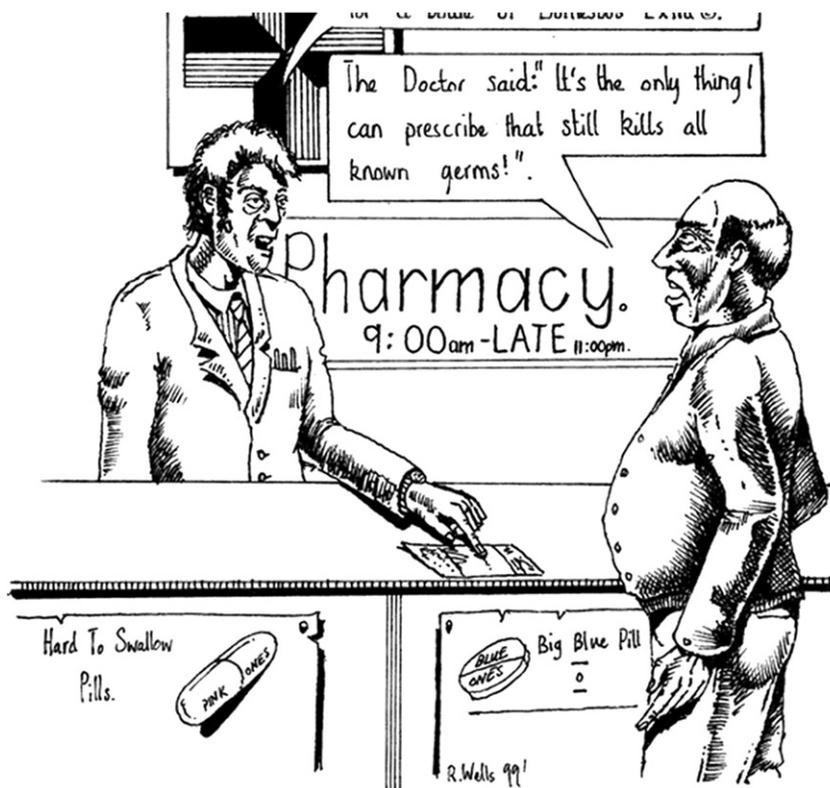


Fig. 9. A cartoon drawn by a Leeds patient with CF expressing his view of antibiotics.

spread of infection, or alteration in microbial community composition? Is combination therapy really necessary? These important questions need to be answered through well-designed appropriately powered multicentre trials yielding results that impact on the effectiveness of treatment and on the risk of serious complications such as drug hypersensitivity, renal failure and bacterial resistance. With an ageing population more emphasis needs to be placed on balancing the relative risk of bacterial resistance, potential synergy, ease of use, cost and limiting drug induced complications (Fig. 9).

Key to future success is reducing patient treatment burden while improving adherence to conventional therapy. This is especially the case in vulnerable adolescents who often have accelerated pulmonary decline [93]. On average adults with CF spend almost 2 h per day taking their treatment and in some cases, regimens are so onerous that they are incompatible with normal life, making it increasingly difficult for patients to meet the expectations of clinicians [94]. The psychological consequences of living with CF are also significant with over 20% of patients suffering from anxiety and 10% from symptoms of depression [95,96]. The combination of low mood and poor adherence can result in individuals failing to engage with clinical teams, resulting in a worse quality of life and a poorer clinical outcome [97,98]. Clinical teams responsible for CF care must ensure that each patient is empowered and has appropriate education as well as a clear personalised management plan. This has the potential to improve health, reduce exacerbation rates and the need for intravenous antibiotics.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jcf.2013.04.014>.

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