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Fluoroquinolones in the treatment of bronchopulmonary disease in cystic fibrosis

Abstract

Fluoroquinolones are commonly used to treat lung infections in those with cystic fibrosis. Patients with cystic fibrosis are susceptible to lung infection with common bacteria such as *Staphylococcus aureus* and *Haemophilus influenzae*, but also are prone to infection by opportunistic bacteria, including *Pseudomonas aeruginosa*. The good oral bioavailability and broad antimicrobial spectrum of activity, including anti-pseudomonal properties make this class of antimicrobial attractive. We review the evidence assessing the use of fluoroquinolones in the context of preventing and eradicating early lung infection and in managing chronic lung infection and pulmonary exacerbations. The safety of fluoroquinolones and the use of newer agents in the class is also discussed.

Introduction

Fluoroquinolones have a broad spectrum of antimicrobial activity and as a result are often used in the treatment of lung infection in the context of cystic fibrosis (CF). With anti-pseudomonal properties they are used commonly in *Pseudomonas aeruginosa* eradication regimens, the treatment of mild exacerbations in those chronically infected with *P. aeruginosa* and for the treatment of infections with other bacteria, including *Stenotrophomonas maltophilia* [UK Cystic Fibrosis Trust, 2009]. The mode of action of this group of antibiotics is incompletely understood, as are the mechanisms that underlie resistance to their effects. In addition, fluoroquinolones may have additional effects beyond their bactericidal properties. However, the side-effect profiles of some agents in the class are extensive highlighting the need for targeted use [Lapi *et al.*, 2010].

Mechanism of action

Fluoroquinolones are understood to exert their effect at the nucleic acid level of bacterial topoisomerases, in particular DNA gyrase (topoisomerase II) and topoisomerase IV. These two enzymes act as ‘guardians’ over the processes of efficient DNA replication. DNA replication results from ‘unzipping’ of the linked DNA strands, thereafter each single strand is complemented by the addition of DNA bases to form two new DNA molecules. This process occurs sequentially along the DNA molecule, however as the DNA unwinds for replication, bases along the DNA strand may mistakenly complement along the same strand, producing unwanted supercoils and interlocked DNA circles. Unchecked, these conformational changes during DNA replication would inhibit DNA replication. DNA gyrase and topoisomerase IV act to remove these structures to allow DNA replication to proceed unhindered [Bearden *et al.*, 2001]. Fluoroquinolones target these enzymes by binding to the active site of these molecules and inhibiting their action and through inhibition of DNA repair mechanisms eventually lead to cell death [Zhanel *et al.*, 2002].

Antibiotic resistance to fluoroquinolones is understood to occur as a result of either mutations in the topoisomerase genes, decreased permeability of the bacterial cell wall and/or the activity of efflux pumps [McDermott *et al.*, 2003, Muller *et al.*, 2011]. Efflux pumps act on specific substrates to remove toxins, metabolites and quorum sensing signal molecules from within the bacterial cell. Fluoroquinolones are a substrate of efflux pumps

and over-expression of efflux pumps occurs in *P. aeruginosa*. Co-administration of levofloxacin with an efflux pump inhibitor is being developed as a strategy that may potentiate the antibacterial activity levofloxacin *in vitro* [Renau *et al.*, 2002]. Clinical trials are awaited.

Pulmonary infection in CF may involve organisms growing in an anaerobic niche (e.g. within mucus plugs) and it is advantageous for an antibiotic to be active against obligate anaerobes or organisms such as *P. aeruginosa*, which can be facultative anaerobes. Many antibiotics have reduced activity in anaerobic conditions [Tunney *et al.*, 2008]. However, some quinolones, such as levofloxacin, are equally active in an aerobic or anaerobic environment [King *et al.*, 2010].

Pharmacokinetics and pharmacodynamics

It has previously been reported that the pharmacokinetics of antibiotics in those with CF is altered compared with healthy individuals [Touw, 1998]. The same appears to hold true for fluoroquinolones in that patients with CF experiencing an exacerbation may have increased bioavailability of ciprofloxacin given orally compared to healthy volunteers (80% vs. 57%). Increased clearance was also observed suggesting that there is no need for a dose alteration [Christensson *et al.*, 1992]. In a comparison of the pharmacokinetics of ciprofloxacin and ofloxacin, ciprofloxacin was cleared more quickly [Pedersen *et al.*, 1987]. While studies in adults have varying results (as reviewed by Touw [1998] none of the differences appear to be clinically meaningful. There are few studies however of the pharmacokinetics of fluoroquinolones in children with CF. In two separate studies, while the majority of pharmacokinetic indices were similar to those observed in adults with CF, there was a suggestion of age-related increases in drug clearance, with children eliminating the drug more quickly, and as such the authors suggested that an increase in dose in younger compared to older patients may be required [Schaefer *et al.*, 1996, Rubio *et al.*, 1997].

Using a population pharmacokinetic model, a 400mg dose of ciprofloxacin twice or three times daily may be inadequate to treat an exacerbation as the area under the curve (AUC)/minimum inhibitory concentration (MIC) was suggested to be suboptimal in 70-90% of simulated patients [Montgomery *et al.*, 2001]. Estimates of ciprofloxacin sputum penetration also vary and while it is difficult to understand the reasons for this, whether the drug level reaches the MIC appears to depend largely on the MIC of the individual organism isolated [Pedersen *et al.*, 1987].

Pseudomonas aeruginosa prevention and eradication

Preventing infection with *P. aeruginosa*, or treating early infection when it does occur, is a strategy aimed at deferring chronic *P. aeruginosa* infection for as long as is possible so that the damage incurred as a result is reduced. While it has not been demonstrated that benefits in clinical outcomes result from such an approach, eradication regimens appear to render *P. aeruginosa* undetectable from respiratory secretions several months after antibiotic therapy commences [Langton-Hewer *et al.*, 2009]. Unfortunately however the Cochrane review examining this area had insufficient data with which to determine an optimal regimen.

A recent trial reported results that go in some way to further our understanding of how difficult it can be to prevent *P. aeruginosa* infection. In a three year blinded randomised controlled trial, 65 children who were *P. aeruginosa* negative (absence of *P. aeruginosa* positive cultures, serology and anti-pseudomonal antibiotics) were randomised in three age blocks (0-5 years, 6-11 years and 12-18 years) to receive either twice daily nebulised colistin with oral ciprofloxacin or dual placebo for 3 week periods every three months for three years [Tramper-Stranders *et al.*, 2010]. Respiratory cultures (from cough swab or sputum)

were taken at three-monthly intervals along with six-monthly lung function for those over 4 years, serum anti-*Pseudomonas* antibodies and annual X-ray and blood work up. Of these children, 19 met the end point of *P. aeruginosa* isolation on two occasions one week apart. The median age at acquisition of *P. aeruginosa* was 6.8 years with no difference between the treatment and placebo groups ($p=0.101$). No ciprofloxacin or colistin resistance was noted in any of the initial infecting strains. Non-fermenting Gram-negative bacteria (excluding *P. aeruginosa*) were cultured more frequently in the treated group, a concern as such bacteria are becoming increasingly recognised in the lung microbiome [Tunney *et al.*, 2008]. It is unfortunate however that the nebulised placebo contained mannitol, an agent that has recently been shown to improve lung function in CF probably an osmotic effect improving mucociliary clearance [Bilton *et al.*, 2011, Aitken *et al.*, 2012]. These mannitol studies have shown however no effect on quantitative or qualitative sputum microbiology suggesting that any effect on the control group in the prophylaxis study would be minimal.

A number of studies have previously reported results of *P. aeruginosa* eradication regimens, many of which include ciprofloxacin (Table 1). While noting that the evidence base is weak, UK CF Trust guidelines indicate that ciprofloxacin may be used in the treatment of early infection and its use is commonplace in this context [UK Cystic Fibrosis Trust, 2009].

As can be seen from the table, tobramycin for inhalation (TIS) alone appears to be an effective agent in eradicating early *P. aeruginosa* infection when given at 80mg twice daily for a year [Wiesemann *et al.*, 1998, Ratjen *et al.*, 2001], or at 300mg twice daily for 28 days [Gibson *et al.*, 2003, Ratjen *et al.*, 2010, Treggiari *et al.*, 2011]. Indeed the recent ELITE trial demonstrated no additional benefit of extending the treatment course to 56 days over the standard 28 days, using the 300mg twice daily dose [Ratjen *et al.*, 2010]. Safety and efficacy of inhaled tobramycin has also been demonstrated in a powder formulation, with the suggested advantages of convenience and increased satisfaction, it is possible that adherence may be increased, although this has yet to be confirmed [Konstan *et al.*, 2011].

The recent EPIC trial however, has cast doubt on the benefit of adding ciprofloxacin to a standard regimen of tobramycin inhalation solution (TIS) [Treggiari *et al.*, 2011]. This four-arm randomised placebo-controlled trial was designed to answer two questions – 1) does the addition of oral ciprofloxacin to a standard regimen of TIS confer benefit and 2) is this treatment best given in response to a positive culture (culture-based) or at regular intervals irrespective of cultures (cycled therapy)? The intention-to-treat analysis included 304 children between the ages of 1 and 12 years, 76 children randomly assigned to each arm – cycled TIS and placebo, cycled TIS and ciprofloxacin, culture-based TIS and placebo, culture-based TIS and ciprofloxacin. The cycled and culture-based therapy groups performed equally with 24 of 152 (16%) in the cycled and 26 of 152 (17%) in the culture-based group experiencing a pulmonary exacerbation (hazard ratio 0.95, $p=0.86$). Similarly, 29 of 152 (19%) of those who received ciprofloxacin and 21 of 152 (14%) who received placebo experienced a pulmonary exacerbation (hazard ratio 1.45, $p=0.20$). An equal proportion of patients in each group were able to clear *P. aeruginosa* from respiratory samples. The odds of a *P. aeruginosa* positive culture for the cycled vs. culture-based regimens was 0.78 ($p=0.28$) whereas the odds for those receiving ciprofloxacin vs. placebo was 1.10 ($p=0.67$). There were no differences in the frequency of adverse events between groups except that those receiving ciprofloxacin reported more cough. There were no differences in lung function. On the basis of this trial, it would appear that culture-based TIS alone is sufficient for the treatment of early *P. aeruginosa* infection.

Consensus however remains lacking with the UK CF Trust recommending nebulised colistin and oral ciprofloxacin for three months as first line for the eradication of early *P. aeruginosa* [UK Cystic Fibrosis Trust, 2009]. The use of colistin, in preference to tobramycin, as first

line is based on lower graded evidence and appears to be largely related to more experience of using colistin, as traditionally this was the only inhaled treatment licensed in the UK. It is not licensed for use in the US. The Danish group have extensive experience of using a regime of colistin and ciprofloxacin and have been able to document 80% of their cohort as being free of *P. aeruginosa* for 15 years after first infection [Hansen *et al.*, 2008].

Currently recruiting is a trial to determine if ten days intravenous ceftazidime and tobramycin and nebulised colistin is superior to three months oral ciprofloxacin and nebulised colistin (ISRCTN02734162). The primary endpoint is successful eradication of *P. aeruginosa* three months after treatment commences and the proportion remaining infection free for fifteen months after the start of the allocated treatment.

Treatment of chronic *P. aeruginosa* infection

Once chronic infection with *P. aeruginosa* is established, eradication is no longer possible and the focus of treatment turns to optimisation of nutritional status, treatment of complications and the aggressive management of pulmonary exacerbations when they occur. Unfortunately there is no universally agreed diagnostic criteria for exacerbations and many clinical trials use 'physician-diagnosed' criteria. For the most part patients experiencing a pulmonary exacerbation report deterioration in sputum production, lung function and reduction in ability to attend work or school [Rosenfeld *et al.*, 2001]. There is uncertainty regarding the underlying pathophysiology of exacerbations but some form of host-pathogen response is likely. In the context of chronic lung infection, the use of antibiotics must be balanced between the opposing pressures of aiming to reduce bacterial burden through the frequent or chronic use of antibiotics and keeping adverse effects of those antibiotics, in terms of toxicity, side effects and antimicrobial resistance to a minimum.

Clinical trials of antibiotics (Table 2, Table 3) in the context of chronic infection in cystic fibrosis are complicated by concern that spontaneously expectorated sputum may not reliably represent the heterogeneous pattern of lung infection in any given patient and previous attempts at quantitative microbiology may be misleading [Rogers *et al.*, 2008]. Indeed, pulmonary exacerbations may not be preceded by an increase in sputum bacterial density [Stressmann *et al.*, 2011]. Cautious interpretation of microbiological outcomes in trials is therefore warranted.

It was previously unclear whether antibiotics should be administered in a cycled fashion (elective irrespective of symptoms and cultures), in response to an increase in symptoms or indeed administered by oral, intravenous or inhalation routes. Elborn *et al.* [2000] conducted a pragmatic randomised trial (for which fluoroquinolones were an eligible therapy) to determine the optimal treatment strategy in terms of elective or symptomatic treatment. Antibiotic choice and diagnosis of an exacerbation were left to the treating centre. At the end of the three year trial, there were no differences between the groups in lung function, clinical or radiographic scores, anthropometric measures or bacteriology.

Maintenance treatment

The conventional aim of maintenance antibiotic treatment has been to reduce lung damage by the chronic suppression of bacteria, aiming to slow the gradual decline in lung function. Studies that have been completed (Table 2) suggest that while lung function or clinical score may be improved while receiving the antibiotic, when this is stopped the decline resumes. Concerns of inducing antibiotic resistance by such a strategy, remain. There is, however, a lack of consensus on the significance of antibiotic resistance as determined by antibiotic susceptibility testing, as clinical treatment success and *in vitro* antibiotic susceptibility appear not to be closely correlated [Fothergill *et al.*, 2010, Hurley *et al.*, 2012b]

Treatment of pulmonary exacerbations

Pulmonary exacerbations are independently associated with a poor outcome [de Boer *et al.*, 2011] and so optimising treatment of these is a priority for those with CF. The trials involving fluoroquinolones that have reported are considered in Table 3 and a Cochrane review considering the intravenous antibiotic treatment of pulmonary exacerbations is underway [Hurley MN *et al.*, 2012a]. It is important to note that many of the trials that have been completed are small and may have been underpowered to detect a small difference, should one exist. In a study directly comparing conventional intravenous ceftazidime and tobramycin with iv ciprofloxacin followed by oral dosing, all patients improved, compared to baseline, with no significant difference between the two groups in clinical score and lung function [Church *et al.*, 1997]. In both arms clinical score and lung function deteriorated after end of treatment and equal numbers of patients in both arms developed a degree of antibiotic resistance. There was a 13% relapse rate (all in severely affected female Caucasians) in both groups.

Nebulised fluoroquinolone therapy

A Cochrane review has considered the efficacy of nebulised antibiotics and suggests that while inhaled antibiotics probably improve lung function and reduce exacerbation rate, there is currently insufficient evidence to recommend a particular drug or dose [Ryan *et al.*, 2011]. They conclude that trials of a longer duration are required.

Since the publication of this Cochrane review, trials of nebulised levofloxacin have reported results. In a randomised double blind placebo controlled study involving 151 patients randomised to receive either 120mg daily, 240mg daily, 240mg twice daily or placebo for 28 days with follow-up for 56 days, the primary efficacy endpoint was change in sputum density of *P. aeruginosa*. Secondary endpoints were change in lung function, time to administration of other anti-pseudomonal antibiotics and changes in symptom score [Geller *et al.*, 2011]. Treatment commenced during a period of clinical stability. For the primary outcome, change in sputum density, this showed the largest fall from baseline at the 240mg twice daily dose, with less significant decreases observed in the other two doses. Unfortunately no detail is given for the microbiological methods used and as previously mentioned in the light of recent evidence questioning the aetiology of exacerbations, such endpoints should be treated with caution. Nevertheless, when considering FEV₁ and respiratory symptom score, those receiving 240mg twice daily responded with a significant improvement 8.6% above that of placebo at 28 days of the treatment phase, although this effect returned to baseline after cessation of the drug. The lower doses had a minimal effect. Two phase III trials of levofloxacin are currently underway, one placebo-controlled (NCT01180634), the other a comparison against tobramycin inhalation solution (NCT01270347).

The side effect profile of nebulised levofloxacin appears to be good with numbers of adverse events in the treatment arms being similar to that in the placebo group, except for complaints about taste which was attributed to the study drug [Geller *et al.*, 2011].

An inhaled preparation of ciprofloxacin (NCT00645788) has recently completed a phase II randomised double blind placebo controlled study, results are awaited.

Safety and adverse effects

Adverse events reported in clinical trials may or may not be attributed to the drug regime under investigation. Many reported adverse events relate to the disease and infection for which the antibiotic is intended to treat. In a controlled trial, both treatment groups may

experience adverse events. When the rates of reported events are significantly greater in the treatment group, compared to the comparator, or adverse effects in the treatment group are severe (e.g. causing death or hospital admission) then this requires careful scrutiny.

Recognised side effects of fluoroquinolones, for all indications, include gastrointestinal disturbance (nausea reported in 6-10% of those receiving moxifloxacin, but less for ciprofloxacin), headache and dizziness (levofloxacin and moxifloxacin 1-5%), rash and photosensitivity (1-5% ciprofloxacin (highest of all in the group [Lapi *et al.*, 2010], very low levofloxacin and not reported for moxifloxacin) and musculoskeletal effects [Zhanel *et al.*, 2002].

With regard to cardiac toxicity, sparfloxacin and grepafloxacin have been removed from the market following concerns about QT-prolongation cardiac toxicity. The development of garenoxacin was also stopped after phase I trials. While this appears to be a class effect, the dual-elimination of most agents in the class make the risk of QT-related cardiac events unlikely, currently only levofloxacin and gatifloxacin are solely renally-excreted and so may require dose adjustment in renal insufficiency. In fact the rates of QT prolongation are very low, however it is suggested that some in the class, particularly moxifloxacin, levofloxacin are not used in combination with certain anti-arrhythmics.

Less common, but important adverse effects of fluoroquinolones include retinal detachment (number needed to harm 2500) [Etminan *et al.*, 2012] and a case report of suicidal ideation that resolved after cessation of ciprofloxacin, after having recently receiving levofloxacin [Labay-Kamara *et al.*, 2012]

There have been particular concerns of fluoroquinolone use in children after reports of drug-related arthropathy [Adefurin *et al.*, 2011]. A prospective comparative cohort study in France recruited 276 children who were receiving a fluoroquinolone and 249 controls, a quarter of who were younger than 2 years and a third had CF [Chalumeau *et al.*, 2003]. Ten musculoskeletal events (10 patients) were experienced in the treatment group (18.2% perfloracin, 3.3% ciprofloxacin). The doses given to these patients were the same as those who did not report musculoskeletal side effects, with symptoms consisting of myalgia and arthralgias of large joints [Chalumeau *et al.*, 2003]

It must be noted however that often the most informative generation of safety data occurs in the post-marketing phase facilitated, in the UK, by the yellow card adverse event reporting system. With this in mind the case of trovafloxacin is apt [US Food and Drug Administration, 2009]. It was through post-marketing surveillance reports that unpredictable severe liver reactions (leading to transplant or death) were noted and the use of trovafloxacin restricted to those with limited indications.

New fluoroquinolones

There are numerous members of the quinolone family that have reached various points of development (Table 4), many have fallen by the wayside due to side effects. While many have not been specifically evaluated in the context of infection in CF, some agents appear to show impressive levels of potency against *P. aeruginosa* (e.g. prulifloxacin [Roveta *et al.*, 2005]). Other agents appear to have specific non-antibiotic effects, such as effects on the host (moxifloxacin appears to inhibit activation of specific inflammatory mediators in CF epithelia [Blau *et al.*, 2007]), or anti-virulence effects on the pathogen (moxifloxacin may decrease adhesion and biofilm formation of *Stenotrophomonas maltophilia* [Pompilio *et al.*, 2010]). In addition, levofloxacin appears to be effectively delivered in a newly developed inhalation vehicle.

Summary

Fluoroquinolones are a useful component in the antibiotic arsenal against the wide range of pathogens that cause infection in CF. The oral administration of ciprofloxacin is particularly attractive for those experiencing a mild exacerbation of symptoms with good oral bioavailability. Newer inhaled agents are convenient to administer and may be suitable for maintenance treatment. Administration of agents in this class has been associated with improvements in lung function and clinical score however in the majority of these studies a sustained effect is not seen once the antibiotic course is completed. Concerns about side effects however, remain. Weighing up between the benefits in lung function and clinical scores observed in patients receiving these antibiotics against risks of side effects and alterations in the antibiotic sensitivity of infecting bacteria and perhaps increased possibility of infection with other bacteria, is very difficult. Long term well conducted trials are needed to determine the optimal frequency of the use of maintenance antibiotics in this context. In addition studies that further our understanding of the mechanisms underlying infection, pulmonary exacerbations and the relationship between the host, bacteria and antibiotics are urgently needed.

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Table 1Controlled trials of regimens for eradication of early *P. aeruginosa*

Study	Study design	Eradication regime		Result
		Intravenous/inhaled antibiotic	Oral quinolone	
Valerius 1991 [Valerius <i>et al.</i> , 1991]	Placebo controlled trial	Colistin twice daily (3 weeks)	Ciprofloxacin (3 weeks)	14% intervention vs. 58% placebo became chronically infected (p<0.05).
Wiesemann 1998 [Wiesemann <i>et al.</i> , 1998]	Double-blind placebo-controlled randomised trial.	Tobramycin inhalation (80mg) twice daily (1 year)	-	10/11 tobramycin PA-ve, 5/11 placebo PA-ve
Gibson 2003 [Gibson <i>et al.</i> , 2003]	Double-blind placebo-controlled randomised trial. Bronchoscopy sampling	TIS (300mg) twice daily (28 days)	-	100% eradication (8 patients) in treatment arm compared to 1/13 in placebo arm (p<0.001). (Study stopped early).
Ratjen 2010 [Ratjen <i>et al.</i> , 2010]	Open label two arm randomised study	TIS 300mg twice daily (28 days vs. 56 days).	-	Equal rates of eradication in both arms (28 day 93% & 56 days 92%). Rate of recurrences was equal (p=0.593).
Treggiari 2011 [Treggiari <i>et al.</i> , 2011]	Randomised controlled trial TIS +/- ciprofloxacin (cycled every 3 months / culture based therapy)	TIS 300mg twice daily (28 days)	Ciprofloxacin 30-40mg/kg/day (14 days)	No difference between cycled and culture based therapy and no difference between ciprofloxacin or placebo.

(TIS – tobramycin inhalation solution)

Table 2

Controlled trials of maintenance therapies for chronic infection that include fluoroquinolones

Study	Study design	Maintenance regimen		Result
		Intravenous/inhaled antibiotic	Quinolone	
Jensen 1987 [Jensen <i>et al.</i> , 1987b]	Randomised double blind placebo controlled cross-over trial (cycled therapy)		14 days treatment cycled 3 monthly oral ciprofloxacin 750mg twice daily+ ofloxacin 400mg twice daily	Improved clinical score and lung function at end of 14 day treatment in both arms (p<0.05). Clinical score returned to baseline by 3 months.
Jensen 1987 [Jensen <i>et al.</i> , 1987a]	Randomised trial (cycled therapy – 3 monthly – 2 courses conventional, 2 courses quinolone – 1 ciprofloxacin, 1 ofloxacin).	Conventional – tobramycin + beta-lactam.	Ciprofloxacin 750mg twice daily or ofloxacin 400mg twice daily	11/26 failed to complete - 5 of these because of little improvement on first course of quinolone. Two preferred quinolone and others had oral antibiotic for a mild exacerbation in the interim. All courses yielded improvement in FEV ₁ but conventional treatment improved the most.
Geller 2011 [Geller <i>et al.</i> , 2011]	Randomised double-blind placebo controlled trial (maintenance therapy study)		Neb levofloxacin 120mg once daily, 240mg once daily or 240mg once daily	FEV ₁ improved with increasing dose (8.7% difference between 240mg twice daily and placebo), and decreased in the placebo group (p=0.003).

Table 3

Controlled trials of fluoroquinolone-containing regimens for treatment of pulmonary exacerbations

Study	Study design	Exacerbation regimen		Result
		Intravenous/inhaled antibiotic	Quinolone	
Bosso 1987 [Bosso <i>et al.</i> , 1987]	Randomised trial (exacerbation treatment – ciprofloxacin vs. tobramycin & azlocillin)	iv tobramycin iv azlocillin	Oral ciprofloxacin 750mg twice daily	No difference between groups. More ciprofloxacin patients completed 14 day course 7/10 vs. 5/10.
Hodson 1987 [Hodson <i>et al.</i> , 1987]	Randomised trial (exacerbation study – azlocillin & gentamicin vs. ciprofloxacin)	Iv gentamicin 80mg iv azlocillin 5g	Oral ciprofloxacin 500mg	Significant improvement in lung function from baseline in both groups. Cipro group maintained improvement at 6 weeks, but not iv group.
Black 1989 [Black A <i>et al.</i> , 1989]	Randomised trial (exacerbation treatment - ciprofloxacin treatment for 4 successive exacerbations vs. alternate ciprofloxacin / iv azlocillin & tobramycin for 4 successive exacerbations)	iv tobramycin iv azlocillin	oral ciprofloxacin	Interval abstract report during an on-going trial. Equal clinical efficacy.
Bosso 1989 [Bosso, 1989]	Randomised controlled trial (exacerbation treatment – ciprofloxacin vs. tobramycin & azlocillin)	iv tobramycin iv azlocillin 75mg/kg thrice daily	Oral ciprofloxacin 750mg twice daily	No significant difference between two arms.
Church 1997 [Church <i>et al.</i> , 1997]	Randomised double blind trial (paediatric exacerbation treatment - ciprofloxacin oral/iv vs. iv ceftazidime & tobramycin)	iv ceftazidime and tobramycin (10 days)	iv ciprofloxacin 10mg/kg thrice daily (7 days) oral ciprofloxacin 20mg/kg twice daily (3 days)	All patients in both arms improved compared to baseline ($p<0.001$). Both arms were equivalent
Schaad 1989 [Schaad <i>et al.</i> , 1989]	Randomised trial (exacerbation treatment – aztreonam & amikacin vs. ceftazidime & amikacin each followed by ciprofloxacin for 4 weeks)	iv aztreonam iv amikacin iv ceftazidime	Oral ciprofloxacin	Improved clinical outcome from baseline but no additional improvement from end iv to end ciprofloxacin phase.
Schaad 1997 [Schaad <i>et al.</i> , 1997]	Randomised trial (exacerbation study – initial conventional iv antibiotic followed by ciprofloxacin vs. ciprofloxacin & amikacin inh).	Inhaled amikacin	Oral ciprofloxacin	After conventional iv therapy both arms continued to improve in 'clinical symptoms' although after cessation of iv treatment lung function gradually deteriorated in both arms.

Table 4

Fluoroquinolones past, present and future

First generation	Second generation	Third generation	Fourth generation
Nalidixic acid	Ciprofloxacin	Levofloxacin	Trovafloxacin
Cinoxacin	Norfloxacin	n	Clinafloxacin
	Lomefloxacin	Sparfloxacin	Moxifloxacin
	Enoxacin	Grepafloxacin	Garenoxacin
	Ofloxacin	n	Besifloxacin
	Perfloxacin	Gatifloxacin	Prulifloxacin
	Fleroxacin	Gemifloxacin	Gatifloxacin
		n	Sitafloxacin
		Tosufloxacin	Altrofloxacin
		n	
		Temafloxacin	
		n	