Newer fluoroquinolones in the treatment of acute exacerbations of COPD

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Abstract: Acute exacerbations of COPD are a major cause of morbidity and mortality. Bacteria are implicated in about half of all cases. The frequency of exacerbations is related to decline in lung function and poorer quality of life. 25% of patients with COPD have bacterial colonization of the lower airways in stable state whereas non-smokers without COPD have airways that are sterile. The significance of the colonization is unclear, but there is emerging evidence that it may be detrimental. Much of the data recommending antibiotic treatment are based on findings more than 10 years old and do not take into account emerging bacterial resistance. This article reviews these data and that from newer antibiotic trials. It also reviews current antibiotic prescribing guidelines from major respiratory societies around the world. Recent antibiotic trials have compared fluoroquinolones with "standard" antibiotics and found, in the main, longer exacerbation-free intervals and better bacterial eradication rates in those treated with fluoroquinolones.

Keywords: COPD, exacerbation, antibiotics, fluoroquinolones

Introduction

COPD is predicted to be the third most common cause of death and chronic disability in the world by 2020 (Lopez and Murray 1998). In the UK it is the most common respiratory disease in adults affecting 1.5 million people, primarily aged over 45 (BTS 2004). COPD causes 30 000 deaths a year in the UK. In the winter months, admission to hospital with acute exacerbations of COPD is the commonest medical emergency. Outcomes when hospitalized are poor, with 34% being re-admitted and 14% dying within 3 months (Roberts et al 2002). The term COPD encompasses several conditions. These include airflow obstruction with little reversibility, chronic bronchitis, emphysema, and small airways disease. Chronic bronchitis is defined by the presence of a productive cough for at least 3 months a year during 2 consecutive years. Emphysema is characterized by enlargement of air spaces distal to the terminal bronchi accompanied by destruction of lung parenchyma. Obstruction as demonstrated on pulmonary function tests by a reduction in the forced expiratory volume (FEV_1) which does not improve significantly after inhalation of a bronchodilator (distinguishing COPD from asthma) is usually present but not essential for the definition. Small airways disease refers to chronic inflammation and narrowing of the terminal and respiratory bronchioles. It is difficult to distinguish between these conditions as they may all be present and contributing to different degrees in each individual patient.

Various risk factors have been identified for the development of COPD. The primary cause worldwide is tobacco smoke. Other factors include environmental and occupational pollutants, childhood respiratory tract infections, bronchial

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hyperreactivity, and genetic conditions such as alpha-1 antitrypsin deficiency (Sherill et al 1990).

Patients with COPD present with a combination of symptoms characterized by dyspnea, wheeze, coughing, and sputum production. Patients are prone to exacerbations during which there is an increase in these symptoms, and the sputum may become purulent. There are a number of reasons, which will all cause an increase in airway inflammation and usually obstruction. Viral and bacterial infections are thought to be the major cause of exacerbations of COPD (Murphy and Sethi 1992; Seemungal et al 2001; Wilson 2001; Sethi et al 2002). Bacterial infections more commonly occur in patients with chronic bronchitis as opposed to those at the emphysema end of the spectrum. Bacteria have an affinity for the excess mucus secretions that are characteristic of chronic bronchitis. This mucus is poorly cleared, particularly when during an exacerbation airway inflammation leads to increased volume and impairment of mucociliary clearance, which gives bacteria the time to infect the mucosa (Wilson et al 1996). Mucus hypersecretion is particularly associated with mortality in COPD due to an infectious cause as well as a more rapid rate of decline in FEV_1 (Prescott et al 1995; Vestbo et al 1996). The frequency of exacerbations regardless of their cause leads to more rapid loss of lung function and also to deterioration in quality of life (Seemungal et al 1998; Kanner et al 2001; Andersson et al 2002; Donaldson et al 2003).

Pathogenesis of bacterial infection in COPD

Airway inflammation is stimulated by bacterial infection and the level of inflammation is proportional to the number of bacteria present (Hill et al 2000). Bacterial products stimulate mucus production, impair ciliary function, and cause epithelial cell injury. Bacteria attract and stimulate neutrophils via mediators such as IL8, LTB4, and other chemoattractants. Neutrophils spill proteinases and oxidants during phagocytosis, which also damage the mucosa. This host-mediated, bacteria-stimulated damage may be more important than direct damage from the bacteria themselves (Wedzicha 2001; Wilson 2001). Patients with COPD can also have lower airway bacterial colonization (LABC) when their condition is stable in contrast to the airways of non-smokers without COPD, which are sterile (Monso et al 1999). Bacterial colonization could simply be a consequence of damaged airways, but it has been shown to be associated with both an increase in the severity and frequency of future exacerbations (Patel et al 2002).

The most frequent species isolated in acute exacerbations of COPD are non-typeable *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. These species colonize the nasopharynx of healthy individuals and can therefore be picked up during expectoration of sputum and not truly represent lower airway infection (Wilson 2001). A number of bronchoscopic studies have been performed to avoid this contamination and to examine the lower airways directly. The protected specimen brush (PSB) is introduced via the bronchoscope and is used to sample lower respiratory tract mucosa. Monso et al (1995) studied COPD patients in a stable phase and a separate group during an exacerbation. Using the PSB they found 25% of stable patients colonized mainly with *H. influenzae* and *S. pneumoniae*. The number of positive PSB cultures increased to 50% at times of exacerbation, and very importantly the concentration of bacteria during exacerbations was much higher. Zalacain et al (1999) did a similar study and found 40% had LABC. Both studies found that current cigarette smoking was associated with LABC.

The presence of LABC should not necessarily be viewed as a cause of disease, but there is emerging evidence to suggest that LABC may be detrimental (Soler et al 1999). It has been shown that there are higher neutrophil counts, IL-8, and tumor necrosis factor (TNF-α) levels in bronchoalveolar lavage performed on stable chronic bronchitic patients with LABC with potentially pathogenic species. These important findings have been confirmed in a recent study, and the increased inflammation was independent of current tobacco smoke exposure (Sethi et al 2006). It was also shown in this study that neutrophil counts were significantly inversely correlated with FEV_1 (Soler et al 1999; Wilson 2001). White et al (2003) suggested that resolution of bronchial inflammation following an exacerbation is dependent on bacterial eradication. Banerjee et al (2004) showed that patients with clinically stable moderate-to-severe COPD who had pathogenic bacteria in their sputum had an increased inflammatory response. This was demonstrated by the fact that more sputum neutrophils, and higher levels of IL8, LTB4, and other chemoattractants were present in those with pathogenic bacteria in their sputum compared with those without. These patients also had increased systemic inflammation as demonstrated by higher concentrations of fibrinogen in plasma. Health status was also poorer than in those with non-pathogenic microorganisms present.

LABC in the stable phase probably represents a balance in which impaired local host defences are able to limit spread of, but not eliminate, bacteria (Wilson 2005). LABC is a dynamic process and specific strains of bacteria may change quickly whilst others persist for a long time. Gump et al (1976) followed a cohort of patients many years ago and found that bacteria were isolated with identical frequency whether the patient was in a stable phase or having an exacerbation. A newer study by Sethi et al (2002) have used molecular techniques now available to identify bacteria and differentiate new strains from those that have been present for a longer time. Sethi et al (2002) showed that there were symptoms of an exacerbation present in 33% of clinic visits in those with presence of a new strain as compared with 15% of visits where a new strain was not found. New strains one might speculate would be able to evade host defences, increase in numbers, and invade the mucosa. This would then lead to systemic inflammation and symptoms of an exacerbation. They went on to show that when a new strain was associated with an exacerbation, a specific systemic antibody response occurred that gave positive results in a bactericidal assay (Sethi et al 2004). That finding adds weight to the argument that the bacteria are playing a causative role in the exacerbation by participating in the generation of a host response intended to eliminate them.

Antibiotic treatment

The cause of exacerbations is multifactorial, involving viral infections, environmental pollutants, and allergic responses as well as bacteria. Bacteria are involved in about half of cases. A meta-analysis of nine placebo-controlled trials concluded that, overall, there was a small but significant benefit in outcome from antibiotic treatment of acute exacerbations of COPD (Saint et al 1995). There have since this analysis been two further placebo-controlled trials of note supporting antibiotic use. Nouira et al (2001) enrolled 93 patients with exacerbations severe enough to require ventilatory support in an intensive care unit. These patients were randomized to receive either the quinolone ofloxacin or placebo. Ofloxacin reduced mortality and the need for additional antibiotic treatment. Allegra et al (2001) published a re-analysis of an older trial. They compared the use of amoxicillin–clavulanate with that of placebo for 414 exacerbations. The clinical success rate was significantly superior with the antibiotic compared with placebo (86.4% vs 50.6%).

The older study by Anthonisen et al (1987) is the largest and most widely quoted trial favoring antibiotic treatment. In this study, 173 patients with COPD were followed for 3.5 years during which time they had 362 exacerbations. Exacerbations were classified into three levels of severity: type I exacerbations (the most severe) was defined as increased dyspnea, sputum volume, and sputum purulence. Type II involved two of the above symptoms, and type III was only one of the symptoms with evidence of fever or upper respiratory tract infection. Patients were randomized to receive placebo or one of amoxycillin, trimethoprim–sulphamethoxazole, or doxycycline. There was a significant benefit from antibiotics that was largely accounted for by patients with type I exacerbations. In type III exacerbations there was no significant benefit. However, even with type I exacerbations 43% of patients recovered in the placebo group within 21 days. This result suggests that resolution is not necessarily dependent on antibiotics and can occur spontaneously due to the host immune response to infection. Antibiotic treatment should therefore be judicious. A major consideration is to prevent progression of an exacerbation into pneumonia or respiratory failure which might be more likely in patients with more severe COPD, older patients and those with comorbidity. Treatment should also aim to hasten recovery even in patients who might otherwise recover in any case. This would reduce time lost from work and relieve suffering. In the Anthonisen study, the duration of antibiotic-treated exacerbations averaged 2.2 days less than in those given placebo. However, when treatment failures were eliminated from the analysis, the benefit from antibiotics on speed of recovery was only 0.9 days. Another consideration, which at present remains a hypothesis to be tested, is that better treatment of an exacerbation might lengthen the time until the next exacerbation, and so reduce the frequency of exacerbations.

The recommendations made by learned societies are summarized in Table 1. The British Thoracic Society have recommended that those with an increase in sputum purulence should receive antibiotics. In the absence of an increase in sputum purulence or radiographic changes consistent with pneumonia, antibiotics should not be given. They recommend an aminopenicillin, a macrolide, or tetracycline as first-line treatment (BTS 2004).

The American Thoracic Society and European Respiratory Society opinion is similar. They stipulate there should be an increase in either sputum volume or purulence, and if this is the case, then antibiotics should be used. Amoxycillin–ampicillin (depending on local prevalence of bacterial β-lactamase), cephalosporins, doxycycline, or macrolides are suggested. If a patient has failed prior

antibiotic treatment then consideration should be given to amoxicillin–clavulanate or fluoroquinolones as first-line antibiotics (Celli et al 2004).

The Canadian guidelines differ from those of the three previous organizations. They stratify patients into risk groups 0–4. Those in group 0 have no underlying lung disease. Onset of a cough with sputum production is likely to be caused by a virus and no antibiotic is needed unless there is a more protracted course. Group 1 has chronic bronchitis but only mild to moderate impairment of lung function (FEV_1 >50% predicted). These patients have fewer than four exacerbations a year and no evidence of cardiac disease. These guidelines suggest treatment with aminopenicillins, doxycycline, or trimethoprim–sulphamethoxazole is indicated. They do, however, accept that data showing the efficacy of the aforementioned antibiotics is from trials conducted over 10 years ago and it may be more prudent to use selected second- or third-generation cephalosporins or second-generation macrolides in view of emerging *S. pneumoniae* and *H. influenzae* resistance. Group 2 patients will have significant airway obstruction (FEV_1 <50% predicted) and may have other co-morbidities. The Canadian guidelines suggest treatment should be better directed at resistant organisms using for example fluoroquinolones or amoxicillin–clavulanate, because these patients are more at risk of such strains largely due to the frequency with which they have received antibiotics previously. Group 3 patients suffer from chronic bronchial suppuration with continuous purulent sputum production. They will have frequent exacerbations and the antibiotic choices are similar as for those in group 2 but it should be noted these patients are more at risk of *Pseudomonas aeruginosa* infection (Balter et al 2003).

In view of the number of antibiotics available on the market, it is surprising more data are not available demonstrating superiority of one antibiotic over another. This is because unfortunately most antibiotic trials look for equivalence, and are not powered to show superiority. The limitations of previous studies are summarized in Table 2. Enrollment of patients with milder COPD, who have a greater chance of spontaneous recovery, has almost certainly affected results. Other flaws include lack of long term follow up, choice of end points up to three weeks after the start of treatment (when spontaneous recovery will have occurred), and absence of assessment of speed of symptom improvement (Sethi 2005; Wilson 2005).

As previously mentioned, many current guidelines recommend the use of amoxycillin, trimethoprim–sulphamethoxazole, and doxycycline for the treatment of acute exacerbation of COPD (BTS 2004; Celli et al 2004). This is evidence based but does not take into account the fact that much of the data are greater than 10 years old, and since that time there has been emergence of resistance in common pathogens. Before 1987 less than 1% of pneumococci in the USA demonstrated a high level of resistance to penicillin (Wilson 2001). In 1997, overall penicillin resistance had reached 43.8%. Penicillin-resistant

Table 1 Summary of major respiratory society guidelines

Society and classification	Symptoms	Antibiotic treatment
British Thoracic Society	No increase in sputum purulence or radiographic changes consistent with pneumonia	Nil
	Increased sputum purulence	Aminopenicillin, macrolide, or tetracycline as first-line treatment
American Thoracic Society/European Respiratory Society	Increase in sputum volume or purulence	Amoxycillin–ampicillin, cephalosporins, doxycycline, or macrolides
	Increase in sputum volume or purulence and failed prior antibiotic treatment	Consider amoxicillin–clavulanate or fluoroquinolones as first-line antibiotics
Canadian Respiratory Society		
Group 0	Cough with sputum production in patient with no underlying lung disease	Likely caused by virus therefore no antibiotic unless protracted course
Group 1	Chronic bronchitis with mild to moderate impairment of lung function and less than 4 exacerbations a year	Aminopenicillins, doxycycline, or trimethoprim–sulphamethoxazole although may be better to use second-/third-generation cephalosporins or macrolides
Group 2	Significant airway obstruction and other co-morbidities for example cardiac disease	Direct treatment at resistant organisms using for example amoxicillin–clavulanate or fluoroquinolones
Group 3	Chronic bronchial suppuration with continuous purulent sputum production	Treatment as with Group 2 patients but note more at risk of *Pseudomonas aeruginosa*

S. pneumoniae also have decreased susceptibility to other antibiotic classes including macrolides, cephalosporins, and tetracyclines. *H. influenzae* and *M. catarrhalis* have also shown increased resistance due to β-lactamase production, and in the case of the former species other mechanisms as well (Wilson 2001). There is of course considerable geographical variation but the trend in all areas is increased resistance to commonly prescribed older antibiotics.

A retrospective study by Adams et al (2000) on patients treated for acute exacerbation of COPD in the emergency department showed patients had a decreased relapse rate (19%–32%) if treated with antibiotics. Another retrospective study by Destache et al (1999) showed use of a third-line agent (ciprofloxacin, azithromycin, or amoxycillin–clavulanate) as compared with a first-line agent (trimethoprim–sulphamethoxazole, amoxicillin, or tetracycline) resulted in fewer clinical failures, relapses, and admissions. The results of both these studies suggest that use of older first-line antibiotics may have, in some patients, a suboptimal response and this could in turn be due to limited in vitro activity against resistant bacterial pathogens (Sethi 2005). However, the retrospective design of the studies diminishes the weight of evidence that can be given to them.

Table 2 Limitations of older antibiotic study design in acute exacerbations of COPD

Small number of enrolled patients limits study power
Enrollment of patients with mild COPD or normal lung function with high rates of recovery diminishes perceived efficacy of antibiotics
No assessment of speed of recovery
Use of end points 3 weeks post treatment when spontaneous recovery may have occurred
Lack of long-term follow up and therefore no assessment of time to next exacerbation
No evaluation of concurrent medication likely to affect clinical outcome, allowing potential bias

Recent antibiotic studies

One of the current authors has been the lead investigator in two recent studies designed to show significant differences in outcome when comparing antibiotics. In an earlier study, Treatment of Acute exaCerbaTions of chronic bronchitis (TACTIC), the quinolone moxifloxacin was compared with clarithromycin (Wilson et al 1999). Patients with chronic bronchitis and symptoms of an Anthonisen type I or II exacerbation were enrolled. The primary end point was physician judgment at day 14 assessing whether the patient had improved sufficiently not to need further antibiotic treatment. The outcome showed equivalence with 89% in the moxifloxacin group and 88% in the clarithromycin group achieving a successful outcome. The study did, however, show that moxifloxacin was superior (77%) compared with clarithromycin (62%) in bacterial eradication. This was due to persistence of *H. influenzae* in the clarithromycin-treated patients. This disparity in outcome between bacterial eradication and clinical success might be explained by the severity of the patients enrolled (Anthonisen type 2 included) and/or the clinical end points chosen.

This study was followed by the GLOBE study (Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations). In this study the quinolone gemifloxacin was compared with clarithromycin (Wilson et al 2002). Again there was no statistically significant difference in the two treatment groups on the basis of short-term clinical outcome, and again the bacteriological eradication was higher with the quinolone. Patients were then followed up for 26 weeks. During this period, the primary outcomes were health-related quality of life, hospitalization, and frequency of repeated exacerbations. Gemifloxacin was associated with more patients remaining free of a further exacerbation (71% vs 58.5%) than clarithromycin. The rate of hospitalization in the gemifloxacin group was also lower (2.3% vs 6.3%). The hypothesis put forward was that incomplete bacterial eradication by the macrolide antibiotic may have led to a shorter interval until the next exacerbation.

The MOSAIC study (Moxifloxacin Oral tablets to Standard oral antibiotic regimen given as first line therapy in outpatients with Acute Infective exacerbation of Chronic bronchitis) was a large, multicenter, double-blind trial with 730 patients (Wilson et al 2004). These patients were randomized to receive the quinolone moxifloxacin, or standard therapy (amoxycillin, cefuroxime, or clarithromycin). The patient population enrolled were those thought most likely to benefit from antibiotics: an older population, greater than 20 pack-year smoking history, chronic bronchitis for more than 10 years, and significant co-morbidity. Patients were assessed in a stable phase to assess their health status so that post exacerbation a judgment could be made whether they had made a full or partial recovery. When patients had an Anthonisen type 1 exacerbation they were randomized to one of the two groups. The choice of the antibiotic in the second group was made by the physician. The patients were then assessed shortly after the end of treatment as in previous studies, but they were also followed up for 9 months. Once again in terms of symptomatic improvement the two groups showed equivalence. However, moxifloxacin had a superior rate of

clinical cure (return of patient to baseline status) compared with standard treatment. Moxifloxacin was also associated with fewer requirements for additional antibiotics in the weeks following the exacerbation (fewer cases of rapid relapse) and an extended time to the next exacerbation (14 days).

Not all studies have shown a longer exacerbation-free interval in patients treated with a quinolone as opposed to a macrolide. The recent study by Lode et al (2004) compared levofloxacin with clarithromycin. Levofloxacin was associated with a higher bacteriological eradication rate but similar exacerbation-free interval to patients treated with clarithromycin. The Lode study suggested that although bacteriological eradication rate was higher with levofloxacin, exacerbation-free interval was the same. A reason for this may have been that approximately 75% of patients recruited for the study only had moderate airflow obstruction and would therefore potentially have fewer exacerbations over a year. Another consideration may have been that patients who were non-smokers were also recruited. If our interpretation of the data from this study and others is correct, then the use of fluoroquinolones should be directed to an identifiable group of patients with COPD: older patients with more severe disease and comorbid illness.

Fluoroquinolone antibiotics

The first fluoroquinolone developed was nalixidic acid in 1962. Since then there have been various structural modifications resulting in the development of newer fluoroquinolones. The fluoroquinolones fall into three groups. Older agents such as ciprofloxacin and ofloxacin have excellent Gram negative cover but poorer Gram positive cover. The former remains the quinolone of choice against *P. aeruginosa*. Drugs such as levofloxacin were the next group of quinolones developed. They had better Gram positive cover especially against pneumococci. A third group of quinolones was developed including moxifloxacin and gemifloxacin that offered even better pneumococcal activity, and provided excellent broad-spectrum coverage, including the atypical species. However, the *P. aeruginosa* activity was correspondingly less. The therapeutic activity of the fluoroquinolones is influenced by the relationship between the plasma concentration profile, the area under the time-concentration curve (AUC), and the minimum inhibitory concentration (MIC) for particular organisms. The newer fluoroquinolones exhibit ratios that are greater for common respiratory pathogens than older members of the class (Balfour 1999; Perry 1999).

The fluoroquinolones work by their action on two enzymes involved in bacterial DNA replication: DNA gyrase and topoisomerase IV (Jones 2000). Point mutations resulting in single amino acid substitution in these enzymes result in resistance to fluoroquinolones. Another resistance method is an active efflux mechanism that extrudes the drug from the bacterial cell. Newer fluoroquinolones are less susceptible to efflux. It appears that more than one mutation is needed for significant resistance to the newer fluoroquinolones to develop (Obaji and Sethi 2001). Resistance to older fluoroquinolones such as ciprofloxacin or levofloxacin is more likely to occur and this in turn translates into partial resistance to newer fluoroquinolones such as moxifloxacin. Thus it may be preferable to use newer fluoroquinolones rather than the older classes for respiratory tract infections which require the antibiotic to cover all common respiratory pathogens including the pneumococcus. Drugs such as moxifloxacin with its favorable pharmacokinetic and pharmacodynamic properties allied with the above could, it is argued, delay the emergence of significant resistance (Obaji and Sethi 2001; Sethi 2005).

The newer fluoroquinolones have excellent oral bioavailability. Their prolonged half-lives allow once-daily administration which should have a positive benefit on compliance. The cytochrome p450 system in the liver is not extensively involved in the metabolism of the newer fluoroquinolones thus decreasing potential for drug–drug interactions (Obaji and Sethi 2001). The extent and rate of absorption may be reduced by cations such as magnesium, aluminium, or iron products (commonly found in antacids) which bind the antibiotic.

The most common side-effects of fluoroquinolones are gastrointestinal (nausea and diarrhea) and headache. Tendonitis, tendon rupture, and convulsions can occur very rarely (Fogarty et al 1999). Gatifloxacin may cause disturbances in glucose metabolism and therefore it should be used with caution. This finding is not solely in those with diabetes, but particular care should be taken with this group of patients (Park-Wyllie et al 2006). Another potential side-effect of the class is photosensitivity. The incidence of this has been observed most in those taking sparfloxacin and lomefloxacin. Fluoroquinolones are associated with prolongation of the QTc interval and associated torsades de pointes. With moxifloxacin and gatifloxacin the mean QTc prolongation is 6 msec and 5 msec respectively. The estimated incidence of torsades de pointes is 1–3 per million exposures. It is important to note that those who experience

torsades de pointes whilst receiving QTc-prolonging drugs often have multiple risk factors. These include ischemic heart disease, electrolyte abnormalities, congenital QTc syndromes, and concomitant use of other QTc-prolonging drugs (De Ponti 2000). The use of fluoroquinolones should be with caution in these patients. The fluoroquinolone grepafloxacin was withdrawn because of rare but significant incidence of torsades de pointes. Trovafloxacin use has been markedly restricted in the US and withdrawn in the UK because of a risk of severe liver toxicity.

Fluoroquinolones and exacerbations of COPD

There has been considerable debate about whether, and to what extent, fluoroquinolones should be used in COPD. There is concern over resistance developing if the drugs are used to treat common conditions, their side-effects, and the perceived lack of superiority over comparators (Obaji and Sethi 2001; Sethi 2005; Wilson 2005). Antibiotics should be used judiciously during COPD exacerbations and guidelines have highlighted purulent sputum, disease severity, and comorbid illness as important factors when making the decision. Using newer fluoroquinolones with an improved spectrum of activity for respiratory pathogens, shorter courses of treatment and correct dosage will make emergence of resistance less likely. The MOSAIC and GLOBE trials have shown that to demonstrate superiority against older comparators there needs to be different end points (Wilson 2002; Wilson 2004). Superior bacterial eradication in these trials led to longer time intervals between exacerbations, and in the MOSAIC trial fewer rapid relapses. However, these were secondary end points and the primary end points showed equivalence. Furthermore, this increase in exacerbation-free interval was not found by Lode et al (2004) with levofloxacin. Therefore, at this time, despite the promising results of the MOSAIC and GLOBE trials, there is insufficient evidence to recommend fluoroquinolones compared with other classes of antibiotic to treat all exacerbations of COPD. The frequency of exacerbations regardless of cause contributes not only to loss of lung function but also to poorer quality of life (Seemungal et al 1998; Kanner et al 2001; Andersson 2002). Bacterial colonization is associated with an increase in severity and frequency of future exacerbations (Patel et al 2002). In view of this, perhaps bacterial eradication should be a goal of greater importance. Bacterial eradication is least likely to occur in patients in whom the host defences are most impaired. Future antibiotic studies should at least follow patients up for several weeks after the end of treatment to study bacterial eradication and capture rapid relapses.

COPD is a heterogenous disease, and acute exacerbations can be of varying severity, partly dependent upon the type of patient in which they occur (Sethi 2005). Identifiable risk factors for poor outcome include older age (over 65 years old), severe obstructive lung disease (FEV_1 <50%), frequent exacerbations (>4 per year) and the presence of co-existent cardiac disease (Adams et al 2000; Balter et al 2003; Obaji and Sethi 2001; Wilson et al 2006). Patients with one or more of these risk factors may benefit most from fluoroquinolones. This group is also likely to have had more frequent courses of antibiotics and therefore be more susceptible to carrying resistant organisms (Wilson 2005). When fluoroquinolones are used in COPD exacerbations (with the exception of those infected with *P. aeruginosa* for which ciprofloxacin is the most active) the newer members of the class should be used. They have favorable pharmacokinetic and pharmacodynamic characteristics, a broad spectrum of cover, fewer drug interactions, as well as a lower potential for the development of resistance. These comments are similar to those proposed in the Canadian guidelines (Balter et al 2003), but future clinical studies should seek to strengthen the evidence base for this approach.

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