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Editorial

The need for a new fluoroquinolone

Nearly 80% of the acute exacerbations of chronic bronchitis (AECB) are of infectious origin, with 40–50% caused by bacteria, 30% by viruses, and 5–10% by atypical bacteria [1]. Pathogens commonly associated with AECB are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* [2]. Other less common pathogens related to AECB include *Haemophilus parainfluenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* family [1]. Moreover, *Chlamydia pneumoniae* has been associated with a small portion of AECB, an observation based on serological evidence [1].

A number of clinical investigations have demonstrated the efficacy of antibiotics in AECB, especially in patients with at least two of the three symptoms, namely increased dyspnoea, increased sputum volume and sputum purulence [3], and with more severe airflow obstruction [4]. Therefore, the choice of antibiotic is important. Since office-based physicians can rarely, if ever, obtain sputum samples allowing them to identify pathogens causing lower respiratory tract infections, the initial antimicrobial therapy by the primary-care physician is usually empiric and needs to cover the most likely pathogens [5]. Usually, empiric therapy is left to the physician's judgment. This decision takes into consideration factors concerning the individual patient, together with the microbial and resistance patterns found in the physician's local territory [6]. The empiric antibiotic treatment of AECB has been accepted as standard practice in general also due to the recognized inaccuracies of sputum culture and the time required before culture results are available [5].

Older antimicrobial therapies for acute exacerbation of chronic bronchitis, such as amoxicillin, doxycycline, early-generation cephalosporins (e.g. cefaclor or cephalexin) and trimethoprim-sulphamethoxazole, have all been used extensively in the past to treat episodes of acute exacerbation of chronic bronchitis [7]. Since the 1970s, ß-lactam resistance and resistance to multiple classes of antibiotics have been steadily increasing worldwide, limiting the therapeutic options for treatment of some infections [8]. A report on 1998–2000 data from the Alexander Project found ß-lactamase production in 29.6% of *H. influenzae* from the US, showing a 6.3% increase compared to the 1997 data [9]. Penicillin-resistant *S. pneumoniae* has also been identified worldwide with a prevalence of penicillin resistance varying from very low in Northern Europe to approximately 40% in France, Spain, and the US, and up to 80% in Hong Kong and South Korea. Macrolide resistant *S. pneumoniae* has recently spread worldwide resulting, for many countries, in a higher prevalence of macrolide resistant *S. pneumoniae* than penicillin-resistant *S. pneumoniae*. Strains of *S. pneumoniae* resistant to both penicillin and macrolides are common, posing treatment problems with these classes of antibiotics [10]. Multidrug-resistant *S. pneumoniae* (MDRSP) are strains resistant to three or more classes of antibiotics, and 26% of *S. pneumoniae* are currently resistant to at least three different classes of antibacterial agents [9].

Fluoroquinolone antibacterial agents have been available for over 15 years; however, with the increasing resistance to ß-lactams and macrolides, fluoroquinolones have now begun to be widely used for treatment of respiratory tract infections including AECB. The original quinolone, nalidixic acid, had a limited use due its to low intrinsic activity and the rapid development of bacterial resistance. The addition of fluorine to the quinolone molecule expanded the spectrum of activity of quinolones, as exemplified by ciprofloxacin, which was introduced in 1987. However, whilst it has a broad spectrum of activity against Gram-negative bacteria, it also shows less active against Gram-positive bacteria, particularly *S. pneumoniae*. A further manipulation of the quinolone nucleus has led to development of fluoroquinolones with enhanced in vitro activity against *S. pneumoniae*, which jointly with their wide spectrum of activity, justifies their use in the empirical treatment of respiratory tract infections [11]. Of these newer fluoroquinolones, levofloxacin, gemifloxacin and moxifloxacin are currently available, whereas grepafloxacin, sparfloxacin and trovafloxacin have been withdrawn because of severe side effects.

Indeed, due to their potency, their broad spectra of antimicrobial activity, favourable pharmacokinetics, and safety profile, newer fluoroquinolones have been recommended as first-line therapy for patients with AECB who are at higher risk of failure with standard therapies [12,13]. The excellent distribution of fluoroquinolones in the respiratory tissue may contribute to explain the high-efficacy rates observed in patients with respiratory

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infections. The emergence of fluoroquinolone resistance among respiratory pathogens has been uncommon, although sporadic examples of resistance developing in patients with chronic obstructive pulmonary disease or bronchiectasis have been observed [14].

The inventory of tools for treating AECB, including those caused by antibiotic-resistant organisms, has significantly expanded over the past few months with the marketing of prulifloxacin, the lipophilic prodrug of ulifloxacin, a novel oral fluoroquinolone antibacterial agent with a broad spectrum of in vitro activity against Gram-negative and -positive bacteria [15].

A careful evaluation of the activity of prulifloxacin against *S. pneumoniae* needs to be made before it can be considered suitable for the empirical therapy of AECB. Susceptibility of *Streptococcus* spp. (including *S. pneumoniae*) to ulifloxacin varies between countries [16,17]. Italian community isolates of *S. pneumoniae* were susceptible to ulifloxacin (MIC_{90} 1.0 mg/L) [16], while ulifloxacin (and ciprofloxacin) showed moderate or low activity against Spanish penicillin-susceptible, -intermediate or -resistant strains of *S. pneumoniae* (ulifloxacin or ciprofloxacin MIC_{90} values of 2–4 mg/L), unlike moxifloxacin (all MIC_{90} 0.12 mg/L) [17].

Although a useful measure of relative antibacterial activity, the MIC value is not a precise indicator of clinical utility because pharmacokinetic characteristics are not accounted for. The combined effect of pharmacokinetic characteristics and intrinsic activity (i.e. MIC) dictate the pharmacodynamic properties of each antibacterial [18]. The MIC represents the pathogen-specific variable in pharmacodynamic ratios [19]. It has been suggested that the AUC_{24}/MIC ratio is the most important pharmacokinetic characteristic for concentration-dependent antibacterial agents, such as fluoroquinolones. With fluoroquinolones, a ratio of at least 30 is required to expect a positive clinical or microbiological outcome against infections caused by *S. pneumoniae* [20]. The most likely reason for a drop in fluoroquinolone AUC_{24}/MIC ratio (unless a patient has an underlying physiological problem) is an infection caused by a fluoroquinolone-resistant *S. pneumoniae*, which has a high MIC. However, it must be emphasized that MICs can vary significantly depending on the methodology and specimen source used. Moreover, the site of infection may also affect the 'true' MIC for a given pathogen owing to the effects of environmental conditions on MIC [21]. It is clear that values defined for pharmacodynamic outcome parameters based on the site of infection may be necessary.

Ulifloxacin has an extended elimination half-life that in humans, ranged from 10.6 to 12.1 h after prulifloxacin 300–600 mg single-dose [15], allows for once-daily dosing, and penetrates extensively into the respiratory tissues. Lung tissue concentrations exceed those of plasma or serum, and the drug persists in the lung tissue for 24 h after a single dose [15]. The high and prolonged penetration of prulifloxacin into the pulmonary tissues leads to a greater AUC_{24}/MIC ratio when tissue pharmacokinetics and pharmacodynamics are considered, that is rather different from that in blood. This essential difference may explain why prulifloxacin has shown active in vivo against the majority of *S. pneumoniae* strains present in the sputum of patients with AECB [15].

Prulifloxacin's pharmacokinetic/pharmacodynamic behaviour and the possibility of using this agent on a once-daily basis, favouring patient compliance with therapy—a key factor in the successful treatment of any infection [22]—accounts for considering prulifloxacin an interesting antibacterial option for the treatment of AECB.

This prospect is explored in the light of currently available evidence-based data in the papers of this Supplement, with particular regard to the scientific background and the clinical experience in the use of prulifloxacin in AECB, which represents one of the most stimulating challenges for the clinician in view of the impact of exacerbation on the progression of the underlying disease.

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