Lower respiratory tract infections: etiology, current treatment, and experience with fluoroquinolones

Ethan Rubinstein¹, Claude Carbon², Manickam Rangaraj³, Jose Ignacio Santos⁴, Jean-P. Thys⁵ and Pierre Veyssier⁶

¹Infectious Diseases Unit, Sheba Medical Center, Tel Aviv University School of Medicine, Tel-Hashomer, Israel; ²Internal Medicine Unit, CHU Bichat–Claude Bernard, Paris, France; ³Clinical Studies Operations, Hoechst Marion Roussel, Romainville, France; ⁴Faculty of Medicine, UNAM, San Jeronimo, Mexico; ⁵Department of Infectious Diseases, Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium; ⁶Department of Internal Medicine, Centre Hospitalier de Compiegne, Compiegne, France

INTRODUCTION

Lower respiratory tract infections (LRTIs) are among the most common infections in humans, comprising approximately 45% and 25% of all community-acquired and nosocomial infections, respectively [1]. Early diagnosis is often essential to avoid the severe morbidity and the risk of hospitalization associated with many LRTIs. Identification of the relevant pathogens before antibiotic therapy is initiated is still problematic, however, and treatment is frequently empirical. Consequently, antibiotics with a spectrum adapted to the range of pulmonary pathogens are generally preferred.

The ability to penetrate into pulmonary tissues, cells, and fluids, reaching concentrations which inhibit or kill the causative organisms, seems to be an important characteristic of the ideal antimicrobial agent for the treatment of LRTIs, although its clinical relevance in humans has not been fully assessed. Fluoroquinolones penetrate very well into the lung, and may achieve bronchial and pulmonary concentrations that equal or exceed serum concentrations [2]. In addition, intracellular concentrations are also within the therapeutic range for the majority of intracellular pathogens causing LRTIs. Conversely, most β-lactam antibiotics do not exceed 50% of their serum level within bronchial secretions, and some agents, such as aminoglycosides, only reach 30–40% of their serum level in the lung, and less in the inter- and intracellular milieu [2,3].

There is, at present, a general trend to reduce the duration of therapy in order to reduce the possible development of adverse events and resistance, whilst maintaining clinical efficacy, and to improve the cost-effectiveness of treatment and decrease hospitalization time. Also important is the increasing use of step-down or switch therapy, whereby treatment is started with intravenous administration and then continued with an oral formulation [4]. This has several advantages, including pharmacoeconomic advantages and improved patient compliance.

This paper focuses on the causative pathogens in LRTIs, the current approaches to treatment, and the experience to date with fluoroquinolones. Although the use of some fluoroquinolones, particularly ciprofloxacin, in the treatment of cystic fibrosis is well documented, the topic was not discussed at this meeting, which was focused on the treatment of infections in adult patients.

CHRONIC BRONCHITIS (ACUTE EXACERBATIONS)

Definition and diagnosis

Chronic bronchitis is persistent inflammation and irritation of the bronchial tree which is classically defined as symptoms of cough with sputum production
during 3 consecutive months over 2 consecutive years with periodic acute exacerbations during which symptoms worsen [5]. It is generally a progressive condition which is closely linked to smoking, and is most frequently found in older men (> 40 years old). Chronic bronchitis is very common, affecting up to 25% of the adult population. During periods of acute exacerbation, when inflammation and infection are worsened, antibiotic therapy is usually instituted. Signs and symptoms of acute exacerbations include: a change in the amount, consistency and color of the sputum; increased dyspnea; productive cough; tachypnea; chest tightness; increased fatigue; and, especially in the elderly, confusion. In addition, physical examination may reveal rales and ronchi and, at times, prolonged exhalation.

Etiology
The bacterial species commonly associated with acute exacerbations of chronic bronchitis are relatively non-virulent, usually forming part of the flora of the upper respiratory tract [6]. Non-typeable *Haemophilus influenzae* accounts for approximately 70% of isolates from patients with acute exacerbations of chronic bronchitis. The airways are thought to become colonized through interaction between specific bacterial adhesions and epithelial cell receptors [7]. When *H. influenzae* is introduced into the respiratory tract, it is normally removed rapidly by mucociliary clearance, but in individuals with impairment of this host defense mechanism it remains attached longer to pooled mucus, allowing surface contact with areas of damaged bronchial epithelium. Further damage to the epithelium, resulting from bacterial toxins and metabolic products, could help the bacterium to spread through the respiratory tract [6]. *Streptococcus pneumoniae* is another commonly encountered bacterium responsible for purulent exacerbation, and *Moraxella catarrhalis* may also be implicated in a smaller number of cases [8,9]. *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are infrequent causes. Other bacteria that can be involved in acute exacerbations of chronic bronchitis as either exclusively predominant or mixed pathogens include *Neisseria* spp., *Bordetella* spp., *Rhodococcus* spp. and anaerobes. The role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in chronic bronchitis should be considered.

Treatment
Oral penicillins are effective against Gram-positive cocci and bacilli and are used to treat infections caused by penicillin-susceptible pneumococci and streptococci in adults and children [10]. They are not active against β-lactamase-producing microorganisms or ‘atypical’ pathogens. Oral cephalosporins are often used and the oral first-generation cephalosporins (cefalexin, cefadroxil, cefadine and cefaclor) are effective against penicillin-susceptible Gram-positive organisms but show restricted efficacy against penicillin-resistant Gram-positive organisms but show restricted efficacy against penicillin-resistant *Streptococcus pneumoniae*, Enterobacteriaceae and β-lactamase-positive *H. influenzae* [10]. Trimethoprim, sulfamethoxazole and amoxycillin/clavulanic acid are also time-honored treatments.

**Fluoroquinolones**
In the treatment of acute exacerbation of chronic bronchitis, ciprofloxacin (500 mg twice daily) has been shown to be as effective as amoxycillin/clavulanic acid (875 mg/125 mg twice daily) or cefixime (400 mg once daily) in a study of 218 outpatients [11]. Eradication rates of 81%, 82% and 78% were reported with ciprofloxacin, amoxycillin/clavulanic acid and cefixime, respectively. Moreover, clinical success was obtained in 86% of patients treated with ciprofloxacin, 91% of the cases treated with amoxycillin/clavulanic acid, and 81% of the cefixime group.

Ofloxacin has also been shown to be effective [12-14]. Chodosh reviewed the use of enoxacin, ciprofloxacin, ofloxacin and temafloxacin in acute exacerbations of chronic bronchitis, and the last three were generally more effective than enoxacin [15]. DeAbate et al compared sparflaxacin and ofloxacin in a double-blind study. Overall response rates, defined as cure or improvement of clinical signs and symptoms and eradication or presumed eradication of pathogens, were 85.4% and 88.8%, respectively [16]. The combined eradication and presumed eradication rates were 89.9% and 92.5%, respectively.

The results of two multicenter studies of levofloxacin in the treatment of acute bacterial exacerbations of chronic bronchitis are summarized in Table 1 [17,18]. In the first study, in which levofloxacin was compared with cefaclor, the greatest difference in terms of response of individual pathogens was seen with *H. influenzae* (100% versus 71% eradication) [17]. Eradication rates for *Streptococcus pneumoniae* and *Staphylococcus aureus* were 90% and 89%, respectively, for levofloxacin, compared with 86% and 67% for cefaclor. Moreover, overall rates of bacteriologic resistance were 24% in the cefaclor group and 2% in the levofloxacin group. In the second study, levofloxacin was found to have comparable efficacy to that of cefuroxime axetil, with clinical success in 95% of levofloxacin-treated patients and 93% of patients treated with cefuroxime axetil [18].
### Table 1  Levofloxacin in the treatment of acute exacerbations of chronic bronchitis [17,18]

<table>
<thead>
<tr>
<th>Drugs and dosage</th>
<th>Duration (mean days)</th>
<th>Clinical response (no.)</th>
<th>Bacteriologic response (no.)</th>
<th>Overall rate of adverse events (no.)</th>
<th>Most common adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 (Habb et al [17])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral levofloxacin, 500 mg o.d.</td>
<td>6.6</td>
<td>92% (154)</td>
<td>94% (103)</td>
<td>7% (187)</td>
<td>Nausea (2.1%)</td>
</tr>
<tr>
<td>Oral cefadroxil, 250 mg t.i.d.</td>
<td>8.7</td>
<td>92% (155)</td>
<td>87% (89)</td>
<td>4.9% (186)</td>
<td>Diarrhea (2.2%)</td>
</tr>
<tr>
<td>Study 2 (DeAbate et al [18])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral levofloxacin, 500 mg o.d.</td>
<td>7</td>
<td>95% (222)</td>
<td>96% (134)</td>
<td>9.9% (NR)</td>
<td>Vomitus (2%)</td>
</tr>
<tr>
<td>Oral cefuroxime axetil, 250 mg b.i.d</td>
<td>10</td>
<td>93% (229)</td>
<td>93% (147)</td>
<td>7.9% (NR)</td>
<td>Diarrhea (3%)</td>
</tr>
</tbody>
</table>

NR, not reported.

o.d. once daily.

### ACUTE BRONCHITIS

#### Definition and diagnosis

Acute bronchitis is characterized by an acute inflammation of the bronchi, usually caused by viral infections such as influenza, rhinovirus or the 'common cold'. In general, it is clinically characterized by the presence of an acute, non-productive cough in patients without underlying lung disease. On the other hand, bacterial infection usually causes fever and sometimes chills and is usually an acute, severe illness compared with viral infection, which is accompanied by a low fever and milder symptoms in the early stages. Sputum is purulent and plentiful in bacterial infection and rare in viral infection.

#### Etiology

Acute bronchitis is a viral illness (influenza virus, adenovirus and rhinovirus account for the majority of cases). The incidence of primary bacterial infection is difficult to assess. The roles of *H. influenzae* and *Streptococcus pneumoniae* are unclear and those of *Mycoplasma pneumoniae*, *Chlamydia pneumonia* and *B. pertussis* also need to be considered.

#### Treatment

Viral respiratory infections usually have a benign course without fever and purulent sputum production. Symptoms decline within 7 days of onset. Antibiotics are not usually recommended. In prolonged cases, or documented bacterial infection, β-lactams and macrolides have been used.

### NOSOCOMIAL PNEUMONIA

The microbiological etiology of pneumonia is extremely variable, depending on whether it is community-acquired or nosocomial [19]. The virulence of the causative organism is the main determinant of the disease process, although there may be a predisposition to pneumonia caused by reduced host defenses, particularly suppression of the cough reflex, impairment of mucociliary clearance, the presence of a foreign body or reduced systemic and local immunity.

#### Definition and diagnosis

Patients with nosocomial pneumonia usually have a variety of severe underlying diseases and are often immunocompromised. They also receive a wide range of medication and supportive management which increases their susceptibility to infectious complication: intubation, in particular, poses an extreme risk for the development of pneumonia. Clinical signs and symptoms are characterized by a sudden onset of malaise, fever, chills, increased sputum production and leukocytosis. In almost all cases, an infiltrate is recognizable on chest X-rays.

#### Etiology

The spectrum of nosocomial pneumonia pathogens includes, in addition to most bacteria causing community-acquired pneumonia, Gram-negative bacteria such as *K. pneumoniae*, *Escherichia coli*, *Acinetobacter spp.*, *P. aeruginosa* and related organisms, *Staphylococcus aureus* and, occasionally, fungi. However, Gram-negative bacteria are the predominant pathogens, while *Streptococcus pneumoniae* and *H. influenzae* are not generally considered significant. A polymicrobial etiology is detected in 10–30% of cases of nosocomial pneumonia.

#### Treatment

Nosocomial pneumonia is the second most important nosocomial infection. It prolongs hospital stay and is also associated with substantial mortality. In most cases, parenteral drug administration is used. The choice of antibiotic and dosage regimen vary depending on the spectrum of potential pathogens, and the assessment of a variety of factors, including the severity of the pneumonia, the presence of specific coexisting illness, prior therapy (including antibiotics), and the
duration of hospitalization. Monotherapy with second-generation cephalosporins has been shown to be highly successful in cases without severe underlying illness [20]. Patients who belong to special risk groups, such as patients with underlying diseases or elderly patients with pronounced clinical symptoms, are often treated with second-generation cephalosporins in conjunction with aminoglycosides, or ureidopenicillins (piperacillin, azlocillin, mezlocillin) in combination with aminoglycosides, or with third-generation cephalosporins, with or without the addition of a macrolide. Erythromycin and other macrolides have good activity against streptococci, pneumococci and Legionella, Mycoplasma and Chlamydia spp. but borderline activity against H. influenzae [21]. Erythromycin has the disadvantage of a gastrointestinal intolerance rate of up to 30%. The new macrolides have fewer gastrointestinal side effects [22]. For patients with severe concomitant diseases and respiratory insufficiency, third-generation cephalosporins such as ceftazidime, cefepime, cefpirome, ceftiraxone or carbapenems, at high dosage, may be prescribed as monotherapy or in combination with other antibiotics. An alternative therapy in patients who cannot be treated with β-lactams is the use of intravenous and, subsequently, oral fluoroquinolones.

Fluoroquinolones
Ciprofloxacin has been shown to be as effective as imipenem as monotherapy in treating severe nosocomial pneumonia [23]. In a multicenter study of 189 patients with severe hospital- (84%) or community-acquired (16%) pneumonia, intravenous ciprofloxacin at high doses (400 mg every 8 h) resulted in significantly better rates of clinical cure or improvement than that achieved with imipenem (1 g every 8 h) and a significantly higher rate of bacteriologic eradication [24]. This was thought to result from the significantly higher rate of bacteriologic eradication of Enterobacteriaceae in the ciprofloxacin group (93% versus 66%, p = 0.001). In an open study in 50 patients, Peloquin et al showed that intravenous ciprofloxacin 200 mg twice a day was effective against Gram-negative pathogens, although P. aeruginosa was eradicated in less than 50% of patients [25]. Gentry et al reported that ofloxacin (400 mg b.i.d.) was effective in nosocomial pneumonia, and Petermann reported an overall satisfactory response rate of 93% in 109 patients treated with ofloxacin 200 mg twice a day [26,27].

COMMUNITY-ACQUIRED PNEUMONIA

Definition and diagnosis
Pneumonia is defined as inflammation and consolidation of the lung tissue due to an infectious agent. Symptoms indicative of pneumonia are fever, chills, pleuritic chest pain and cough with purulent sputum. Microbiological diagnosis is often difficult, particularly if the patient does not produce sputum.

Etiology
Streptococcus pneumoniae is responsible for the majority of cases of community-acquired pneumonia (CAP). Complications usually result from invasion of the bloodstream, causing bacteremia with shock, meningitis and septic arthritis. H. influenzae infection is another major cause, and other common pathogens include Monaxella catarrhalis and respiratory viruses. Staphylococcal pneumonia is associated with viral (influenza) infection. Gram-negative pathogens are found most frequently in high-risk patients such as the elderly or multimorbid patients, or during immunosuppressive treatment [28]. Up to 10% of cases of CAP may be caused by two or more aerobic pathogens, with Streptococcus pneumoniae and H. influenzae being the most commonly identified combination. The most common atypical pathogen is Mycoplasma pneumoniae, followed by Chlamydia pneumoniae and L. pneumophila, and together they account for approximately 30–40% of cases. The incidence of Coxiella burnetii is diversely reported.

Treatment
Although a Gram stain of bronchial secretions can help direct therapy, the treatment strategy for CAP is necessarily empirical in most cases, including in the outpatient setting. Immediate therapy is necessary as soon as possible after diagnosis because of the potential for severe morbidity, particularly at onset. An antibiotic with a spectrum adapted to the potential pathogens is generally recommended. There are no characteristic and specific clinical features that correlate with the etiologic diagnosis. Erythromycin and clarithromycin have been shown to be effective against most of the causative pathogens, including Mycoplasma, Chlamydia and Legionella. Aminopenicillins or oral cephalosporins may be used when atypical pathogens are not thought to be the causative organisms.

Various countries have developed guidelines for the empirical treatment of CAP. The American Thoracic Society, the British Thoracic Society, the Canadian Community-acquired Pneumonia Consensus Group and the French guidelines are summarized in Table 2 [29–31]. The existence of different guidelines which incorporate varying recommendations highlights the need for consensus in this therapeutic area.

Fluoroquinolones
Fluoroquinolones are characterized by an antibacterial spectrum adapted to most respiratory pathogens and
Table 2  Recommendations for the empirical treatment of community-acquired pneumonia [29–31]

<table>
<thead>
<tr>
<th>British Thoracic Society (1993)</th>
<th></th>
</tr>
</thead>
</table>
| Uncomplicated pneumonia of unknown etiology without features indicating severe or non-pneumococcal disease | Preferred: an aminopenicillin (amoxycillin 500 mg orally t.i.d. or ampicillin 500 mg IV q.i.d. or benzylpenicillin 1.2 g IV q.i.d.)  
Alternative: erythromycin (500 mg orally or IV q.i.d.) or second- or third-generation cephalosporin (ceftaxime or cefotaxime)  
Severe pneumonia of unknown etiology | Preferred: erythromycin (1 g IV q.i.d.) + second- or third-generation cephalosporin (ceftaxime 1.5 g or cefotaxime 2 g IV t.i.d.)  
Alternative: ampicillin 1 g, fluociclovinit 2 g, and erythromycin 1 g. all IV q.i.d.  |

|--------------------------------|----------------------------------|
| Outpatient pneumonia without co-morbidity and age ≤60 years | Preferred: macrolide (erythromycin; alternative (clarithromycin or azithromycin) with erythromycin intolerance and in smokers (to treat H. influenzae)  
Alternative: tetracycline  |
| Outpatient pneumonia with co-morbidity and/or age ≥60 years | Second-generation cephalosporin, trimethoprim-sulphamethoxazole, or β-lactam-β-lactamase inhibitor ± erythromycin or other macrolide if Legionella suspected  |
| Hospitalized patients | Second- or third-generation cephalosporin or β-lactam-β-lactamase inhibitor ± erythromycin if legionellosis is a concern; rifampin may be added if Legionella is documented  |
| Severe community-acquired pneumonia | Macrolide (with rifampin if legionellosis) plus third-generation antipseudomonal cephalosporin or other antipseudomonal therapy; including imipenem or ciprofloxacin plus an aminoglycoside  |

<table>
<thead>
<tr>
<th>Canadian Community-acquired Pneumonia Consensus Conference Group (1993)</th>
<th></th>
</tr>
</thead>
</table>
| Not severe | Previously well and ≤65 years  
Macrolide or tetracycline  
Co-morbid illness or > 65 years  
Second-generation cephalosporin, trimethoprim-sulphamethoxazole, or penicillin + β-lactamase inhibitor ± macrolide  
Nursing home acquired  
Second-generation cephalosporin, trimethoprim-sulphamethoxazole, or amoxycillin-clavulanic acid ± macrolide  |
| Severe | Hospital ward  
Second- or third-generation cephalosporin ± macrolide ± rifampin; penicillin allergy: trimethoprim-sulphamethoxazole + macrolide  
Intensive care unit  
Macrolide (rifampin ± antipseudomonal cephalosporin, imipenem or ciprofloxacin  
Nursing home acquired (treatment in nursing home)  
Oral penicillin + ciprofloxacin or second-generation cephalosporin ± oral macrolide or cotrimoxazole (TM) ± oral macrolide; penicillin allergy: ciprofloxacin plus clindamycin (TM)  |

<table>
<thead>
<tr>
<th>French Language Society of Infectious Diseases (1992)</th>
<th></th>
</tr>
</thead>
</table>
| Apparently healthy adults with no features indicating severe disease | Aminopenicillin (usually 1 g t.i.d.) or a macrolide. Treatment should be reappraised after 48–72 h  
Debilitated high-risk adults | Aminopenicillin/clavulanic acid or oral cephalosporin. Macrolide or fluoroquinolone if L. pneumophila suspected  
Severe | Parenteral combination therapy. Aminopenicillin/clavulanic acid or third-generation cephalosporin + macrolide or fluoroquinolone  |

Adapted from Bartlett and others [29–31].

rapid bactericidal activity. They are active against Gram-negative bacilli, including *H. influenzae*, *Enterobacteriaceae*, *Pseudomonas* spp. and *Acinetobacter* spp., and Gram-positive bacteria, including *Staphylococcus aureus*, coagulase-negative staphylococci and some streptococci, with variable activity against *Streptococcus pneumoniae*. They have good activity against *H. influenzae*, *Mycoplasma catarrhalis* and all the pathogens that cause atypical pneumonia. Prior to the introduction of ciprofloxacin, their spectrum was limited, as it did not encompass the main respiratory pathogens. When ciprofloxacin was introduced, it was initially hoped that it might provide an adequate therapy for CAP. However, problems with ciprofloxacin's poor activity against *Streptococcus pneumoniae* meant that ciprofloxacin itself, and the fluoroquinolones as a class, would not be suitable for the treatment of pneumococcal pneumonia. This situation is now changing with the introduction of the newer fluoroquinolones, with improved activity against these pathogens, particularly...
Table 3 In vitro activity (MIC₉₀ range or mean (mg/L)) of selected fluoroquinolones against respiratory tract pathogens [19,32–40]

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Sparfloxacin</th>
<th>Trovafloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0.5–4</td>
<td>1.91</td>
<td>0.25–1</td>
<td>0.2</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin susceptible</td>
<td>0.25–2</td>
<td>0.12–0.78</td>
<td>0.06–0.25</td>
<td>0.12</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin resistant</td>
<td>0.5–16</td>
<td>0.39–0.78</td>
<td>0.06–0.25</td>
<td>0.03</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>0.003–0.006</td>
<td>0.02–0.05</td>
<td>0.008–0.06</td>
<td>0.05</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>0.01–0.25</td>
<td>0.02–0.11</td>
<td>0.01–0.12</td>
<td>0.05</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>0.78–2</td>
<td>0.5–1</td>
<td>0.1–0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>2</td>
<td>0.5</td>
<td>0.01–0.25</td>
<td>0.5–1</td>
</tr>
<tr>
<td><em>Legionella spp.</em></td>
<td>0.05</td>
<td>0.05–0.1</td>
<td>0.025</td>
<td>0.004</td>
</tr>
<tr>
<td><em>L. pneumophila</em></td>
<td>0.008–0.06</td>
<td>0.125</td>
<td>0.004–0.06</td>
<td>0.004</td>
</tr>
</tbody>
</table>

MIC₉₀ = minimum concentration required to inhibit 90% of pathogens.

*Streptococcus pneumoniae.* Table 3 summarizes the in vitro activity of one of the established fluoroquinolones, ciprofloxacin, and the activities of three new fluoroquinolones, levofloxacin, sparfloxacin and trovafloxacin against the main respiratory tract pathogens [19,32–40].

Ciprofloxacin has been extensively prescribed in the treatment of LRTIs [41]. However, a succession of anecdotal reports of relatively poor performance of ciprofloxacin against *Streptococcus pneumoniae* led to a change in the package labeling in the USA, cautioning against the use of currently available fluoroquinolones in the treatment of pneumococcal infections [42–45]. This was also partly responsible for an increase in the recommended dosage regimen of intravenous ciprofloxacin from 200 mg twice daily to 400 mg twice or three times daily.

Several studies have reported the use of ofloxacin in the treatment of CAP. In a comparative study with erythromycin, Nielsen et al showed combined cure/improvement rates of 96% for ofloxacin and 82% for erythromycin [46]. Plouffe et al showed that ofloxacin was as effective as standard therapy (β-lactam alone or plus a macrolide) in patients hospitalized for CAP (clinical success rates of 92% and 87%, respectively) [47]. An overall satisfactory response rate of 93% in 212 patients was reported by Petermann [27].

Carbon et al compared tamiroxacin and amoxicillin in a study of 246 hospitalized patients [48]. Overall, there were no significant differences between tamiroxacin and amoxicillin in clinical recovery rates (85%, 80%) and bacterial eradication rates (98%, 96%). Both were equally effective in treating pneumococcal infections. Although several additional studies demonstrated the efficacy of tamiroxacin in CAP, this antibiotic was withdrawn from use in 1992 due to the high incidence of serious adverse events.

Sparfloxacin is active against all major LRTI pathogens, including atypical organisms such as *L. pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [49]. However, severe phototoxic reactions have been associated with its use which have led to prescribing restrictions. Sparfloxacin shows rapid and high diffusion into respiratory tract tissues and fluids, with concentrations of 2.6 mg/L in bronchial mucosa, 9.8 mg/L in the epithelial lining fluid and 61.3 mg/L in alveolar macrophages 12 h after an oral loading dose of 400 mg [50].

Several studies in CAP have been performed with this antibiotic. Two double-blind studies compared the efficacy of sparfloxacin (200 mg once daily, following a 400-mg loading dose) with that of amoxycillin/clavulanic acid (500/125 mg three times daily), erythromycin (1000 mg twice daily) or amoxycillin (1000 mg three times daily) [51]. The results of these studies were pooled to encompass 1137 episodes of CAP in hospitalized patients (560 were treated with sparfloxacin and 577 were randomized to the comparator agents), showing that sparfloxacin had similar efficacy to that of the comparators, with global efficacy rates of 88% and 84%, respectively.

Another study compared sparfloxacin 200 mg once daily with a combination of amoxycillin 1 g three times daily and ofloxacin 200 mg twice daily for 10 days [52]. The placebo-controlled, double-blind randomized study was conducted in 211 hospitalized elderly patients or in cases of first antibiotic treatment failure. Of the isolated pathogens, 40% and 36% were identified as *Streptococcus pneumoniae* in the sparfloxacin and amoxycillin plus ofloxacin groups, respectively. At the end of treatment, the overall efficacy rates (defined as successful clinical cure and resolution or improvement of signs or symptoms) for the sparfloxacin and amoxycillin plus ofloxacin treatment groups were 92% and 82%, respectively. Oral treatment with sparfloxacin in CAP (caused by *Streptococcus pneumoniae* in 20% of cases) has also been shown to be superior to roxithromycin (82% success rate versus 72%) in another controlled study of 304 patients [53].
Levofloxacin, the \(-\)isomer of ofloxacin, is generally twice as potent as ofloxacin, with a broad range of activity against most Gram-negative and Gram-positive bacteria, including atypical organisms [34]. Like that of ofloxacin, the oral bioavailability of levofloxacin approaches 100\%, permitting oral dosing for all but the most seriously ill and debilitated patients [54,55]. In addition, levofloxacin has good penetration into lung tissue, bronchial mucosa, epithelial lining fluid and alveolar macrophages after a 500-mg single dose. In a mouse pneumonia model, oral levofloxacin (20 and 40 mg/kg) significantly reduced the number of viable \textit{Streptococcus pneumoniae} organisms in the lungs, whereas ciprofloxacin was no more effective than no therapy [34].

Animal studies and recent pharmacokinetic studies in humans also suggest that, unlike enoxacin or ciprofloxacin, levofloxacin does not significantly impair theophylline metabolism [34,56]. Levofloxacin may also have a much lower potential for photosensitivity reactions in comparison with other fluoroquinolones, such as nomefloxacin, sparfloxacin and enoxacin [57].

Two published studies have demonstrated the efficacy of levofloxacin in CAP. In an open, non-comparative, multicenter study in 68 patients, intravenous or oral levofloxacin once daily was highly effective in mild-to-moderate and severe CAP, with a successful clinical response in 100\% of the 60 clinically evaluable patients [58]. All the pathogens isolated in this study, including \textit{Streptococcus pneumoniae}, \textit{H. influenzae}, \textit{Staphylococcus aureus} and \textit{Chlamydia pneumoniae}, were eradicated. Intravenous or oral levofloxacin (500 mg once daily) was compared with parenteral ceftriaxone (1–2 g once or twice daily) and/or cefuroxime axetil (500 mg twice daily) in a randomized, open label, active-control trial in patients with a primary diagnosis of CAP [59]. Patients received the study medications for 7–14 days; levofloxacin 500 mg once daily either as a 1-h infusion or orally; ceftriaxone 1 or 2 g once or twice daily; oral cefuroxime axetil 500 mg twice daily. Overall, 456 patients were evaluable for efficacy (226 levofloxacin, 230 ceftriaxone/cefuroxime). Clinical success (defined as cure or improvement) was achieved in 96\% of patients treated with levofloxacin and 90\% of those treated with ceftriaxone/cefuroxime. The pre-treatment pathogen was eradicated in 98\% of those treated with levofloxacin compared with 85\% of those treated with ceftriaxone/cefuroxime. An eradication rate of 100\% was achieved for the two most common pre-treatment pathogens, \textit{Streptococcus pneumoniae} and \textit{H. influenzae}, in the levofloxacin treatment group compared with 94\% and 79\%, respectively, in the ceftriaxone/cefuroxime group. Levofloxacin was well tolerated, with nausea (2\%) and diarrhea (1\%) being the most common adverse events.

Trovafloxacin has comparable activity to ciprofloxacin against \textit{H. influenzae} and \textit{Moraxella catarrhalis}, and improved activity against \textit{Streptococcus pneumoniae} and group A streptococci [40]. In addition, it is highly active against \textit{Legionella spp.} and \textit{Chlamydia pneumoniae} and equally effective against both penicillin-susceptible and -resistant pneumococci. The potent in vitro activity of trovafloxacin against pneumococci and other respiratory tract pathogens is currently being assessed in clinical trials.

**CONCLUSIONS**

The diverse nature of LRTI pathogens and the need for empirical treatment, especially in CAP, necessitates the use of an antibiotic with a spectrum adapted to the range of pulmonary pathogens. The increasing problem of resistance to currently used antibiotics necessitates the use of alternative agents. The new fluoroquinolones, in contrast to ciprofloxacin, which does not have reliable antipneumococcal activity, have a broad antibacterial spectrum, enhanced activity against \textit{Streptococcus pneumoniae}, and rapid bactericidal activity. Sparfloxacin was the first of these new agents to be introduced and there are many compounds currently in development. Levofloxacin, which has recently become available in the USA, has a similar safety profile to ofloxacin, appears to be well tolerated and is not associated with the phototoxicity problems reported with sparfloxacin.

The newer fluoroquinolones could be considered for first-line monotherapy for community-acquired LRTI because of their wide spectrum of activity, clinical efficacy and good safety profile. In nosocomial pneumonia, however, because of the prevalence of \textit{P. aeruginosa} or \textit{Staphylococcus aureus} as causative pathogens, the results of susceptibility tests and of clinical studies should determine the therapy to be selected. Confirmation of their cost-effectiveness is required in CAP but, at present, the results of the necessary pharmaco-economic studies are not available. They could also be used as second-line therapy, in cases of failure with other antibiotics, such as macrolides or \(\beta\)-lactams. Currently, there is insufficient information to support their use in combination therapy. However, in the case of levofloxacin, there are considerable supporting data on the use of ofloxacin in combination therapy. The option of step-down or switch therapy (from oral to intravenous administration or vice versa) is an important advantage of the new fluoroquinolones.

In order to determine fully the place of these agents in the treatment of lower respiratory tract infections,
more studies are needed. These include studies to determine: the cost-effectiveness of fluoroquinolones compared with other agents; the optimal duration of treatment based on clinical endpoints rather than on fixed duration of treatment; the impact of the use of fluoroquinolones on the microbial ecology of the patient and people in close contact with the patient; and the pediatric use of fluoroquinolones, other than in cystic fibrosis. On the basis of the information available to date, however, the new fluoroquinolones should prove to be useful agents for the treatment of lower respiratory tract infections.

References