Critical evaluation of guidelines for the treatment of lower respiratory tract bacterial infections

M. CAZZOLA*, F. BLASI† AND L. ALLEGRA‡

*Divisione di Pneumologia e Allergologia e Unità di Farmacologia Clinica Respiratoria, Ospedale A. Cardarelli, Napoli, Italy and †Istituto di Malattie dell'Apparato Respiratorio, Università degli Studi di Milano, IRCCS, Ospedale Maggiore, Milano, Italy

Introduction

Lower respiratory tract infections are common in the adult population, with an estimated incidence of approximately 44% (1). This high incidence rate signifies that clinicians are daily called to face a disease that may become extremely threatening if not adequately treated. Unfortunately, treatment of respiratory infections is a complex and continuously evolving process. The emergence of new pathogens, variations in antibiotic susceptibility among traditional pathogens, and the ever-increasing presence of complex immunocompromised patients at high risk for the development of severe lower respiratory tract infections determine the need for continual modification of the treatment schemes in use. Open problems such as the clinical utility of distinguishing between typical and atypical pneumonia, doubts concerning antibiotic treatment in the elderly and the validity of antibiotic associations, are as yet unresolved due to the size, complexity and expense of the studies that would be required to give definitive answers. This further complicates the decision-making processes that are complex enough in the first place (2).

Although beset by the difficulties arising from several therapeutic uncertainties, the clinician must nonetheless deal with newly arising socioeconomical contingencies. We are now entering an era in health management in which clinicians no longer take treatment decisions on the basis of scientific reasoning alone, but predominantly based on economical considerations. In practice, the clinician must reduce the cost of therapy, or at least slow its growth, while still maintaining the clinical efficacy of treatment with more expensive and often more innovative drugs.

The clinical complexity associated with infectious diseases and the call for a reduction in health expenses have urged scientific societies to develop guidelines to assist clinicians in the management of lower respiratory tract bacterial infections. Practice guidelines have the opportunity to support primary care physician decision-making by providing current treatment and triage recommendations at the time of patient encounter.

Guidelines for the management of acute exacerbations of chronic bronchitis

It must be stressed that exacerbations of chronic bronchitis are generally inadequately discussed in most currently available guidelines [American Thoracic Society (ATS) (3), European Respiratory Society (ERS) (4) and British Thoracic Society (BTS) (5)]. This is probably because current guidelines are generally focused on the overall management of COPD. The only document which specifically focuses on acute exacerbations of chronic bronchitis is the Canadian guideline (Table 1) (6).

The reluctance in addressing this aspect in a more thorough manner is certainly justified by the strong controversy surrounding the role of antibiotic treatment in acute exacerbations of chronic bronchitis (AECB) (7). The decision to prescribe antibiotics in patients with an AECB has been debated in the literature (8–19). Many studies have shown either no benefit, or minimal benefit, when antibiotics are prescribed for an AECB. A recent study conducted in Great Britain showed that patients recover from exacerbations irrespective of treatment employed, except when past history reveals co-existent cardiopulmonary diseases or frequent exacerbations (20).

On the other hand, Murphy and Sethi (21) suggested that most infectious events in chronic bronchitis are spontaneously resolving processes involving the mucosal lining alone, that need no treatment.

In effect, the role of infection in exacerbations of chronic bronchitis remains controversial and incompletely understood. Some investigators believe that bacteria are not important for patients with exacerbation (22). However, when strictly defined by application of several newer investigative techniques, it is likely that 80% of AECB are infectious in origin, with 40–50% caused by bacteria, 30% by viruses and 5–10% by atypical bacteria (23). Concomitant infections by more than one infectious pathogen appear to occur in 10–20% of patients.
Secondary antibiotics: 2nd or 3rd generation cephalosporins, co-amoxiclav, new macrolides, quinolones

Initial antibiotics: Aminopenicillin, tetracyclines, co-trimoxazole

<table>
<thead>
<tr>
<th>TABLE 1. Canadian guidelines for the treatment of chronic bronchitis exacerbations (6)</th>
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<tbody>
<tr>
<td>Bacteria involved</td>
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<tr>
<td>When to treat</td>
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<tr>
<td>Initial antibiotics</td>
</tr>
<tr>
<td>Secondary antibiotics</td>
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</tbody>
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<tr>
<th>TABLE 2. European guidelines (ESOCAP) for the treatment of chronic bronchitis exacerbations (31)</th>
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<tbody>
<tr>
<td>Bacteria involved</td>
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<tr>
<td>Secondary antibiotics</td>
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</table>

*Streptococcus pneumoniae, Haemophilus influenzae, H. parainfluenzae, and Moraxella catarrhalis* are the bacteria primarily incriminated. However, *Enterobacteriaceae* and *Pseudomonas aeruginosa* are isolated more frequently than other organisms and should be taken into account in infective exacerbations of patients with severe disease, as reflected by low levels of FEV\(_1\), deeper hypoxaemia, malnutrition and more frequent hospitalizations (24,25). In any case, even when clinical deterioration is caused by infection, identification of the causal organism is often difficult (26). Although the initial insult causing increased cough and expectoration is probably viral in origin (27), bacterial invasion may be demonstrated in many patients, in addition to cases where viral exacerbations are complicated by secondary bacterial infections (28).

Murphy et al. (29) think that the available data about antibiotic therapy for exacerbations of COPD support a role for their use, probably because bacteria are often responsible for exacerbations. Several studies confirm this opinion. The study by Anthonisen et al. (14) showed a definite benefit for antibiotics in >80% of patients with chronic bronchitis with exacerbations who had at least two of the following three cardinal symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence. The benefits of antibiotics were more dramatic for patients with all three symptoms than for those with two symptoms, but the benefits included more antibiotic treated patients who responded to therapy than those who did not, compared to placebo-treated patients. Moreover, a recent meta-analysis (16) investigation revealed that antibiotic treatment is associated with a modest but significant benefit in patients with AECB that is clinically most relevant in patients with severe underlying functional impairment. We are confident that antibiotic treatment will continue to be used in the future because there is a subset of patients that does not spontaneously remit from the exacerbation (30). *A priori* identification of this subset of patients is impossible.

The recommendations of ERS (4) move along these lines: the need for exacerbation severity and functional impairment assessment is beginning to break through. Antibiotic therapy is always recommended in severe exacerbations, but also in non-severe exacerbations if an increase in sputum purulence and volume are present together with worsening dyspnoea.

According to the British school of thought (5), older antibiotics are usually effective, whereas more recent drugs are rarely appropriate. For this reason, amoxicillin and tetracycline are considered first-choice agents in the U.K., unless previously shown to be ineffective. For more severe exacerbations, or in case of lack of response to the above-mentioned agents, second-line alternatives may be taken into consideration, such as broad spectrum cephalosporins or a recent macrolide.

The ATS guidelines (3) suggest a broader choice of agents as first-line treatment, including tetracyclines, erythromycin, co-trimoxazole, doxycycline, amoxicillin and cefaclor. Broad spectrum penicillins and cephalosporins are recommended alternative antibiotics.

European (4) and Canadian (6) guidelines suggest that less expensive antibiotics are sufficient, and recommend amoxicillin and tetracycline derivative as initial antibiotics. However, Europeans have recently suggested co-amoxiclav as first-choice treatment, and macrolides, new cephalosporins and fluoroquinolones as alternative antibiotics (Table 2) (31). On the contrary, the Canadian guidelines (13) advise that patients presenting a poor initial response should be treated with a same antibiotics that the ATS (10) indicates as alternative antibiotics, but go on to suggest that these agents may be considered as appropriate first-choice drugs in complicated cases: age >65 years, FEV\(_1\) <50% of predicted, significant co-morbidity, multiple exacerbations during the previous year.

The recommendations of the different guidelines appear too generic and often are not the most economical. In fact, even though the proposed antibiotics are generally effective in individual cases and are scarcely expensive, they seldom guarantee an optimal cost-effectiveness ratio. The impact on the cost of treatment differs widely according to the antibiotic employed, although drug costs never account for more than 10–16% of total costs. The rate of relapse...
following antibiotic treatment is a fundamental determinant of costs, because patients with more relapses use more health resources. On the other hand, slow remission of an exacerbation also expands total treatment costs.

Comparing the time span between one exacerbation and the next after the use of the so-called first-choice (amoxicillin, tetracycline, erythromycin or co-trimoxazole), second-choice (oral cephalosporins), or third-choice antibiotics (co-amoxiclav, ciprofloxacin and azithromycin), it has been shown that first and second line drugs allow exacerbation-free intervals of 18-3 and 23-7 weeks, respectively, whereas third choice antibiotics gave an interval of 33 weeks (32).

Recently, Grossman et al. (33) evaluated costs, consequences, efficacy and tolerability of ciprofloxacin compared to traditional first-line antibiotics such as amoxicillin, tetracycline, or co-trimoxazole in patients with initial or recurrent exacerbations of chronic bronchitis over a 1-year period. Treatment with ciprofloxacin tended to hasten exacerbation remittal when compared to traditional treatment; however, the differences were not statistically significant. Apparently, data from the above study seem to rule out the need for relatively recent antibiotics in the treatment of patients with AECB. It must nonetheless be pointed out that the same study showed that ciprofloxacin was the most effective antibiotic in patients with four or more exacerbations during the previous year.

This aspect is of extreme importance because it clearly indicates that patient stratification into risk categories allows the choice of optimal antibiotic therapy. This may reduce the number of treatment failures and achieve the selection of cost-effective options (34). However, a recent paper by Dewan et al. (35) have demonstrated that patients who had severe underlying lung disease and had greater frequency and severity of exacerbation were more likely to fail and the choice of an antibiotic did not affect the treatment outcome. Nonetheless, current Canadian (6) recommendations already include a stratification of risk factors, limiting innovative drug use to highest risk patients. Ball (36) also suggests limiting fluoroquinolones, new macrolides and co-amoxiclav to patients belonging to stage III of the scale, determined by a British study on AECB. Stage III includes patients with acute exacerbation accompanied by dyspnoea and increase in sputum volume and purulence, as well as co-morbidity and more than three or four exacerbations a year. In these patients, resistant organisms may co-exist with factors that inactivate antibiotics or reduce their penetration capacity. It is possible that the selective use of newer antibiotics based on stratification would also limit the emergence of drug-resistant organisms.

Nevertheless, Adams et al. (37) have recently demonstrated that relapse from AECB was not related to the severity of underlying disease or to the severity of the acute exacerbation. Patients treated with antibiotics had significantly lower relapse rates than those who did not receive antibiotics. However, the specific choice of antibiotic was important because those treated with amoxicillin had the highest relapse rates of all groups, which were probably related to the increasing emergence of pathogen resistance. All the contrasting findings that are present in the literature clearly show that the recommendations addressing the management of AECB are over-simplified and do not include risk factors predicting failure of initial antimicrobial therapy. They are potentially useful for treating patients with mild-to-moderate acute exacerbations, but they do not consider that patients with more advanced lung disease harbour different organisms and, thus, may need a different therapy than patients with milder disease. We trust that antibiotic treatment is an essential action in most patients with AECB and an aggressive approach to treatment of high-risk patients might improve outcome. For this reason, we consider classification based on a better understanding of risk factors and treatment outcome with antibiotics proposed by Grossman (34) the best present approach to the management of AECB (Table 3). The only criticism against this classification we have is the lack of consideration for the potential presence of C. pneumoniae and multi-drug-resistant S. pneumoniae (DRSP). Since the newer fluoroquinolones (levofloxacin and moxifloxacin) have a broad spectrum of action covering these two pathogens and also multi-resistant H. influenzae, we believe that their inclusion, at least for stages II and III of Ball’s classification (20), is extremely useful.

Community-acquired pneumonia guidelines

Guidelines on community-acquired pneumonia (CAP) have been issued in many countries. Considering the guidelines of four European countries (Table 4): Italy (38) France (39), Spain (40) and Great Britain (41), it is evident that in all cases indications are given for the management of two patient groups: severe and non-severe. In particular, all the above guidelines suggest the use of a penicillin or a macrolide for non-severe patients because, although S. pneumoniae remains the most common aetiological agent, C. pneumoniae and Legionella pneumophila are also important causes. There is no universally accepted definition for CAP severity but some factors are certainly important (Table 5). If one or more of the conditions listed in Table 5 are present, pneumonia is defined as severe. The guidelines differ in recommending a penicillin or an aminopenicillin, in suggesting single or combined use with a macrolide, and in the routine prescription of a β-lactamase inhibitor. Each document recommends the use of an association between a second- or third-generation cephalosporin and a macrolide in severe patients.

Although the above guidelines have apparently been accepted by the scientific community, there are widely differing antibiotic prescribing habits in general practitioners in Western Europe (42). An analysis of the empirical prescribing behaviour of European clinicians in the treatment of CAP has shown that macrodilides, aminopenicillins with or without clavulanic acid and cephalosporins are the most commonly used antibiotics, although the order with which they are prescribed varies greatly among different countries. Aminopenicillin was first or second choice in four out of seven nations. Cephalosporin use was very common in Germany and Southern Europe. In Italy,


parenteral treatment with third-generation cephalosporin or imipenem was the most common choice (almost 40% of cases). The differences in prescribing habits are certainly not attributable to guidelines recommendations, nor can they be explained by scientific reasoning, such as differences in infection aetiology, penicillin-resistant pneumococcus rate, pharmacokinetics and safety, and are not linked with ecological or economical considerations. The differences are presumably multi-factorial, and at least partly due to diversities in local health systems (for example, in the U.K. 9% of patients with CAP are admitted to hospital, in contrast to 2-5% in Spain, 2-7% in Germany and 5-1% in France) (43) and to the sources of information at the clinician's

<table>
<thead>
<tr>
<th>Baseline clinical status</th>
<th>Criteria/risk factors</th>
<th>Pathogens</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>I. Acute tracheobronchitis</td>
<td>No underlying structural disease; acute cough and sputum production</td>
<td>Usually viral</td>
<td>None, for prolonged symptoms consider macrolide or tetracycline</td>
</tr>
<tr>
<td>II. Simple chronic bronchitis</td>
<td>FEV₁ &gt; 50%, increased sputum volume and purulence, no additional risk factors</td>
<td><em>H. influenzae</em>, <em>Haemophilus</em> spp., <em>M. catarrhalis</em>, <em>S. pneumoniae</em></td>
<td>Aminopenicillin Tetracycline Co-trimoxazole</td>
</tr>
<tr>
<td>III. Complicate chronic bronchitis</td>
<td>Increased sputum volume and purulence + FEV₁ &lt; 50%, advanced age, ≥4 exacerbation/year significant co-morbidity, malnutrition, chronic oral steroid usage</td>
<td>As for group II; Gram-negatives more likely in patients with FEV₁ &lt; 50%; resistance to β-lactams common</td>
<td>Quinolone β-lactam/β-lactamase inhibitor-2nd or 3rd generation cephalosporin 2nd generation macrolide</td>
</tr>
<tr>
<td>IV. Chronic bronchial suppuration</td>
<td>Continuous purulent sputum production with frequent exacerbations</td>
<td>As for group III+ <em>Enterobacteriaceae</em> and <em>P. aeruginosa</em></td>
<td>Ciprofloxacin or other i.v. antipseudomonas agents</td>
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<table>
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<tr>
<th>Country</th>
<th>Non-severe patient</th>
<th>Severe patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Amoxicillin 1 g t.i.d. or macrolide</td>
<td>Co-amoxiclav+(macrolide or fluoroquinolone) or 3rd generation cephalosporin+(macrolide or fluoroquinolone)</td>
</tr>
<tr>
<td>Italy</td>
<td>β-lactam/β-lactamase inhibitor + macrolide</td>
<td>2nd/3rd generation cephalosporin + macrolide</td>
</tr>
<tr>
<td>Spain</td>
<td>Procaine penicillin 1,200,000 U b.i.d. or erythromycin (ethyssuccinate) 2-4 g day⁻¹</td>
<td>3rd generation cephalosporin+ erythromycin</td>
</tr>
<tr>
<td>Great Britain</td>
<td>Aminopenicillin (amoxicillin 500 mg t.i.d. or benzyl-penicillin (1·2 g q.i.d.)</td>
<td>Erythromycin+2nd or 3rd generation cephalosporin or ampicillin+ fluoxacillin+erythromycin</td>
</tr>
</tbody>
</table>

**Table 3. Proposed classification and antimicrobial treatment of bronchitis (34)**

**Table 4. Recommendations for initial empirical antibiotic treatment of community-acquired pneumonia (38–41)**

**Table 5. Factors that allow the definition of community-acquired pneumonia severity. Adapted from El-Ebiary (106)**

- Respiratory rate > 30 breaths min⁻¹
- *P*O₂/FIO₂ ratio > 250
- Rapid radiographic worsening (≥50% increase in infiltrate size within 48 h)
- Bilateral or multi-lobar involvement
- Shock
- Need or vasopressors for more than 4 h
- Evidence of sepsis with organ dysfunction
disposal. Local therapeutic traditions, marketing factors and
scientific rationale are probably equally important in the
empirical choice of the treatment for CAP (44).

The North American guidelines are more articulate
(45,46) including considerations on comorbidity, patient
age, disease severity, need for hospitalization and the
selection of one or more appropriate antimicrobial agents.
Specifically, the Canadian guidelines (45) divide non-severe
patients into those aged <65 years without comorbidity,
and those aged 65 years or more with comorbidity. Among
the former, macrolides are first-choice antibiotics, followed
by tetracyclines as second-line treatment. In patients with
comorbidity, second generation cephalosporins or a
combination of β-lactam/β-lactamase inhibitor, or co-
trimoxazole are recommended treatment choices. Macro-
lides may be added as an option to each of the above drugs,
Severe patients require hospitalization and may be divided
into those referred to a general ward or to an intensive care
unit (ICU) (Table 6). For the former, use of a second- or
third-generation cephalosporin is suggested, with the
addition of a macrolide as an option. For patients admitted
to an ICU, intravenous macrolide is recommended, with
the possible addition of rifampin and one or more anti-
pseudomonas drugs, in view of the most commonly
occurring pathogens in this setting (Fig. 1). The ATS (46)

TABLE 6. Treatment of severe community-acquired pneu-
monia*, adapted from Mandel and Niederman (46)

<table>
<thead>
<tr>
<th>Macrolide + anti-pseudomonas antibiotic</th>
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<tbody>
<tr>
<td>Third generation anti-pseudomonas cephalosporin, imipenem, ciprofloxacin, aztreonam, anti-pseudomonas penicillin</td>
</tr>
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</table>

*If Legionella is identified, rifampin must be added.
†Due to the high mortality associated with P. aeruginosa pneumonia, an aminoglycoside should be added so as to obtain double coverage towards Pseudomonas (at least during the first few days of treatment) when using a third-
generation cephalosporin, imipenem or ciprofloxacin.

![Graph showing bacteriology of severe community-acquired pneumonia. Data from three studies (110–112).](image)

Fig. 1. Bacteriology of severe community-acquired pneumonia. Data from three studies (110–112).
S. pneumoniae cefotaxime and cefuroxime in view of concerns regarding (51). Nonetheless, the BTS recommends the use of cephalosporin-resistant strains within hospital environment (41). However, the BTS recognizes the need for cephalosporins as first-choice treatment in CAP, may be considered an alternative good approach. This conviction is sustained by English language recent literature. For example, in a recent large study, ceftazidime was shown to be highly effective in hospitalized patients with CAP, irrespective of the presence or absence of fundamental risk factors such as age (>65 years, male sex, serum urea >7 mmol l⁻¹, serum albumin <35 g l⁻¹) and difficult pathogens (59). However, the authors correctly underline the need to consider risk factors in approaching CAP. It must be remembered that the number of elderly patients with CAP is extremely high. In the U.K., more than 90% of patients with pneumonia are aged over 65 years and associated mortality is approximately 16–40% (60). For this reason, we do not agree with Wort and Rogers’s opinion (57) that there is no need for cephalosporins as first-line treatment in CAP. Wesel et al. (61) compared intravenous ceftiraxone (2 g once daily), cefotaxime (2 g three times daily), cefuroxime (750 mg three times daily, followed by 500 mg orally three times daily), and co-amoxiclav (1-2 g intravenously three times daily, followed by 625 mg orally three times daily). Data analysis showed that ceftiraxone gave the best probability of therapeutic success. The emerging trend in the U.S.A. is that parenteral treatment with a cephalosporin (primarily ceftriaxone, or alternatively ceftazidime) outside the hospital setting is a valid, safe, and low cost alternative (62–64). In fact, Douglas Campbell (65) affirms that parenteral third-generation cephalosporin plus a macrolide could be considered. Parenteral antibiotics can now be practical options for outpatients; new infusion pump technologies as well as new reimbursement systems

**Table 7. Empirical antibiotic selection for patients with community-acquired pneumonia according to the Infectious Diseases Society of America guidelines (50)**

<table>
<thead>
<tr>
<th><strong>Non-hospitalized patients</strong></th>
<th>Generally preferred: macrolides*, fluoroquinolones † or doxycycline</th>
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<tbody>
<tr>
<td><strong>Modifying factors:</strong></td>
<td></td>
</tr>
<tr>
<td>Suspected penicillin-resistant Streptococcus pneumoniae: fluoroquinolones †</td>
<td></td>
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<tr>
<td>Suspected aspiration: co-amoxiclav</td>
<td></td>
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<tr>
<td><strong>Hospitalized patients</strong></td>
<td></td>
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<tr>
<td>General medicine ward</td>
<td>Generally preferred: β-lactams with or without macrolides*, or fluoroquinolones † (alone)</td>
</tr>
<tr>
<td>Alternatives: cefuroxime with or without macrolides*, or azithromycin (alone)</td>
<td></td>
</tr>
<tr>
<td>Admitted to Intensive Care Unit for severe pneumonia</td>
<td>Generally preferred: erythromycin, azithromycin or a fluoroquinolone +cefotaxime, ceftriaxone</td>
</tr>
<tr>
<td>Alternatives: β-lactam/β-lactamase inhibitor †</td>
<td></td>
</tr>
<tr>
<td><strong>Modifying factors</strong></td>
<td></td>
</tr>
<tr>
<td>Structural lung disease: anti-pseudomonas penicillin, a carbapenemic, or cefepime+a macrolide* or a fluoroquinolone †</td>
<td></td>
</tr>
</tbody>
</table>
An aminoglycoside |
| Allergy to penicillin: a fluoroquinolone with and without clindamycin|  
A fluoroquinolone+clindamycin or metronidazole or β-lactam/β-lactamase inhibitor †(alone)|

*Azithromycin, clarithromycin or erythromycin.  
†Levofloxacin, sparfloxacin, grepafloxacin or other fluoroquinolone highly active towards S. pneumoniae.  
‡Ampicillin/sulbactam, or ticarcillin/clavulanate or piperacillin/tazobactam (for structural lung disease, ticarcillin/clavulanate or piperacillin).

caphalosporin-resistant strains within hospital environment (51). Nonetheless, the BTS recommends the use of cefotaxime and cefuroxime in view of concerns regarding S. pneumoniae penicillin-resistant strains (41). However, the current resistance rate (MIC for penicillin >0·1 μg ml⁻¹) in England and Wales is as low as 3·8% (52), although regional variations are reported. Moreover, there is no solid evidence that these levels of resistance are clinically relevant in pneumococcal pneumonia when adequate doses of penicillin are administered (53). Three large S. pneumoniae studies, enrolling a total of >1100 patients, showed no difference in outcomes among patients infected with S. pneumoniae that was sensitive to penicillin, had intermediate resistance to penicillin, or was highly resistant to penicillin, but only a handful of patients had DRSP with a MIC to penicillin of 4·0 mg m⁻¹ (54–56). This information suggests that high-dose (150 000–250 000 mg kg⁻¹ day⁻¹) penicillin are probably appropriate for therapy in this setting. For this reason, Wort and Rogers (57) feel there is no need for cephalosporin use as first-choice treatment in CAP, although local epidemiological considerations on penicillin resistance must be kept in mind. For many British clinicians, amoxicillin and ampicillin are still first-choice oral treatment (58), with co-amoxiclav as an alternative for its greater activity towards H. influenzae. Intravenous penicillin is restricted to severe cases. Only if local resistance trends preclude such treatment should cephalosporins be used.

We feel that the British approach, although scientifically correct, is not the most effective in clinical practice. Since the mortality rate for CAP in Italy is among the lowest in Europe (31), we suggest that the so-called ‘Italian empirical model’, according to which parenteral cephalosporins are first-choice treatment in CAP, may be considered an alternative good approach. This conviction is sustained by English language recent literature. For example, in a recent large study, ceftazidime was shown to be highly effective in hospitalized patients with CAP, irrespective of the presence or absence of fundamental risk factors such as age (>65 years, male sex, serum urea >7 mmol l⁻¹, serum albumin <35 g l⁻¹) and difficult pathogens (59). However, the authors correctly underline the need to consider risk factors in approaching CAP. It must be remembered that the number of elderly patients with CAP is extremely high. In the U.K., more than 90% of patients with pneumonia are aged over 65 years and associated mortality is approximately 16–40% (60). For this reason, we do not agree with Wort and Rogers’s opinion (57) that there is no need for cephalosporins as first-line treatment in CAP. Wesel et al. (61) compared intravenous ceftiraxone (2 g once daily), cefotaxime (2 g three times daily), cefuroxime (750 mg three times daily, followed by 500 mg orally three times daily), and co-amoxiclav (1·2 g intravenously three times daily, followed by 625 mg orally three times daily). Data analysis showed that ceftiraxone gave the best probability of therapeutic success. The emerging trend in the U.S.A. is that parenteral treatment with a cephalosporin (primarily ceftriaxone, or alternatively ceftazidime) outside the hospital setting is a valid, safe, and low cost alternative (62–64). In fact, Douglas Campbell (65) affirms that parenteral third-generation cephalosporin plus a macrolide could be considered. Parenteral antibiotics can now be practical options for outpatients; new infusion pump technologies as well as new reimbursement systems.
for home healthcare in the U.S.A. and Canada make such treatment feasible.

Resistance to pneumococci in vitro is not always accompanied by a lack of clinical response, but there are increasing reports of treatment failures in pneumococcal infections caused by strains with reduced susceptibility to the drug in vitro (66,67). Resistance in pneumococci has developed not only to penicillins, but in some strains this is accompanied by decreased susceptibility to cephalosporins (68,69). Macrolide resistance has also grown, with most erythromycin-resistant strains showing cross-resistance to other macrolides (67). Macrolide resistance is often linked with penicillin resistance, and strains with concurrent resistance to a number of unrelated antimicrobials (β-lactams, macrolides, tetracyclines and co-trimoxazole) are not uncommon (67,70). The growth of multi-resistant pneumococci has encouraged the development of fluoroquinolones with improved Gram-positive activity. Several new fluoroquinolones possess a similar range of activity. Among those in the market, levofloxacin (71) and moxifloxacin (72) are the most promising.

The role of the newer fluoroquinolones is also important considering the incidence of C. pneumoniae, L. pneumophila and Mycoplasma pneumoniae as pathogens in CAP and their resistance to β-lactams. In fact, both levofloxacin and moxifloxacin are active against atypical bacteria. All guidelines suggest the addition of a macrolide. Evidence is accumulating that new macrolides, such as clarithromycin, are superior to erythromycin, both in terms of antibiotic spectrum and greater activity towards C. pneumoniae (73). We think that macrolide utility against S. pneumoniae depends on community susceptibility and, furthermore, macrolides are less active than levofloxacin (74) and moxifloxacin (75) against H. influenzae, and a high percentage of S. pneumoniae are macrolide-resistant.

In any case, a recent U.S.A. study on elderly patients showed that the routine use of macrolides is not to be encouraged because only 7-5% of patients presented an organism needing macrolide treatment, and no mortality was present among these patients (76). Woodhead (77) suggested that a randomized, comparative controlled study should be carried out to compare β-lactam alone with a β-lactam and a macrolide before recommending use of a macrolide in elderly patients with CAP because a true definition of the current frequency with which C. pneumoniae causes CAP is lacking. In fact, during clinical trials the presence of co-pathogens is a common occurrence. This suggests that C. pneumoniae may simply initiate pathological events, but a different pathogen is the true cause of pneumonia. Therefore, it is hardly surprising that treatment with an antibiotic ineffective towards C. pneumoniae is equally capable of obtaining clinical remission in approximately the same time span obtainable following administration of an antibiotic presenting activity towards this atypical pathogen (77).

However, it may be supposed that co-infection with C. pneumoniae and other pathogens does have some effect on the course of pneumonia. In a recent study by Kauppinen et al. (78), three groups of patients with pneumonia were examined: those with C. pneumoniae infection; those with S. pneumoniae infection; and those with mixed infection. The authors report that in the presence of C. pneumoniae infection alone the clinical course was mostly mild, with a mean hospital stay of 8-4 days, although only 36% had received adequate antibiotic treatment for this infection. In the presence of S. pneumoniae infection, all patients had received adequate antibiotic treatment and the mean hospital stay was 10-5 days. However, even when both pathogens were present, subjects were treated only for pneumococcus and the mean hospitalization reached 21-9 days. These data suggest a possible role for co-infection in determining increased pneumonia severity. This role seems to be confirmed by Gordon et al. (79) who retrospectively analysed the records of 4448 patients admitted to the hospital, but not in the ICU, with CAP. The study found that patients who received guideline-recommended therapy had a significantly lower chance of dying than those patients who received non-recommended therapy, but that the lowest mortality rate of all was in those patients who received both a β-lactam and a macrolide. These findings again suggest that routine therapy directed at atypical pathogens may be beneficial for all types of patients with CAP.

We believe that both these findings and the documentation that C. pneumoniae has been reported to cause pneumonia frequently in association with other microorganisms, mainly S. pneumoniae (80,81), support our opinion that newer fluoroquinolones may be considered a valid first-choice option due to their enhanced activity against Gram-positive and atypical organisms while maintaining activity against Gram-negative bacteria. Should ongoing clinical trials and clinical practice demonstrate that newer fluoroquinolones are a valid and safe monotherapy in CAP, it is likely that future guidelines will have to keep this class of drugs in due consideration (82). However, Campbell (65) highlights that for hospitalized patients with mild-to-moderate infection without DRSP risk, the recommendation is a β-lactam plus macrolide (or doxycycline) combination, or a fluoroquinolone alone (83). If there is DRSP risk, the recommendation is cefotaxime or ceftriaxone combined with a macrolide or a fluoroquinolone alone (84).

Apart from the above considerations and the need for changing the suggestions of guidelines according to the evolution of pharmaceutical market that offers new and more effective agents, we must highlight that therapeutic recommendations contained in guidelines often clash with factors affecting the total costs of treatment of pneumonia such as the need for hospitalization, attempts to reach an aetiological diagnosis, the selection of empirical antibiotic therapy, time span needed for switching from parenteral therapy to oral treatment and length of hospital stay. Moreover, the management habits of single clinicians, often reflecting local practices, must not be ignored and may equally substantially affect the total cost of treatment. For example, an interesting American study (85) has recently demonstrated that the use of medical procedures and consultations was more common for patients discharged from University Hospitals than from general hospitals, causing an 11% increase in costs in the former hospitals. Similarly, costs were 15% greater in urban compared to rural hospitals. Internal medicine and pulmonology
clinicians made more use of diagnostic procedures, and on
the whole were associated with greater expenses, than
general practitioners. Notwithstanding the variability in
procedure use and treatment expenses concerning CAP,
there were no differences in mortality and in re-admission
rates.

However, one of the first and probably most important
decisions concerning cost of treatment is not the choice of
antibiotic, but rather the need for hospital admission. In
fact, with increasing pressures on healthcare resources
everywhere, the question of which patients require hospi-
talization and which do not is very pertinent. Pneumonia is
an important cause of hospital admission, but frequency
varies greatly according to the study and the clinicians
conducting the study. This suggests the need for efficient
and widely accepted predictive indices for negative out-
come. A large study involving over 50 000 patients
identified valid criteria for predicting the outcome of CAP
(86). The predictive rule allots scores based on age and
the presence of comorbidity, abnormal physical examination
(respiratory rate > 30 or body temperature > 40°C) and
laboratory findings (pH < 7.35, serum urea > 30 mg dl⁻¹,
or serum sodium < 130 mmol l⁻¹) on admission. Home
treatment for class I patients (no risk factors), brief
observation as inpatient for class II patients (score between
71 and 90), and hospital admission for class IV (score
between 91 and 130) and class V patients (score > 130) may
significantly reduce the number of hospital admissions by
approximately one-third. However, in our opinion the
above scoring system is too complex for use in routine
clinical practice. Decreased admission rate was observed
after implementation of admission decision support in
combination with specific recommendations for outpatient
antibiotic therapy (87). Favourable outpatient outcomes
suggest that implementation of decision support was safe.

In hospitalized patients, the length of stay is a primary
determinant of the management costs of pneumonia. Data
from the National Healthcare Cost and Utilization Project,
the National Ambulatory Medical Care Survey and the
National Hospital Ambulatory Medical Care Survey were
employed to determine the cost of treatment in patients
aged 65 or over (88). Figures soared to a total cost of S.U.S.
4.8 billion for the treatment of patients aged 65, and
over S.U.S. 3.6 billion for the treatment of patients aged
under 65 years. The mean length of hospital stay was 7-8
days with a mean cost of S.U.S. 7166 for patients over 65, and 5-8
days with a mean cost of S.U.S. 6042 for younger patients.

Obviously, given the high cost of CAP requiring
hospitalization, every treatment that allows home manage-
ment may result in substantial savings, particularly among
patients under 65 years of age.

One of the key elements determining length of hospital
stay is the duration of parenteral antibiotic treatment.
Ehrenkranz et al. (89) reported a reduction in mean
hospital stay by 2-4 days and a S.U.S. 884 reduction per
patient/therapy when parenteral treatment was switched
to oral treatment and the patient was discharged on the
third day of hospitalization. It is interesting to note that in
this study the disease severity indices and the outcome
following discharge were similar for those inpatients who
had continued parenteral treatment and prolonged hospital
stay. Generally, by cautiously applying specific criteria for
the identification of candidates for switch therapy (Table 8),
most patients may be treated orally within 3 days from
initiation of therapy.

By altering the prescribing habits of hospital-based
clinicians in CAP, it may be possible to lower costs with
no significant increase in the risk of negative outcome.
Proof of this is found in the study by Omidvari et al. (90).
The authors treated a group of patients with cefamandol
1 g intravenously every 6 h for 7 days, and a second group
with cefamandol (1 g intravenously every 6h for 2 days)
followed by oral treatment with cefaclor (500 mg every 8 h
for 5 days). Between the two groups there was no difference
in clinical course, remission rate, survival rate and clearing
of radiographic abnormalities. Average length of treatment
(6.88 days for the conventional group compared to 7-30
days for the group with switch therapy), and the rate of
overall symptom improvement (97% vs. 95%, respectively)
was similar in both groups. Patients receiving precocious
oral treatment required a shorter hospital stay (7-3 vs.
9-71 days, P = 0-01), and overall expenses were lower

Although only the ISDA guidelines highlight that
patients can usually be switched from i.v. to oral therapy
within 3 days, provided a good oral antibiotic is available
and that the patient is in clinically stable condition and can
tolerate the drug (50), we believe that this action is
extremely important and useful. In fact, the early hospital
dischage associated with switch therapy will decrease the
patient’s risk for nosocomial infections such as urinary or
respiratory tract infections. Moreover, switch therapy is
associated with a clinical cure rate that is equivalent to
conventional therapy. In the era of cost-effective use of
antibiotics, switch therapy should be considered as one of
the primary options for healthcare cost containment.

**Table 8. Criteria used to identify candidates to switch from
parenteral to oral treatment. Adapted form Ramirez et al.
(107), Fine et al. (108) Ramirez (109)**

<table>
<thead>
<tr>
<th>Improvement in cough</th>
</tr>
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<tbody>
<tr>
<td>Improvement in respiratory distress</td>
</tr>
<tr>
<td>Absence of fever for &gt; 24 h</td>
</tr>
<tr>
<td>Absence of high risk for resistant pathogens, for example S. aureus</td>
</tr>
<tr>
<td>Absence of concomitant unstable medical disease</td>
</tr>
<tr>
<td>Absence of complications, for example congestive heart failure</td>
</tr>
<tr>
<td>Intact gastrointestinal absorbance</td>
</tr>
<tr>
<td>Improvement in leucocytosis</td>
</tr>
</tbody>
</table>

**Nosocomial pneumonia guidelines**

The aetiology of nosocomial pneumonia (NP) is substan-
tially different from that of CAP, which explains the need
for different guidelines. Gram-negative bacilli, including *P. aeruginosa*, *Klebsiella*, *Acinetobacter* spp., *Enterobacter* and Gram-positive cocci such as *S. aureus* are common causes of nosocomial pneumonia (91,92). In particular, it has been demonstrated that early-onset NP (i.e. occurring within 48–96 h of ICU admission) is most often reported to be due to antibiotic-sensitive pathogens including *H. influenzae*, oxacillin-sensitive *S. aureus* and *S. pneumoniae*, while late-onset NP (i.e. occurring >48–96 h after ICU admission) is frequently attributed to antibiotic-resistant pathogens such oxacillin-resistant *S. aureus*, *P. aeruginosa*, *Acinetobacter* spp. and *Enterobacter* spp. (93,94) although antibiotic-resistant pathogens can also be isolated in early-onset NP patients (95). Disease caused by these virulent pathogens is often severe and commonly complicated by pulmonary necrosis, multi-lobar involvement, micro-abscesses or empyema. Mortality attributable to NP is significant in most patient populations and prompt administration of appropriate empiric antibiotic therapy in these groups is associated with improved outcomes (96,97).

Guidelines on NP are relatively scarce. Except for U.S.A. and Canadian guidelines, the only other national recommendations appear in Australia, Sweden and France (98). However, due to the lack of useful data for the drawing up of guidelines based on clinical evidence, it is probably more appropriate to refer to these documents as consensus among experts rather than true guidelines. Specifically, the ATS (Table 9) recommends that antibiotic choice should take into account disease severity, length of hospital stay and the presence of specific risk factors (99). When pneumonia arises within 5 days from hospitalization, a β-lactam/β-lactamase inhibitor or a second- or third-generation cephalosporin is recommended. When pneumonia arises later during hospital stay, it is imperative that antibiotics active against *P. aeruginosa* be used, such as the association between an aminoglycoside or a fluoroquinolone and a wide spectrum β-lactam. When anaerobic infection is present, clindamycin or an association β-lactam/β-lactamase inhibitor is suggested, whereas vancomycin is recommended when methicillin-resistant *S. aureus* is suspected. Conversely, when *Legionella* infection is susceptible a macrolide should be used (100).

Unfortunately, the ATS therapeutic recommendations for early-onset NP would result in under-treating patients who are infected with oxacillin-resistant *S. aureus* or *P. aeruginosa*. The antimicrobial recommendations for patients who develop late-onset NP should also apply to patients with early-onset NP when significant rates of early-onset NP are demonstrated to be due to potentially antibiotic-resistant bacteria (95). Such pathogens should most commonly be observed in patients with risk factors for infection due to antibiotic-resistant bacteria including prior antibiotic therapy and prolonged mechanical ventilation (93).

It is important to underline that several studies demonstrate that all treatment approaches suggested by the different guidelines are ineffective in up to 30–40% of cases (101,102). The presence of unresponsive pathogens is the main cause of treatment failures. These may be common NP pathogens that develop in unexpected environments or with unusual resistance patterns. Prevalence of particular nosocomial pathogens and prevailing antibiotic resistance levels vary from one hospital to another, depending on many factors. In most hospitals, effective empirical therapy will require activity against Gram-negative bacilli, especially *Pseudomonas* and *Acinetobacter*, as well as Gram-positive organisms. Thus, at least initially, multi-drug therapy will be required (103). Many authors feel that two-drug regimens are insufficient to reduce the incidence of bacteria not covered by antibiotic therapy (104).

It must be remembered that when using empirical antibiotic treatment in a hospital ward, unresponsive patients must be quickly identified and alternative treatment schemes must be available. Treatment may require modifications on the basis of patient culture results and/or clinical response. The latter may be difficult to assess due to the variable course of NP, and is also associated with host and bacterial factors and the co-existence of other pathological processes.

Deplorably, currently available guidelines do not suggest reliable alternatives, but rather consider risk factors and the severity of the disease, with little attention being brought to previously mentioned aspects. As a result, we think the best way to treat patients with NP is to prescribe a therapy with three antibiotics with different spectrums and mechanisms of action, and to narrow the treatment as soon as microbiological data are available. We know that this approach is expensive and might elicit resistance, but we also know that an inappropriate therapy can induce the death of our patient.

**Conclusions**

The present critical evaluation of existing guidelines on the treatment of lower respiratory tract infections shows the great effort displayed in optimizing therapeutical approach. However, the fundamental debate on the possibility that current guidelines may induce changes in prescribing habits is as yet unresolved. We feel that guidelines will be effective and will improve management quality, with a clear-cut reduction in expenses, only when the concept that empirical therapy in the absence of diagnostic tests is effective has been validated by fulfilment of all adequate end points.

Clearly, the selection of drugs to be inserted in guidelines must not be based solely on drug selling prices. This clashes with the conclusions of a solid Canadian study conducted to determine variations in antibiotic use, expense of antibiotic treatment, and clinical outcome of patients according to the institution in which the patient was treated (105). This study not only showed that wide variations in prescribing habits between different institutions caused significant variations in expenses, but also demonstrated that patients treated in institutions with low antibacterial treatment costs did not present worse clinical outcomes.

Nonetheless, we feel that antibiotics with the lowest selling price may not necessarily be the best choice on the
basis of the cost-effectiveness ratio, particularly considering factors that condition health expenses. At least three outcomes are relevant in the management of lower respiratory tract infection: effects on the patient, those on bacteria and economical aspects. Therefore attention must not be limited to drug costs.

Considering economical endpoints, attention to resource employment is essential. Hospital administrations focus

### Table 9. Organisms associated with nosocomial pneumonia and antibiotics recommended by the American Thoracic Society guidelines (99)

<p>| Group 1: mild-to-moderate nosocomial pneumonia, no unusual risk factors, onset at any moment, or early-onset severe nosocomial pneumonia |</p>
<table>
<thead>
<tr>
<th>Key organisms*</th>
<th>Key antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteric Gram-negative bacteria (non-Pseudomonas such as: <em>Enterobacter, Escherichia coli, Proteus, Klebsiella, Serratia marcescens, Haemophilus influenzae</em> Methicillin susceptible <em>Staphylococcus aureus</em> <em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Cephalosporin (second- or third-generation, non-anti-pseudomonas) or β-lactam/β-lactamase inhibitor or if allergic to penicillin, a fluoroquinolone* or clindamycin+aztreonam</td>
<td></td>
</tr>
</tbody>
</table>

<p>| Group 2: mild-to-moderate nosocomial pneumonia with risk factors associated with specific additional organisms, onset in any moment |</p>
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Key organisms+specific risk organisms*</th>
<th>Key antibiotics+specific additional coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal surgery, aspiration</td>
<td>Anaerobes</td>
<td>Clindamycin, or β-lactam/β-lactamase inhibitor + vancomycin (until MRSA is not excluded)</td>
</tr>
<tr>
<td>Coma, cranial trauma, diabetes, renal failure</td>
<td><em>S. aureus</em></td>
<td>Erythromycin+rifampin</td>
</tr>
<tr>
<td>High-dose steroids</td>
<td><em>Legionella</em></td>
<td>Treat as severe nosocomial pneumonia (group 3)</td>
</tr>
<tr>
<td>Prolonged stay in intensive care, steroids, antibiotics, pulmonary disease</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
</tbody>
</table>

<p>| Group 3: severe nosocomial pneumonia with risk factors, early onset, or severe nosocomial pneumonia, late onset |</p>
<table>
<thead>
<tr>
<th>Key organisms*</th>
<th>Antibiotics</th>
</tr>
</thead>
</table>
| *Pseudomonas aeruginosa*  
*Acinetobacter spp.*  
Consider MRSA | Aminoglycoside or ciprofloxacin+ one of the following: anti-pseudomonas penicillin, β-lactam/β-lactamase inhibitor and + vancomycin (if MRSA is a problem) |

*Recommended treatment does not include immunocompromized patients.  
*If *S. pneumoniae* is not a problem.  
MRSA: methicillin-resistant *S. aureus*. 
attention on the length of stay and the degree of reimbursement from health authorities. For this reason, management of lower respiratory tract infection cases must be shifted to less expensive environments, therefore dismissing the patient as soon as possible. A further, often ignored endpoint, is the economical prospective of the patient (e.g. patient’s inability to work and consequent loss in salary). Only short effective treatment may give satisfactory answers to this last problem. Therefore, it must always be kept in mind that economical effects have driven, and will continue to drive, patient treatment. On the basis of all aspects mentioned above, the utility of guidelines for the treatment of lower respiratory tract infections becomes apparent.

References