REVIEW ARTICLE

Drugs 2005; 65 (14): 1949-1971
0012-6667/05/0014-1949/$39.95/0

Optimal Pharmacological Therapy for Community-Acquired Pneumonia

The Role of Dual Antibacterial Therapy

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Abstract

The optimal pharmacological therapy of community-acquired pneumonia (CAP) is one of the most ardently debated issues in medicine. Presently, most guidelines recommend either a fluoroquinolone alone or dual therapy with a third-generation cephalosporin plus a macrolide in patients hospitalised with CAP, but few provide clinicians with specific considerations for selecting from these agents. Despite a similar spectrum of activity and favourable resistance patterns (for fluoroquinolones and third-generation cephalosporins) against CAP pathogens, there is emerging evidence that dual therapy may be superior to monotherapy in certain populations.

In patients with non-severe CAP, the evidence supports the use of either monotherapy or dual therapy in most patients; however, patients with severe CAP or bacteraemic pneumococcal CAP experience improved survival when treated with dual therapy. It is unclear from this evidence if any specific combination of agents is the most effective, but the combination of a third-generation cephalosporin plus a macrolide is the most extensively studied. Dual therapy was superior to monotherapy irrespective of the susceptibility of the aetiological pathogen, thus insufficient antimicrobial spectrum does not explain the disparity. The most likely explanation for improved outcomes with dual therapy is the

combined effect of optimised antimicrobial spectrum (including atypicals), decreased impact of resistance to a single agent and the immunomodulatory effects of macrolides. Increasing resistance in patients with non-severe CAP warrants the consideration of dual therapy and perhaps a reappraisal of agents usually reserved for second-line therapy, including doxycycline, in these populations as well. In light of the available evidence, dual therapy should be strongly considered in all patients with severe CAP, especially when complicated by pneumococcal bacteraemia.

Remarkable advances in antibacterial therapy during the antibiotic era have dramatically improved the fate of patients with community-acquired pneumonia (CAP). Massive global efforts have been launched in an attempt to elucidate the most effective treatment strategy for patients with CAP. Paradoxically, these extensive efforts have exposed more questions than answers. In reference to CAP, one author wrote that, "few diseases are so characterised by disputes about diagnostic evaluation and therapeutic decisions".[1] The absence of an optimal treatment strategy is unsettling since CAP is a leading cause of hospitalisation and death due to infection. The social burden of CAP in terms of associated morbidity, mortality and cost is colossal.[2] It is the sixth most common cause of death overall and fifth among patients >65 years of age. Hence, tremendous resources have been allocated to efforts attempting to identify the most effective treatment strategy. Paramount in this search has been the pursuit of an ideal antibacterial regimen. Appropriate antibacterial therapy can mitigate the need for hospitalisation, shorten length of stay (LOS), decrease complications and prevent mortality. Despite ardent efforts, identification of the most favourable antibacterial regimen remains an elusive goal.

Over the last decade, many professional organisations and societies from several countries have prepared evidence-based guidelines for the empirical treatment of CAP (table I). The biomedical literature is replete with studies exploring pharmacological therapy for CAP; nonetheless, there is a lack of consensus regarding first-line treatment.[3] Contention exists not only between recommendations from different parts of the world but also among guidelines from the same country. Moreover, such recommendations are dynamic and must evolve to account for shifts in aetiological pathogens, resistance patterns and availability of new antibacterials, thus also generating time-dependent variation. The disparities have spawned debate among experts who study CAP and created confusion among clinicians who treat it. Much of the controversy can be attributed to the fact that clinical trials in patients with CAP have been marred by limitations such as heterogeneity across trials, non-experimental design, power to show equivalence rather than superiority, evaluation of irrelevant antibacterial regimens, and inconsistencies in diagnosis, outcome attainment and follow-up.[4] An emerging dilemma is whether treatment with a combination of two antibacterials, hereafter referred to as dual therapy, is superior to monotherapy for the treatment of CAP.[5,6] This matter is particularly germane in patients with severe CAP, where rapid initiation of effective antibacterial therapy is life saving. Similarly, in an era of growing antibacterial resistance, there are now concerns that monotherapy may be insufficient in patients with mild-to-moderate CAP.

Most guidelines recommend an extended-spectrum cephalosporin (e.g. ceftriaxone) plus an advanced macrolide (e.g. azithromycin or clarithro-

mycin) or monotherapy with a fluoroquinolone for patients treated on a general medical ward.[8-15] However, only one consensus group, the Antibiotic Selection for Community-Acquired Pneumonia Panel (ASCAP),[7] emphasises the use of one regimen over the other. Consequently, it is not surprising that fluoroquinolone use has increased dramatically over the last decade,[16] given the simplicity of monotherapy, once-daily dose administration, and near complete bioavailability that facilitates intravenous to oral conversion and subsequent discharge. It is unclear whether these conveniences yield improved patient outcomes. On the contrary, there is emerging evidence that monotherapy may be inferior to dual therapy.[5] Historically, this has been the case with other infectious entities with a predilection for drug resistance, such as tuberculosis and AIDS in which multidrug regimens are the foundation of effective treatment. Recently, a number of investigations have addressed this perplexing issue in patients with severe[17-21] and non-severe CAP.[22-32] Thus, we reviewed the literature to determine if in fact the available evidence supports dual therapy in patients with CAP.

1. Non-Severe Community-Acquired Pneumonia (CAP)

On average, 30-day mortality among patients with pneumonia is 13.7%, but varies from <1% to 36.5% depending on the presence of risk factors at the time of diagnosis.[33,34] The majority of patients with non-severe CAP can be managed at home, while those with severe disease should be managed in an inpatient setting. The pneumonia severity index (PSI) is the most widely used and validated approach to risk stratification.[34] For the purpose of this review, studies are divided into those examining patients with non-severe or severe CAP, since previous evidence suggests that dual therapy may exert the greatest impact in the sickest patients.[20] Because some studies employed different methods of risk stratification,[22,27,30,31] we have classified such papers on a case-by-case basis considering the specific risk assessment tool applied and the overall mortality in the investigation. Studies comparing dual therapy with monotherapy in patients with predominantly non-severe CAP are summarised in table II.

Plouffe et al.[25] randomised patients hospitalised with CAP to either azithromycin monotherapy or cefuroxime with or without erythromycin. The addition of erythromycin in the cefuroxime arm was left to the discretion of the treating physician. Patients were stratified based on PSI; the majority (80%) of the study population were in classes I–III. The most frequently isolated pathogens were *Streptococcus pneumoniae* and *Haemophilus influenzae*. Clinical outcome data were available for 268 patients. At the 10- to 14-day visit, 106 (77%) azithromycin-treated patients were clinically cured versus 97 (74%) patients in the cefuroxime plus erythromycin arm. Results from the microbiologically evaluable populations mirrored clinical findings. A similar study comparing the same treatment regimens reached the same conclusion.[23] Collectively, these studies suggest that azithromycin is as effective as cefuroxime plus erythromycin in this setting; however, there are important limitations to consider when interpreting these results. A major shortcoming is the treatment regimens examined. The combination of cefuroxime and erythromycin is not presently recommended because of reduced activity of cefuroxime against *S. pneumoniae* (compared with other cephalosporins) and erythromycin against *H. influenzae* (azithromycin exhibits minimum inhibitory concentrations [MICs] that are at least two full dilutions less than erythromycin with *H. influenzae*). Perhaps the results would have been different had a more active cephalosporin (e.g. ceftriaxone) been applied in the dual therapy cohort. Furthermore, the inclusion of erythromycin as the macrolide in the dual therapy arm precludes a true comparison of

Table I. Summary of treatment recommendations for community-acquired pneumonia (CAP)[a]

Organisation (year)	Outpatient management	Inpatient management
North American guidelines		
Antibiotic Selection for Community-Acquired Pneumonia[7] (2005)	Absence of cardiopulmonary disease or other modifiers: azithromycin Cardiopulmonary disease or other modifiers: moxifloxacin or telithromycin	Ceftriaxone plus azithromycin (other considerations that may modify treatment include nursing home residence and risk factors for *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*) Severe CAP: ceftriaxone plus moxifloxacin or levofloxacin
Infectious Disease Society of America (2003)[8]	Absence of cardiopulmonary disease or other modifiers and no recent antibacterial exposure[b]: macrolide; doxycycline. Recent antibacterial exposure: advanced macrolide[c] *plus* high-dose amoxicillin/clavulanic acid; antipneumococcal fluoroquinolone[d]. (Other considerations include aspiration or influenza with bacterial superinfection) Cardiopulmonary disease or other modifier and no recent antibacterial exposure: advanced macrolide[c], antipneumococcal fluoroquinolone[d]. Recent antibacterial exposure: antipneumococcal fluoroquinolone[d]; advanced macrolide[c] plus a β-lactam[e]	No recent antibacterial exposure: antipneumococcal fluoroquinolone[d]; advanced macrolide[c] plus a β-lactam[f] Recent antibacterial exposure: advanced macrolide[c] plus a β-lactam; antipneumococcal fluoroquinolone[d]. (Other considerations that may modify treatment include intensive care unit or nursing home care and risk factors for *P. aeruginosa*)
American Thoracic Society (2001)[9]	Absence of cardiopulmonary disease or other modifiers: advanced macrolide[c] Cardiopulmonary disease ± other modifiers: β-lactam[g] *plus* macrolide or doxycycline; antipneumococcal fluoroquinolone[d]	Absence of cardiopulmonary disease or other modifiers: intravenous azithromycin; doxycycline *plus* β-lactam; antipneumococcal fluoroquinolone[d] Cardiopulmonary disease ± other modifiers: β-lactam[h] *plus* macrolide or doxycycline; intravenous antipneumococcal fluoroquinolone[d]
Canadian Infectious Disease Society, Canadian Thoracic Society (2000)[10]	Without modifier: macrolide; doxycycline With modifiers but without recent antibacterial or corticosteroid exposure: advanced macrolide[c]. With antibacterial or corticosteroid exposure: antipneumococcal fluoroquinolone[d]; β-lactam[g] plus macrolide. (Other considerations include aspiration and nursing home residence)	Nursing home resident or suspected *Streptococcus pneumoniae*, *Legionella pneumophilia* or *Chlamydia pneumoniae*: antipneumococcal fluoroquinolone[d]; cephalosporin *plus* macrolide
European guidelines		
British Thoracic Society (2001)[11]	Non-severe disease: amoxicillin; macrolide if β-lactam intolerant	Non-severe disease: amoxicillin *plus* macrolide; antipneumococcal fluoroquinolone[d]
French Society of Infectious Diseases (2001)[12]	Mild disease: high-dose amoxicillin; antipneumococcal fluoroquinolone[d] (β-lactam intolerant patients) Mild disease with comorbidities: high-dose amoxicillin/clavulanic acid; ceftriaxone. (Other considerations include suspected atypical pathogens or aspiration)	With comorbidities: high-dose amoxicillin/clavulanic acid; ceftriaxone. (Other considerations include suspected atypical pathogens or aspiration)
Spanish Respiratory Society, Spanish Society of Chemotherapy (2000)[13]	Mild disease with typical presentation: high-dose amoxicillin; antipneumococcal fluoroquinolone[d]; macrolide. Atypical presentation: macrolide; antipneumococcal fluoroquinolone[d]	β-Lactam[i] ± macrolide or ciprofloxacin; antipneumococcal fluoroquinolone[d]

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Table I. Contd

Organisation (year)	Outpatient management	Inpatient management
German Respiratory Society, Paul Erhlich Society of Chemotherapy (2000)[14]	Patients <65 years without comorbidities: β-lactam[j]; macrolide; antipneumococcal fluoroquinolone[d]; doxycycline Patients ≥65 years and/or comorbidities: β-lactam[j]; antipneumococcal fluoroquinolone[d]	Severe disease in elderly with comorbidities: β-lactam[j] *plus* macrolide; antipneumococcal fluoroquinolone[d]; carbapenem *plus* macrolide; ciprofloxacin *plus* clindamycin

a Modifying factors vary by guideline and generally include risk factors for more severe disease or drug-resistant aetiologies.

b Within 3 months.

c Azithromycin or clarithromycin.

d Levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin.

e High-dose amoxicillin, high-dose amoxicillin/clavulanic acid, cefpodoxime, cefprozil or cefuroxime.

f Cefotaxime, ceftriaxone, ampicillin/sulbactam or ertapenem.

g Intravenous cefotaxime, ceftriaxone, sulbactam/ampicillin, high-dose ampicillin.

h Parenteral cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin.

i Intravenous amoxicillin/clavulanic acid, ceftriaxone, cefotaxime.

j Aminopenicillin/β-lactamase inhibitor, second- or third-generation cephalosporin.

monotherapy and dual therapy because it is not possible to decipher whether equivocal findings are the result of differences in the effectiveness of the two macrolides or an actual lack of advantage of dual therapy over monotherapy. Moreover, not all patients in the dual therapy group received erythromycin and the decision to prescribe a macrolide may have introduced unforeseen bias. A true comparison would randomise patients to azithromycin monotherapy or the combination of cefuroxime plus azithromycin in all patients. Finally, results from these studies may not be applicable to all practice settings since 30–50% of participants could be considered candidates for outpatient therapy based on their baseline risk assessment.[34,35] These results must be interpreted in the context of these limitations.

A multicentre randomised trial evaluated 283 patients hospitalised with CAP at 45 North American sites (44 sites in the US and 1 in Canada).[27] Antibacterial regimens included gatifloxacin versus ceftriaxone plus provisional erythromycin. Erythromycin was added at the discretion of the investigator if an atypical aetiology was suspected. PSI was calculated retrospectively: 33% of patients were determined to be class IV in severity, while 7% were class V; the remaining 60% were classified as class III or better. A pretreatment pathogen was isolated in 52% of patients: *S. pneumoniae* in 26.3%, *H. influenzae* in 10.3%, atypicals in 15.6% and *Staphylococcus aureus* in 15.6%. Fifty-six patients (39%) in the ceftriaxone arm received erythromycin during the study period. Among the clinically evaluable patients (72% of the intention-to-treat [ITT] population), clinical response was achieved in similar numbers treated with gatifloxacin or ceftriaxone with or without erythromycin (97% vs 91%, respectively; 95% CI −2.5, 17.6). Results for the microbiologically evaluable population were identical to those in clinically evaluable patients. In the dual therapy arm, outcomes for patients who received a macrolide versus those who did not were not reported separately, thereby precluding a direct comparison of dual therapy with monotherapy. Only 39% of the dual therapy arm actually received dual therapy, which would be expected to attenuate any potential benefit of administering two antibacterials.

A multicentre, open-label randomised trial compared levofloxacin with ceftriaxone plus azithromycin in 236 patients with CAP.[28] This study was truly a comparison of monotherapy with dual therapy since all patients in the dual group received azithromycin in addition to ceftriaxone. The authors described the population as having moderate to se-

Table II. Studies comparing monotherapy with dual therapy in patients with non-severe community-acquired pneumonia (CAP)

Study (year)	Study design	Patient population	Exclusion criteria	Antibacterial therapy	Number of patients	Outcome (%)	
						clinical response	mortality
File et al.[22] (1997)	Multicentre, open-label, randomised, parallel group	Adults with clinical and radiographic evidence of CAP treated as inpatients or outpatients	Hypersensitivity to treatment, resistant organisms, other significant lung disease, immunosuppression, nosocomial infection, seizures, psychiatric illness, pregnancy/ nursing, severe renal impairment	Levofloxacin vs ceftriaxone or cefuroxime ± erythromycin	226 230	96 90	
Fogarty et al.[27] (1999)	Multicentre, open-label, randomised, parallel group	≥18 years newly hospitalised with clinical, radiographic and laboratory evidence of CAP	Hypersensitivity to treatments, pregnancy or lactation, severe comorbidities, immunosuppression, renal or hepatic disease, nursing home or long-term care facility residence, conditions affecting gastric absorption	Gatifloxacin vs ceftriaxone ± erythromycin	141 142	97 91	
Vergis et al.[23] (2000)	Multicentre, open-label, randomised, parallel group	≥18 years with clinical and radiographic evidence of CAP	Hypersensitivity to treatments, condition affecting gastric absorption, immunosuppression, severe renal disease, hospitalisation within 14 days, nursing home residence	Azithromycin vs cefuroxime + erythromycin	67 78	91 91	
Plouffe et al.[25] (2000)	Multicentre, open-label, randomised, parallel group	≥16 years hospitalised with clinical and radiographic evidence of CAP, required initial intravenous therapy	Hypersensitivity or intolerance to treatments, pregnancy/lactation, peptic ulcer disease, conditions affecting gastric absorption, drug/alcohol dependence, significant comorbidity, coexisting lung disease renal/hepatic disease, severe CAP, immunosuppression, resistant Gram-negative pathogen, hospitalisation within 14 days	Azithromycin vs cefuroxime ± erythromycin	202 201	77 74	

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Table II. Contd

Study (year)	Study design	Patient population	Exclusion criteria	Antibacterial therapy	Number of patients	Outcome (%)	
						clinical response	mortality
Finch et al.[30] (2002)	Multinational, open-label, randomised, parallel group	≥18 years hospitalised <48 hours with clinical and radiographic evidence of CAP, required initial intravenous therapy	Hypersensitivity to treatments, significant comorbidity, coexisting lung disease, prolonged QT interval or treated with class IA/III antiarrhythmic, aspiration pneumonia	Moxifloxacin vs amoxicillin/clavulanic acid ± clarithromycin	301 321	93.4 85.4	
Lode et al.[29] (2002)	Multicentre, open-label, randomised, parallel group	≥18 years hospitalised with clinical and radiographic evidence of CAP, requiring initial intravenous therapy	Nosocomial/aspiration pneumonia, hospitalisation within 14 days, pregnancy, immunosuppression, drug/alcohol abuse	Gemifloxacin vs ceftriaxone/cefuroxime ± macrolide	172 173	92.2 93.4	
Paladino et al.[24] (2002)	Multicentre, open-label, randomised, parallel group	Adult patients hospitalised with CAP	Hypersensitivity or intolerance to treatments, pregnancy/lactation, renal or hepatic disease, significant comorbidity, immunosuppression	Azithromycin vs cefuroxime ± erythromycin	136 130	78 75	
Frank et al.[28] (2002)	Multicentre, open-label, randomised, parallel group	≥18 years with moderate to severe CAP diagnosed in community or nursing home	Hypersensitivity to treatments, known resistant pathogen, pregnancy/lactation, hospitalised within 14 days, severe renal disease, aspiration pneumonia, immunosuppression, seizures, psychiatric illness	Levofloxacin vs ceftriaxone + azithromycin	115 121	94.1 92.3	
Gleason et al.[32] (1999)	Multicentre, retrospective case analysis of Medicare patients	≥65 years with a principal or secondary discharge diagnosis of pneumonia	Hospitalisation within previous 10 days, immunodeficiency, organ transplantation, death on hospital day 1	1GC only vs 2GC only vs 2GC + macrolide vs 3GC only vs 3GC + macrolide vs β-lactam/β-lactamase inhibitor vs fluoroquinolone alone vs aminoglycoside + additional agent	427 1 592 544 3 430 1 139 971 259 841		11.6 11.7 8.4 14.9 9.1 22.2 10.6 24
Brown et al.[31] (2003)	Retrospective analysis of hospital claims database	>18 years with diagnosis of CAP	Intensive care unit admission, immunosuppression, mechanical ventilation, incomplete antibacterial data, patients at highest risk	Dual therapy vs monotherapy	25 996 18 818		<3 5–8

1GC = first-generation cephalosporin; **2GC** = second-generation cephalosporin; **3GC** = third generation cephalosporin.

vere CAP based on an average PSI of 93.4. There was no breakdown of the number of participants in each PSI class, but the low incidence of bacteraemia (n = 5) and low mortality (n = 6) suggest that patients had primarily mild-to-moderate disease. Treatment regimens in this study were consistent with clinical practice: patients received levofloxacin 500mg intravenously (or orally if appropriate) daily or ceftriaxone 1g intravenously daily for at least 2 days plus azithromycin 500mg intravenously once daily. Clinical success was achieved in 94.1% and 92.3% (95% CI −10.2, 6.58) of the clinically evaluable patients and 91.7% and 94.3% (95% CI −10.67, 15.91) of the microbiologically evaluable patients for levofloxacin and ceftriaxone plus azithromycin, respectively. This trial was hampered by a high clinical attrition rate: only 163 patients (69% of the ITT population) were clinically evaluable. Nonetheless, results were similar in the ITT population and suggest that levofloxacin is as effective as dual therapy with ceftriaxone plus a macrolide in similar, low-risk populations.

In a retrospective case analysis of hospital claim records, Brown et al.[31] explored the relationship between dual therapy and outcomes in 44 814 persons discharged with a diagnosis of CAP. The authors used an older risk assessment tool to stratify patients since inadequate data was available to calculate PSI. More than 90% of patients had mild-to-moderate CAP according to the method applied. Patients were arbitrarily divided into cohorts based on the antibacterial regimen received. The cohorts included monotherapy with: (i) ceftriaxone; (ii) macrolides; (iii) 'other' cephalosporins; (iv) fluoroquinolones; or (v) penicillins; and (vi) dual therapy with the same classes listed (with the exception of macrolides) plus a macrolide. Mortality in the dual therapy cohort was consistently lower regardless of which agent was combined with a macrolide (<3% with dual therapy vs 5–8% with monotherapy; $p < 0.05$); there were commensurate decreases in LOS and total hospital charges ($p < 0.0001$). Dual therapy with ceftriaxone plus a macrolide also prolonged survival ($p < 0.0001$) and shortened LOS ($p < 0.0001$). Monotherapy with either fluoroquinolones or penicillins resulted in the longest LOS and the highest total hospital charges. The penicillin group included agents such as β-lactam/β-lactamase inhibitors, which may be prescribed in more severely ill patients, partly explaining poor outcomes in this cohort. A major limitation in this analysis is the arbitrary classification of antibacterial therapy into groups. For instance, cephalosporins were classified as ceftriaxone or 'other' cephalosporins; patients treated with non-ceftriaxone third-generation cephalosporins (e.g. cefotaxime) were included in the 'other' cephalosporin group despite a similar spectrum of activity among these drugs. In addition, patients were not well matched; those treated with macrolide monotherapy were younger and had a lower baseline risk score. However, this would tend to bias the results in favour of macrolide monotherapy, minimising the differences observed between the two strategies. Finally, the retrospective design relegates the findings to being hypothesis generating. Even in the context of the aforementioned limitations, the finding of improved outcomes in all dual therapy cohorts compared with monotherapy is compelling.

In a retrospective case review, Gleason et al.[32] utilised the Medicare National Claims History File to identify patients with either a primary discharge diagnosis of pneumonia or respiratory failure, the latter having to be accompanied by a secondary discharge diagnosis of pneumonia. A random selection procedure was implemented to select 26 000 discharges, of which 12 945 patients met the inclusion criteria and were enrolled in the study. Trained abstractors reviewed medical records of cases and abstracted data was merged with hospital claims data from the Health Care Financing Administration. PSI was utilised to classify baseline risk; the

majority of patients were in classes III and IV, while 24.2% were class V. The following antibacterial regimens were administered to at least 2% of the entire population: (i) first-generation cephalosporin; (ii) second-generation cephalosporin; (iii) second-generation cephalosporin plus a macrolide; (iv) third-generation cephalosporin; (v) third-generation cephalosporin plus a macrolide; (vi) β-lactam/β-lactamase inhibitor; (vii) fluoroquinolone; or (viii) aminoglycoside plus any other antibacterial. Patients treated with regimens classified as 'other' made up 24.1% of the study population. Overall, 30-day mortality was 15.3%, but was highly dependent on the antibacterial regimen prescribed, ranging from 8.4% in patients treated with a second-generation cephalosporin plus a macrolide to 24.0% in patients treated with an aminoglycoside plus another agent. Three regimens were identified in the adjusted analysis as being independently associated with 30-day mortality: third-generation cephalosporin plus a macrolide (hazard ratio [HR] 0.74; 95% CI 0.60, 0.92), a second-generation cephalosporin plus a macrolide (HR 0.71; 95% CI 0.52, 0.96) or a fluoroquinolone (HR 0.64; 95% CI 0.43, 0.94). Mortality was significantly increased in patients treated initially with a β-lactam/β-lactamase inhibitor plus a macrolide (HR 1.77; 95% CI 1.28, 2.46) or an aminoglycoside plus an additional agent (HR 1.21; 95% CI 1.02, 1.43). Analyses were also performed to determine whether changes in antibacterial therapy after 48 hours or exclusion of patients who died within this window had an impact on the results; the findings were insensitive to these adjustments. Despite the size of the database, the power to detect differences among individual regimens was limited because of the number of different antibacterial regimens evaluated and because 24.1% of patients received treatment that was classified as 'other'. For instance, dual therapy with a second- or third-generation cephalosporin plus a macrolide or monotherapy with a fluoroquinolone was associated with improved survival; however, only 15% of the total population received one of these regimens. The most salient limitation in this analysis is its retrospective design. One appreciable example of how this design introduced bias is the observation of increased mortality in patients treated with β-lactam/β-lactamase inhibitors; it is plausible that use of these agents is merely a surrogate for more severely ill patients rather than inferior treatment.

Limitations in other studies not discussed individually include treatment with, or oral transition to, inappropriate or irrelevant antibacterial regimens, no clear definition of macrolide use in the dual therapy arm, failure to report outcomes separately for patients in the dual therapy groups who were prescribed and were not prescribed a macrolide, lack of risk stratification or use of an outdated risk assessment tool, and failure to report outcomes according to baseline risk assessment.[24,29,30] Summaries of these studies can be found in table II.

2. Severe CAP

The efficacy of monotherapy has been questioned in severe CAP where breakthrough bacteraemia has been reported in patients treated with a macrolide alone.[36-38] Dual therapy may be especially important in patients with pneumococcal bacteraemia where mortality ranges from 21% to 40%.[39] Table III summarises studies that compared dual antibacterial therapy with monotherapy in patients with severe CAP.

A single prospective study addressing this clinical dilemma has been conducted.[20] The international, observational investigation evaluated the effects of dual therapy compared with monotherapy on survival. Consecutive patients, totaling 844, admitted with bacteraemic pneumococcal pneumonia were enrolled from 21 hospitals located in ten countries on six continents, representing a diverse collection of patients. The authors stratified patients based on age, presence of immunosuppression and pres-

Table III. Studies comparing monotherapy with dual therapy in patients with severe community-acquired pneumonia (CAP)

Study (year)	Study design	Patient population	Exclusion criteria	Antibacterial therapy	Number of patients	Mortality (%)
Mufson and Stanek[18] (1999)	Epidemiological investigation	600 consecutive patients with bacteraemic pneumococcal pneumonia	None disclosed	β-Lactam + macrolide vs β-lactam + non-macrolide vs β-lactam	56 95 138	6 28.6 16.7
Waterer et al.[17] (2001)	Retrospective case analysis of medical records from 13 hospitals	≥18 years with clinical and radiographic diagnosis of CAP and ≥1 positive blood culture for *Streptococcus pneumoniae* within 48 hours of admission	Immunosuppression, patients in whom the initial isolate was resistant to treatment	SET vs DET	99 102	18.2 6.9
Martinez et al.[19] (2003)	Retrospective analysis of prospectively collected data	Patients hospitalised with CAP and ≥1 positive blood culture for *S. pneumoniae* who received a β-lactam with or without other antibacterials	None disclosed	β-Lactam + macrolide vs β-lactam alone	238 171	11.4 8.2
Baddour et al.[20] (2004)	Prospective, observational, international	844 consecutive patients ≥15 years with pneumococcal bacteraemia	Suboptimal antibacterial dose, initiation of therapy >24 hours after admission, or no consistent antibacterial regimen during first 2 days of admission	Dual therapy vs monotherapy (overall) Dual therapy vs monotherapy (critically ill)	202 390 47 47	10.4 11.5 23.4 55.3
Weiss et al.[21] (2004)	Retrospective case analysis	95 consecutive patients with bacteraemic pneumococcal pneumonia	Other infectious complications, treatment with antibacterials other than β-lactams or macrolides	Cefuroxime vs ceftriaxone + azithromycin	42 53	25.6 7.5

DET = dual effective therapy; **SET** = single effective therapy.

ence of chronic underlying disease. Patients with critical illness, as defined by the Pitt bacteraemia and APACHE (Acute Pathophysiology and Chronic Health Evaluation) scores were included in an additional analysis. To be eligible for inclusion, patients had to receive at least the minimum recommended dose of an antibacterial with the first dose administered within 24 hours of admission. Monotherapy was defined as treatment with the same single antibacterial for at least 2 days, whereas dual therapy was defined as administration of two different antibacterials concomitantly for at least 2 days. Application of these criteria resulted in 592 patients available for comparison. Overall, 16.5% of patients died (139 of the original 844) by day 14. As expected, patients who were deemed critically ill were significantly more likely to die (54.6% vs 7.3%; $p = 0.0001$) than their healthier counterparts. The 14-day mortality was not statistically different (10.4% vs 11.5%; p-value not significant) between the two treatment strategies. However, when critically ill patients ($n = 94$) were considered alone, dual therapy was associated with a significant survival benefit (14-day mortality 23.4% vs 55.3%; $p = 0.0015$). In this subpopulation, monotherapy was dominated by third-generation cephalosporins (53%) and other β-lactam agents (38%), while macrolides, fluoroquinolones and clindamycin were administered infrequently. The most frequently prescribed dual regimens were a β-lactam plus macrolide (30%), β-lactam plus vancomycin (26%), β-lactam plus aminoglycoside (15%), vancomycin plus other antibacterial (9%) or β-lactam plus a fluoroquinolone (9%). Dual therapy was more effective regardless of pneumococcal susceptibility, which suggests that resistance to the agent selected for monotherapy did not account for the observed differences in outcome. The authors also examined individual regimens to determine if any single agent/regimen was responsible for the survival disparity. Consistent with the observation of Waterer's group,[17] dual therapy was superior to monotherapy irrespective of the combination of drugs prescribed. This study was not a randomised trial and cannot account for unexpected forms of bias such as confounding by indication and, therefore, cause and effect cannot be established. The overall finding of similar survival in patients treated with dual or monotherapy is the culmination of similar mortality in patients who were not critically ill and a significant reduction in mortality in critically ill patients. This is consistent with the overall observation that dual therapy may be most influential in patients with severe disease, whereas in patients with non-severe CAP mortality may be too low for significant differences to be appreciated.

Martinez et al.[19] analysed 10 years of patient data from a single institution in Spain, in order to evaluate the impact of adding a macrolide to β-lactam-based empirical therapy. This analysis was nested within a prospective observational study of consecutive patients admitted with a diagnosis of bacteraemic pneumococcal pneumonia between 1991 and 2000. Patients who had been treated with a β-lactam as part of their routine care were retrospectively identified and reviewed in an attempt to determine if the addition of a second antibacterial, in this case a macrolide, influenced survival. A total of 409 patients were identified who met the inclusion criteria, of whom 238 (58%) were treated with a β-lactam plus a macrolide and 171 (42%) received a β-lactam without a macrolide. Empirical β-lactam therapy consisted of cefotaxime, ceftriaxone, ceftazidime or cefepime in 79% of patients, a second-generation cephalosporin in 5.9%, and penicillin or an aminopenicillin in 3.9%; carbapenems and cloxacillin were used infrequently. Of the macrolides prescribed, erythromycin accounted for the bulk of use (68%) followed by azithromycin (29%) and clarithromycin (3%). Patients who received a macrolide were less likely to have a comorbidity ($p = 0.0002$) or be infected with a resis-

tant organism ($p = 0.02$) than patients not treated with a macrolide. Conversely, patients treated with a macrolide were more likely to present with shock ($p < 0.0001$) or be admitted to the intensive care unit (ICU) [$p < 0.0001$]. Thirty-five patients died during hospitalisation; approximately one-third of those deaths occurred within 48 hours. Factors that were associated with in-hospital mortality were shock ($p < 0.0001$), infection with *S. pneumoniae* resistant to both penicillin and erythromycin ($p = 0.02$), and ICU admission ($p < 0.0001$). After controlling for these and other variables in a stepwise logistic regression model, shock ($p < 0.0001$), age ≥65 years ($p = 0.02$), infection with penicillin-resistant *S. pneumoniae* (PRSP) [$p = 0.04$] and absence of a macrolide in the initial antibacterial regimen ($p = 0.03$) proved to be independent predictors of mortality. Because death within 48 hours after presentation signifies the most severe disease and may not be amenable to antibacterial therapy, the analysis was also performed after exclusion of these patients. In this model, lack of a macrolide as part of treatment remained an independent predictor of in-hospital mortality (adjusted odds ratio [OR] 4.0; 95% CI 1.23, 13.4). Furthermore, when the subgroup of patients who received cefotaxime, ceftriaxone or cefepime plus a macrolide were compared with patients receiving one of these antibacterials without a macrolide, mortality was significantly lower with dual therapy (adjusted OR 0.28; 95% CI 0.009, 0.9). Although the results must be interpreted in the context of the retrospective nature of the study, dual therapy with a third-generation cephalosporin plus a macrolide improved survival compared with monotherapy.

In an epidemiological study, Mufson and Stanek[18] evaluated outcomes in patients with bacteraemic pneumococcal pneumonia during a 20-year period in one city in West Virginia, USA. The study population consisted of 45 children and 328 adults admitted consecutively. The most effective regimen was a combination of a penicillin or cephalosporin plus a macrolide (figure 1). The case fatality rate decreased over time (1978–82, 30.2%; 1983–7, 34.4%; 1988–92, 21.1%; 1993–7, 15.6%; $p = 0.03$). The change in survival paralleled a nearly 3-fold increase in the number of patients treated with a penicillin or cephalosporin plus a macrolide. Epidemiological studies, including this effort, are subject to the usual inherent biases and confounding present in all such analyses. Noteworthy limitations in this study include an inability to account for confounding variables (e.g. immunosuppression, comorbidities, resistance, etc.), it being the experience of a single city and that antibacterials were grouped into broad classes (e.g. 'cephalosporins').

Waterer and colleagues[17] performed a retrospective case analysis of patients aged ≥18 years admitted to any one of three tertiary, two secondary or eight rural community hospitals in Tennessee, USA, with a diagnosis of CAP and pneumococcal bacteraemia between 1996 and 2000. The authors deemed the empirical regimen effective if the pathogen was found to be susceptible to the antibacterial(s) pre-

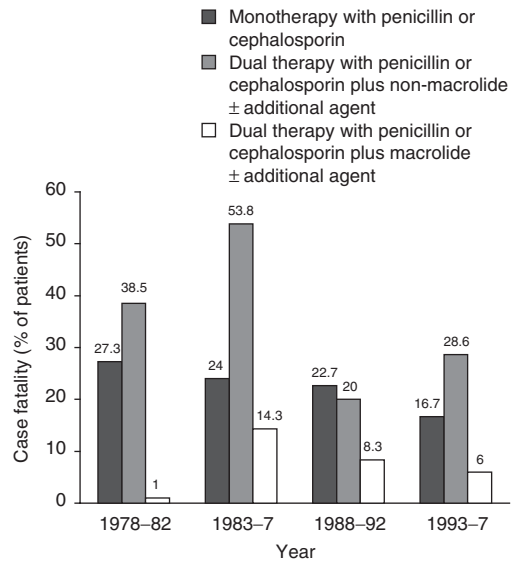

Fig. 1. Survival in patients with bacteraemic pneumococcal pneumonia according to type of antibacterial therapy.[18]

scribed. Therapy was further classified as single effective therapy (SET), dual effective therapy (DET) or more than DET (MET). A multivariate logistic regression model was created to account for potential confounders; covariates included were antibacterial treatment, age, sex, underlying chronic disease, alcohol use and APACHE II score. MET was associated with severity of illness such that patients receiving three or more antibacterials had more severe disease as evidenced by the PSI and APACHE II score. The severity of disease was similar between patients treated with SET and DET. Fluoroquinolones and third-generation cephalosporins were the most frequently used agents in patients prescribed SET. Among patients in the DET group, the combination of third-generation cephalosporin plus a macrolide or a third-generation cephalosporin plus a fluoroquinolone were the most common. The most frequently prescribed fluoroquinolone was levofloxacin (70.4%). Mortality was significantly higher in the SET group compared with the DET group (OR 3.0; p = 0.02). When the analysis was confined to the sickest patients, PSI IV and V, the OR for death in the SET group was 5.5 (95% CI 1.7, 17.5). When deaths occurring within the first 48 hours of admission were excluded, the results were similar (OR 4.9; 95% CI 1.6, 18.3). These findings imply that patients with bacteraemic pneumococcal CAP treated with two effective antibacterials are significantly less likely to die than patients who received a single agent, even if the infecting pathogen was susceptible to the agent administered as monotherapy. Limitations within this study include the non-randomised design, and definition of SET and DET, which was based on the antibacterials administered during the first 24 hours of therapy. The study was unable to control for time until the first dose of antibacterial or subsequent changes to the initial regimen. Also, because multiple antibacterial regimens were used, no conclusion can be made regarding the most effective combination of agents; however, the mortality was numerically lowest in patients receiving a third-generation cephalosporin plus a macrolide.

A retrospective review of all cases of bacteraemic pneumococcal CAP from a single tertiary care centre in Canada was conducted to explore the impact of dual therapy on outcomes.[21] Ninety-five patients met the inclusion criteria and were included in the analysis. The antibacterial regimens prescribed in these patients were cefuroxime monotherapy in 42 patients or a cephalosporin plus a macrolide in 53 patients (46 received ceftriaxone and 7 received cefuroxime). The mean PSI was 114; 68.4% of patients were classified as either class IV or V. Mortality was significantly higher in the group that received monotherapy compared with the dual therapy group (25.6% vs 7.5%; p = 0.02). Penicillin nonsusceptibiltiy was not associated with outcome. Therefore, the improved outcome with dual therapy cannot be attributed to resistance to cefuroxime in the monotherapy group. The observational design, small size and inclusion of cefuroxime in the monotherapy group and ceftriaxone in the dual therapy arm are notable limitations; it is also the experience of a single institution and may not be applicable to institutions that are geographically or demographically different.

3. Additional Considerations in the Comparison of Dual Therapy with Monotherapy

It is essential to select empirical therapy for CAP that is broad enough to cover the most likely pathogens;[40,41] however, if this were the only consideration then the broadest spectrum coverage possible would be administered to every patient. Instead, the goal for selecting empirical treatment is to select the narrowest therapy possible to avoid collateral damage (i.e. unintended and unnecessary exposure of microorganisms to antibacterials that select for antibacterial resistance and subsequent colonisation or

infection with multidrug-resistant organisms), while still providing an adequate spectrum of coverage. With respect to patient outcomes, there is presently insufficient evidence to embrace either monotherapy or dual therapy as the preferred treatment strategy in non-severe CAP, whereas combination therapy may confer a measurable benefit in more advanced forms of the disease. When combination therapy is employed, it is desirable to de-escalate treatment to monotherapy once the patient has stabilised (defervescence, decrease in white blood cell count, etc.); however, data to support this practice are sparse. Anecdotally, many clinicians recommend de-escalation from, for example, ceftriaxone 1 g/day plus azithromycin 500 mg/day to azithromycin 500 mg/day for 7–10 days after 3–5 days of combination therapy, provided the patient has met certain criteria suggesting improvement. Whether this practice is optimal with respect to clinical and microbiological outcomes is an important area for future study.

In the outpatient setting, assuming equivalent patient outcomes, dual therapy is less desirable than monotherapy from a cost and adherence perspective; however, burgeoning resistance to β-lactams and macrolides has, in some cases, left clinicians uncomfortable with prescribing one of these agents alone. *In vitro* resistance to the fluoroquinolones remains relatively uncommon (<2% nationally);[42] therefore, monotherapy with a fluoroquinolone appears attractive unless patients have recently (i.e. in the last 3 months) received an agent from this class.[8] However, it is no longer sufficient to base antibacterial selection decisions solely on clinical efficacy in individual patients; it is imperative that the cumulative impact of antibacterial exposure on the community is also considered. In this manner, fluoroquinolone use contributes to several disturbing resistance patterns, including fluoroquinolone-resistant *S. pneumoniae*,[43] extended-spectrum β-lactamase-producing Gram-negative Enterobacteriaceae,[44] meticillin-resistant *S. aureus*,[45,46] fluoroquinolone-resistant *Pseudomonas aeruginosa*[47] and vancomycin-resistant enterococci (VRE).[48] For example, Neuhauser et al.[47] evaluated 35 790 Gram-negative aerobic isolates recovered from ICU patients across 43 states from 1994 to 2000. Susceptibility to ciprofloxacin decreased steadily from 86% in 1994 to 76% in 2000. The decline in fluoroquinolone activity was significantly associated with increased national use of all fluoroquinolones among inpatients and outpatients. Antibacterials that exert activity against anaerobes[49-51] or *P. aeruginosa*[52] have also been implicated in the selection of resistant organisms, as have the third-generation cephalosporins.[53] As a result, clinicians are often faced with the unenviable task of balancing the need to cure individual patients with preserving the future effectiveness of antibacterials. Figure 2 depicts pathogens and treatment regimens recommended in CAP and their potential to inflict collateral damage.

4. Has Resistance Threatened the Effectiveness of Macrolides as Monotherapy?

Macrolide resistance has, in many locales, surpassed penicillin resistance in *S. pneumoniae*, yet its clinical relevance continues to be debated.[54-58] There is a disparity between substantial rates of *in vitro* macrolide resistance and relatively sparse reports of macrolide failure. Recent data from the TRUST (Tracking Resistance in the United States Today)[59] and ARM (Antimicrobial Resistance Management)[60] surveillance studies have reported that *S. pneumoniae* resistance to the macrolides has reached 25–30%; however, macrolide treatment failure is not yet commonplace. Regardless of the correlation between *in vitro* susceptibility data and clinical outcomes, clinical failure does occur with macrolide therapy.[36-38] One explanation for the divergence of *in vitro* and clinical outcomes is that

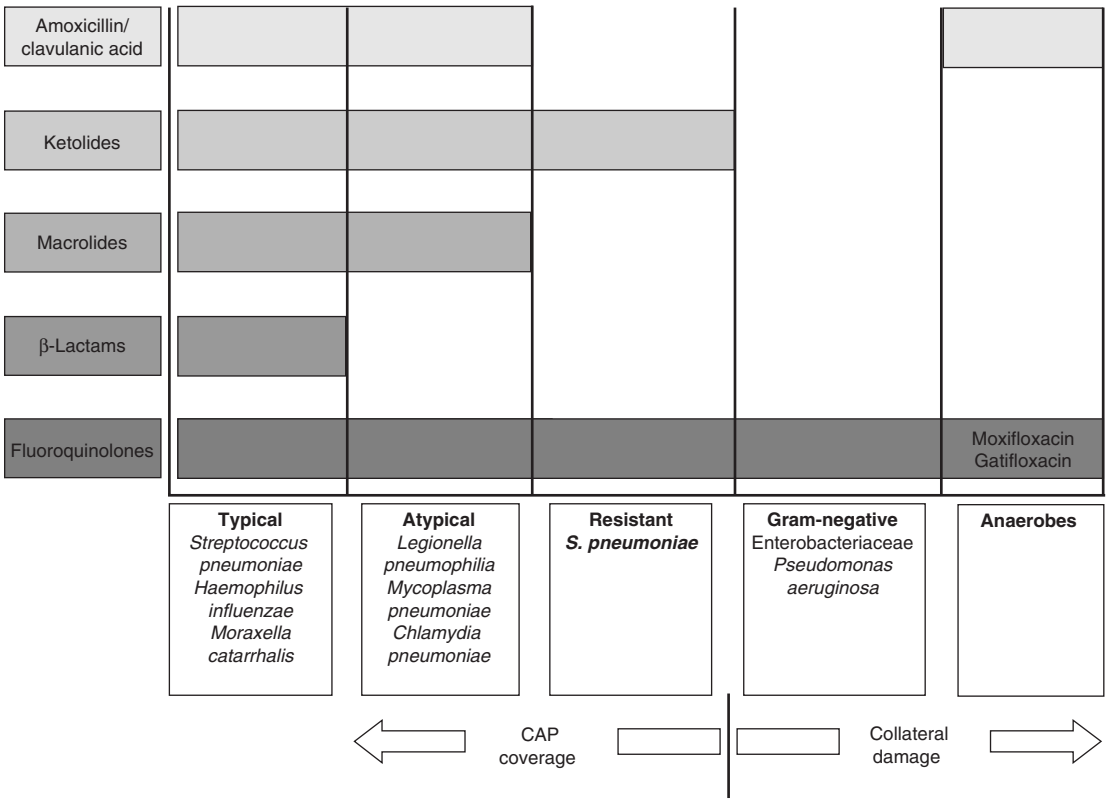

Fig. 2. Collateral damage from antibacterial regimens frequently used to treat community-acquired pneumonia (CAP) in outpatients, where collateral damage is the unintended and unnecessary exposure of microorganisms to antibacterials that select for antibacterial resistance and subsequent colonisation or infection with multidrug-resistant organisms. In the absence of risk factors, empirical coverage of anaerobes and Gram-negative pathogens is unnecessary and may provoke colonisation or infection with resistant bacteria.

patients treated with macrolides alone most often have mild CAP (or upper respiratory tract infection), which in some will resolve even without antibacterials. Hence, the ability to detect the impact of resistance on clinical outcomes is diminished because antibacterial therapy may be unsuccessful, yet some patients will improve anyway. This concept is further supported by a recent study of patients hospitalised with pneumococcal CAP following macrolide treatment failure.[38] Of patients who did not respond to monotherapy with a macrolide, 78.7% had macrolide-resistant pneumococci, suggesting that treatment with a macrolide is more likely to result in hospitalisation when the pathogen is macrolide resistant. Furthermore, azithromycin and clarithromycin exhibit favourable pharmacodynamics in respiratory infections, such as achieving higher concentrations in neutrophils and lung tissue than in serum, thus resulting in a more favourable clinical response than would be expected on the basis of susceptibility testing.[55] Collectively, these observations may partly explain this '*in vivo-in vitro*' phenomenon. For a discussion of the potential impact of penicillin resistance on clinical outcomes, readers are directed to several recent references.[61-63]

5. Is Fluoroquinolone Resistance Among Pneumococci a Legitimate Concern?

In general, pneumococcal resistance to the fluoroquinolones remains low.[60] On the other hand,

current estimates of fluoroquinolone resistance in *S. pneumoniae* are an underestimate of the problem and reports of clinical treatment failure are emerging.[64-67] Fluoroquinolone resistance is the culmination of successive mutations in DNA gyrase (*gyrA*) and topoisomerase (*parC*), which are integral in bacterial DNA synthesis. Current susceptibility tests are insensitive to these mutations (i.e. mutations can be present, yet the isolate is reported as susceptible).[68] In fact, the incidence of first-step mutants, isolates with a mutation at one of these target sites, among *S. pneumoniae* with an MIC of 2 μg/mL (susceptible) to levofloxacin has increased dramatically in the last few years[69-72] (figure 3). Perhaps more disturbing, among 1817 *S. pneumoniae* isolates obtained from patients with community-acquired respiratory tract infections in 44 US medical centres in 2002–3, 21.9% of isolates contained a first-step mutation regardless of MIC compared with just 4.7% in 1997–8.[73] These isolates can produce clinical treatment failure despite appearing to be susceptible on culture and sensitivity.[65,66] Indeed, some authorities have urged for the use of microbiological breakpoints capable of detecting mutations in DNA topoisomerase or gyrase, or a reduction in current clinical breakpoints to better gauge the true incidence of fluoroquinolone resistance.[74,75] The accumulation of first-step mutants is relevant for several reasons. The phenomenon represents a type of MIC 'leakage', whereby the activity of an entire class of agents is silently eroding. Also, the shifting of wild-type organisms to first-step mutants with lower level fluoroquinolone resistance may herald the widespread emergence of high-level resistance. In other words, current measures of fluoroquinolone resistance represent merely the 'tip of the iceberg'. Previous fluoroquinolone exposure serves as the greatest risk factor for fluoroquinolone resistance and colonisation with non-susceptible isolates. Hence, previous fluoroquinolone exposure should be considered a contraindication to their use in CAP.[8,65,66]

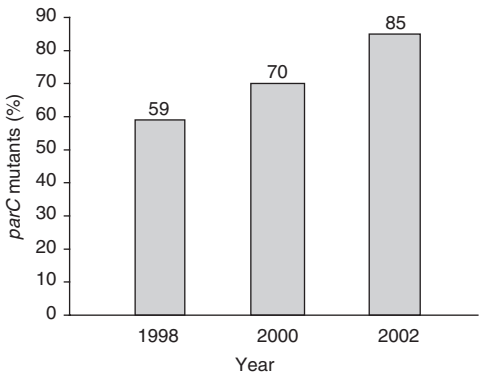

Fig. 3. Prevalence of first-step mutations in *Streptococcus pneumoniae* with a levofloxacin minimum inhibitory concentration (MIC) of 2 μg/mL since 1998.[70-72] Fluoroquinolone resistance occurs via mutations in DNA gyrase (*gyrA*) or topoisomerase IV (*parC*). A mutation at one of these locations will often modestly increase the MIC, without intersecting the breakpoint, and the organism is reported as susceptible. Isolates with a single mutation are far more likely to become fully resistant than are wild-type (isolates without any mutation) isolates. The obvious trend toward increasing levels of *S. pneumoniae* with a *parC* mutation probably foreshadows a dramatic increase in fluoroquinolone resistance in the next few years. This pattern of increasing resistance is not detected by routine susceptibility testing.

Because fluoroquinolone use is extensive and they are often prescribed for self-limiting conditions (e.g. acute bacterial exacerbations of chronic bronchitis or mild CAP), clinicians infrequently appreciate clinical treatment failure in individual patients and may attribute a lack of response to more mundane causes, such as nonadherence. This may engender a false sense of security among clinicians. Even though national resistance rates are minimal, caution is warranted given that substantial increases in fluoroquinolone resistance and treatment failure have been reported. For instance, *S. pneumoniae* resistance to fluoroquinolones in Salem, Massachusetts, USA is 22% and resistance in Hong Kong reportedly is nearing 15%.[76,77] In some locations, 10% of the population is colonised with fluoroquinolone non-susceptible *S. pneumoniae*.[78] A recent examination of the current rate of levofloxacin use and resistance rates in the US was utilised to estimate the level of fluoroquinolone resistance ex-

pected by the end of the decade. This analysis determined that 8.5% of *S. pneumoniae* isolates would be resistant to levofloxacin by 2010, a sobering 4- to 5-fold increase from the level today. The relationship between fluoroquinolone use and resistance is unmistakable, that is, 'fluoroquinolone use equals fluoroquinolone resistance'.[79-82] This is primarily a function of the dosages approved for use in clinical practice, which were designed to cure infection without considering resistance. There is extensive research investigating the dosages required to achieve clinical cure and prevent resistance.[83,84] One such concept that shows promise is the mutant selection window (MSW) hypothesis.[85-88] It has defined dosages of several fluoroquinolones that are capable of not only curing infection but preventing resistance; in most cases the dosages prescribed in practice are the most likely to select for resistance.[89] Fluoroquinolones should be reserved for instances when they are clearly indicated, and then the most active agent from the class should be selected and administered at the highest recommended dosage.[8]

6. Do Other Antibacterials Merit Consideration in Non-Severe CAP?

Dual therapy may confer little advantage over monotherapy in patients with non-severe CAP. This may be attributed to the low intrinsic rate of clinical treatment failure in this population. Notwithstanding the effectiveness of monotherapy in this setting, antibacterial resistance represents one of the greatest single threats to public health.[90] Equally concerning is the dearth of new antibacterials; the antibacterial discovery pipeline has stalled, underscoring the importance of protecting the available agents.[91] Consequently, the selection of monotherapy for non-severe CAP should be tempered by impact of the use of that agent on resistance. A reassessment of 'older' treatment options is in order to determine if it is possible to redistribute resistance pressures from a few new agents to older ones. In this context, we review the utility of doxycycline, a first-line treatment option, in the setting of non-severe CAP.

Doxycycline continues to exert excellent activity against all common respiratory pathogens, including typical, atypical and drug-resistant organisms. Reasons for the relative obscurity of doxycycline are dominated by the lack of an interested corporate sponsor and related under-marketing, resulting in a loss of familiarity, and perhaps lack of confidence, among healthcare providers. Nevertheless, based on data from the PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) surveillance database, tetracyclines are substantially more active against *S. pneumoniae* than penicillin, cefuroxime, erythromycin, clarithromycin, azithromycin or co-trimoxazole (trimethoprim/sulfamethoxazole).[42] In some locales, a phenomenon is occurring whereby resistance to β-lactams and macrolides is increasing in the face of declining resistance to the tetracyclines.[92]

Some clinicians have erroneously relinquished the use of doxycycline because of increasing reports of tetracycline resistance. Automated susceptibility testing systems are designed to test only tetracycline, commensurate with recommendations from the Clinical and Laboratory Standards Institute (CLSI, formerly known as the National Committee for Clinical Laboratory Standards [NCCLS]); however, tetracycline resistance is not a valid surrogate for the antipneumococcal activity of doxycycline. In reality, tetracycline resistance overestimates the true incidence of doxycycline resistance. Disk diffusion testing of 256 clinical pneumococcal isolates confirmed the limitations of current testing standards.[93]Among these isolates, 6% were resistant to doxycycline, whereas 21% and 30% were resistant to tetracycline and penicillin, respectively. A similar analysis of 499 isolates collected in Ohio, USA, found that 99.2% of isolates were susceptible to doxycycline.[94] In addition, doxycycline exhibits

enhanced lipophilicity compared with tetracycline, resulting in greater lung penetration.[95,96] The recommended dosage of doxycycline is 100mg every 12 hours; however, the prolonged half-life of doxycycline (18–22 hours) results in a delay in the time to therapeutic concentrations (~4–5 days). Consequently, some experts have endorsed administration of 200mg on day 1 to expedite the time to therapeutic concentrations.[96,97]

Few recent clinical trials have been conducted with the tetracyclines and none have compared doxycycline monotherapy with dual therapy. Ailani et al.[98] established the cost effectiveness of doxycycline for the treatment of hospitalised patients with mild-to-moderate CAP. Compared with conventional, physician-guided therapy, patients randomised to doxycycline achieved a clinical response 1.5 days earlier ($p = 0.001$), were discharged 2 days earlier ($p = 0.04$) and had significantly lower hospital charges ($US5126 in the doxycycline group vs $US6528 [1997 values] in the control group; $p = 0.04$). Notably, increased use of doxycycline in adults would create a divergence between the agents used in children (i.e. macrolides and β-lactams), a reservoir for drug resistance, and those used in adults, attenuating the selective pressure around any single class of drugs. The spectrum of activity, enviable resistance pattern and cost effectiveness favourably position doxycycline as a first-line, possibly fluoroquinolone-sparing, strategy for the treatment of mild-to-moderate CAP in the community setting.

7. Alternative Regimens for Severe CAP

Other possible regimens for severe CAP that are recommended as alternatives in current guidelines include ampicillin/sulbactam plus a macrolide, and ertapenem. Administration of ampicillin/sulbactam as the β-lactam component of dual therapy is counterintuitive since the mechanism of resistance in *S. pneumoniae* is an alteration in penicillin binding proteins and not production of β-lactamase. While ertapenem is active against common CAP pathogens, its broad spectrum and potential to select for carbapenem cross-resistance must be considered when evaluating the place of this agent in therapy. Furthermore, both of these agents are active against anaerobes and, as a result, they increase the rate of colonisation and infection with VRE[49-51] (figure 2).

8. Summary and Conclusions

There is insufficient evidence to elevate either dual therapy or monotherapy to preferred status in patients with non-severe CAP on the basis of efficacy alone. The results of published studies in patients with severe CAP are more consistent, suggesting a potential benefit of dual therapy over monotherapy even when the single comparator agent is active against the pathogen. The combination of a third-generation cephalosporin plus a macrolide has been extensively evaluated, although several investigations noted that the components of dual therapy were less important than dual therapy itself.[17,20,21]

There are several plausible explanations for the superiority of dual therapy. First, in an era of escalating drug resistance, administration of two drugs increases the likelihood that one of the drugs will be active against the infecting pathogen. However, this is an oversimplification since resistance to any given agent is often connected with other forms of resistance to unrelated drugs. Secondly, when a macrolide is part of the combination, atypical coverage is ensured. However, this does not explain improved outcomes when dual therapy was compared with fluoroquinolone monotherapy, since fluoroquinolones are active against atypical pathogens.[17] Thirdly, resistance can emerge during treatment, as has been reported with macrolide and fluoroquinolone monotherapy.[62,63,96] When dual therapy is prescribed, the target pathogen is attacked at two different sites of action, thereby decreasing the likelihood that resistance will develop.[81] Finally, dual

therapy is unique in that macrolides exert a pleiotropic immunomodulatory action, including suppression of several interleukins (IL-6, IL-1) and tumour necrosis factor (TNF)-α, possibly attenuating tissue damage by neutrophils, which are hyperactive in CAP.[99-101] Such activity would be expected to be particularly important in patients treated with bactericidal agents, such as β-lactams or fluoroquinolones, which trigger the release of numerous intracellular bacterial inflammatory compounds. The advantage of dual therapy is most likely to be a result of some combination of these considerations.

Optimal pharmacological therapy of CAP remains a therapeutic dilemma. The Infectious Disease Society of America (IDSA) recommends monotherapy with a macrolide or tetracycline in patients treated at home without recent antibacterial exposure (i.e. in the past 3 months), a risk factor for drug-resistant *S. pneumoniae* or Gram-negative bacilli. Dual therapy with high-dose amoxicillin or amoxicillin/clavulanic acid plus an advanced macrolide or monotherapy with a respiratory fluoroquinolone is recommended in patients with recent antibacterial exposure. Areas with intrinsically high rates of macrolide resistance might consider dual therapy with a β-lactam and macrolide, or a respiratory fluoroquinolone alone as initial therapy, even in the absence of recent antibacterial exposure. The most active single agents are the fluoroquinolones; however, resistance to this class is increasing and clinical treatment failure is becoming more frequent. This issue has been addressed in the most recent IDSA guidelines, which warn of the "impending demise of this class of antimicrobials should abuse of these agents continue".[8] One alternative to the fluoroquinolones for monotherapy in CAP is doxycycline, a unique alternative to the mainstream first-line agents. Its activity profile has been spared in the resistance era, mainly as a result of reserved usage patterns. The role of new and emerging agents, such as telithromycin, remains to be seen.

Patients with severe disease, such as those that present with bacteraemic pneumococcal pneumonia, have been identified as one of the most critical management issues in CAP.[8] Guidelines continue to recommend a respiratory fluoroquinolone or the combination of a β-lactam (e.g. ceftriaxone, ampicillin/sulbactam or ertapenem) plus an advanced macrolide. Beyond that, clinicians are left with little guidance regarding appropriate selection from these two options. Certainly, monotherapy with a fluoroquinolone is more 'user-friendly': there is just one dose to remember, the frequency is once daily, the spectrum is broad and their high bioavailability facilitate early intravenous to oral conversion. Thus, in many institutions monotherapy with a fluoroquinolone is the prevailing regimen. That being said, studies in this population show that dual therapy has a more favourable impact on survival. This finding was valid even when the infecting pathogen was found to be susceptible to the drug administered in the monotherapy arm and when the spectrum of activity of the two regimens was similar. Consequently, dual therapy should be strongly considered the preferred antibacterial treatment strategy in patients with severe CAP, especially if pneumococcal bacteraemia is also present. An additional consideration will be the generic availability of both azithromycin and ceftriaxone by the end of 2005, thus providing, for the first time, a first-line all generic dual therapy regimen. Pneumococcal resistance to the third-generation cephalosporins remains stagnant. In contrast, increased use of fluoroquinolones can select for autoresistance, cross-resistance to the fluoroquinolone class and resistance to non-fluoroquinolone antibacterials. It is no longer appropriate to neglect the impact of antibacterials on the future of antimicrobial therapy. Otherwise, we may be 'winning the battle but losing the war'.

Acknowledgements

No financial support was provided for this project. The authors have no other financial conflicts.

Note in Proof

Antibacterial-specific results from the CAPITAL (Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin) study, a prospective observational study comparing a clinical management protocol with conventional care in consecutive patients admitted with CAP, were recently published.[102] This *post hoc* analysis compared outcomes among patients receiving levofloxacin from the clinical protocol cohort with those treated with ceftriaxone plus clarithromycin in the conventional arm. Among the 459 patients enrolled, 15 patients in the clinical protocol arm died compared with 25 of the conventionally managed patients ($p = 0.024$). Interestingly, there were no differences in length of stay, duration of parenteral therapy or total duration of therapy, suggesting that the survival finding could be artifact.

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