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International Guidelines for the Treatment of Community-Acquired Pneumonia in Adults

The Role of Macrolides

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Abstract

The significance of community-acquired pneumonia (CAP) has led to the publication of guidelines from numerous international organisations. Because the macrolide class of antimicrobials is active against most of the key pathogens associated with CAP, agents from this class are commonly included in recommendations from these guidelines. However, there are differences among the various guidelines concerning the positioning of the macrolides for empirical therapy.

An important factor concerning the use of macrolides for CAP is the emergence of resistance of *Streptococcus pneumoniae* over the past decade. The rate of *S. pneumoniae* resistance to macrolides ranges from 4 to 70% of strains in

worldwide surveillance studies. The most common mechanisms of resistance include methylation of a ribosomal target encoded by the *erm* gene and efflux of the macrolides by a cell membrane protein transporter, encoded by the *mef* gene. *S. pneumoniae* strains with the *mef* gene are resistant at a lower level (with minimum inhibitory concentration [MIC] values generally 1–16 μg/ml) than *erm* resistant strains; and it is possible that such strains may be inhibited if sufficiently high levels of macrolide can be obtained at the infected site. Currently *mef*-associated resistance predominates in North America, whereas *erm* predominates in Europe. Until recently, reports of failure of treatment of CAP with macrolides has been rare, particularly for patients with low-risk for drug-resistant strains. However, since 2000, several patients treated with an oral macrolide who have subsequently required admission to the hospital for macrolide-resistant *S. pneumoniae* (MRSP) bacteraemia have been reported in the literature.

Major issues, which are fundamental to the use of the macrolides as recommended in the various guidelines, include the importance of providing therapy for 'atypical' pathogens and the clinical significance of MRSP. Presently, the macrolides are more prominently recommended in the North American guidelines than in other parts of the world. The difference in the emphasis placed on the importance of the atypical pathogens as well as the expression of MRSP in North America compared with Europe partly explains this variance.

Community-acquired pneumonia (CAP) is a common disorder that is potentially life threatening, especially in older adults and those with comorbid disease. Several changes have occurred during the past decade that have impacted the management of CAP including: the increasing awareness of 'atypical pathogens' (i.e., *Chlamydia pneumoniae, Legionella* spp. other than *L. pneumophila*) and the emerging resistance of standard pathogens (most notably *Streptococcus pneumoniae*).[1,2] Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death worldwide, and there continue to be major controversies concerning the antimicrobial management of this infection.

The importance of CAP has led to the publication of guidelines from numerous international organisations; the purpose of which is to optimise care and improve outcome. Because the macrolide class of antimicrobials is active against most key pathogens associated with CAP, agents from this class are commonly included in recommendations from these guidelines. Macrolide antibiotics are extensively used for the treatment of CAP. In one study conducted at five centres in the US from 1991 to 1994, macrolides were prescribed for 73.4% of outpatients and 41% of inpatients treated for CAP.[3] In another study of 1113 consecutive patients with CAP who required admission to 20 Canadian medical centres during 1996–1997, >70% received a macrolide, nearly always in combination with a β-lactam.[4]

Despite the common use of the macrolides worldwide, there are differences among the various guidelines concerning the role of macrolides for empirical therapy of CAP. This paper discusses pertinent issues related to CAP in adults regarding the use of the macrolides and reviews the recommendations for utilisation of the macrolides included in representative international guidelines.

1. Aetiology of Community-Acquired Pneumonia (CAP)

An awareness of the likely aetiology in different settings of CAP is important for the appropriate formulation of guidelines related to this infection. Numerous pathogens have been associated as the aetiology of CAP (table I). While *S. pneumoniae* remains the most common causative pathogen, a number of pathogens such as *Legionella* spp. and

Table I. Pathogens associated with community-acquired pneumonia

Traditional pathogens
Streptococcus pneumoniae
Haemophilus influenzae
Mycoplasma pneumoniae
Oral anaerobes
Gram-negative bacilli (less common)
Staphylococcus aureus (less common)
Influenza virus
More recently recognised pathogens
Legionella species
Chlamydia pneumoniae (strain TWAR)
Moraxella (Branhamella) *catarrhalis*
Sin nombre virus (hantavirus)
Parainfluenza
Respiratory syncytial virus
Pathogens with increasing prevalence
Mycobacterium tuberculosis
Pneumocystis carinii (associated with HIV infection)
Less common pathogens in immunocompetent host
Bacteria
Neisseria meningitidis
Streptococcus pyogenes
α-Haemolytic streptococci (i.e., *S. milleri*)
Coxiella burnetti (Q fever)
Chlamydia psittaci
Fungi
Histoplasma capsulatum
Coccidioides immitis
Blastomyces dermatitidis
Viruses
Influenza
Parainfluenza
Adenovirus
Respiratory syncytial
Varicella
Less common pathogens in immunocompromised host
Bacteria
Nocardia spp.
Mycobacterium spp. (i.e. avium complex)
Fungi
Aspergillus spp.
Candida spp.
Cryptococcus spp.
Rhizopus spp.
Viruses
Herpes simplex
Cytomegalovirus
Toxoplasma spp.

C. pneumoniae have been recognised in recent years. On the basis of a review of over 15 published reports from North America that covers over 2 decades and from mostly hospitalised patients, the ranges for prevalence of specific pathogens as causes of pneumonia are reported as: *S. pneumoniae*, 20–60%; *Haemophilus influenzae*, 3–10%; *Mycoplasma pneumoniae*, 1–6%; *C. pneumoniae*, 4–6%; *Legionella* spp., 2–8%; viruses, 2–13%; aspiration, 6–10%; *Staphylococcus aureus*, 3–5%; Gram-negative bacilli, 3–10%; and miscellaneous, 10–20%.[1] Table II lists the most common pathogens associated with CAP based on the collective results of recent studies and based on severity of illness as judged by site of care (outpatient versus inpatient).[5]

Despite the awareness of newly recognised pathogens and the greater number of possible pathogens associated with CAP, *S. pneumoniae* remains the most common cause of fatal CAP.[6] However, the atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, *Legionella* spp.) are increasingly being recognised as important pathogens as well. Although *M. pneumoniae* is generally considered to be more common in ambulatory patients than in those requiring admission to the hospital, recent studies of patients requiring hospitalisation have found a significant percentage are caused by *M. pneumoniae* as well as other atypical pathogens.[5] In several studies that evaluated the aetiology of CAP in ambulatory patients, the percent of infections caused by *M. pneumoniae* ranged from 17 to 37%.[5] A recent study of 170 patients with CAP treated as outpatients from a single centre in Switzerland found 14% and 5% of patients, respectively, with *M. pneumoniae* and *C. pneumoniae* as the likely pathogen (21.8% were attributed to *S. pneumoniae*).[7] Another study evaluating patients with non-severe (mostly ambulatory) CAP from Spain found the most commonly identified organism in patients <50 years of age and without significant comorbid conditions or abnormality of vital signs was mycoplasma (40%), whereas *S. pneumoniae* was the most common pathogen for older patients or those with underlying disease or

Table II. Aetiology of community-acquired pneumonia (reproduced from File et al.,[5] with permission)

Most common causes[a]		
Ambulatory patients	Hospitalised (Non-ICU)[b]	Severe (ICU)
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*H. influenzae*
Haemophilus influenzae	*C. pneumoniae*	*Legionella spp.*
Chlamydia pneumoniae	*H. influenzae*	Gram-negative bacilli
'Viruses'	*Legionella spp.*	*Staphylococcus aureus*
	Aspiration	

a Based on collective data from recent studies.

b Excluding *Pneumocystis* spp.

ICU = Intensive care unit.

abnormality of vital signs.[8] Recent cohort studies of CAP in patients requiring hospitalisation have substantiated the importance of atypical pathogens in this setting as well. Atypical pathogens have been reported with variable prevalence rates, ranging from 7.5 to >50%, largely dependent on the criteria used for diagnosis.[9]

Table III lists the results of four recent studies; one each from North America (US), Europe, South America and Asia.[10-13] Collectively *S. pneumoniae* was the most commonly isolated organism; but of significance, *M. pneumoniae* and *C. pneumoniae* were also prominently represented as pathogens in these studies. *Legionella* sp. was identified more commonly in the US study (3%) and less commonly in the European study. These observations may in part explain differences in recommendations for empirical therapy by guidelines in the different areas.

1.1 Multiple Organisms/Mixed Infections

Although objective confirmation is often difficult, multiple organisms that infect a patient concurrently or sequentially may cause CAP. For example, influenza A or *C. pneumoniae* infection might be followed by a secondary infection with *S. pneumoniae*. The incidence of mixed infection varies among different studies and, to a certain extent, depends upon the criteria used for the diagnosis. In most patients the diagnoses are based on serological diagnosis of an atypical pathogen and microbiological isolation of *S. pneumoniae*. Because many of the serological tests and cut-off criteria lack specificity, the results are often indeterminate. Patients in whom a significant antibody rise to an atypical pathogen is associated with isolation of a pathogen (such as pneumococcus) most likely represent a sequential infection – an initial infection with the atypical organism which then predisposes to secondary bacterial infection. In three well defined studies of patients requiring hospitalisation, the incidence ranged from 2.7 to 10%.[10,14,15] The importance of treating multiple infecting organisms has not been established; however, identification of one pathogen should not preclude evaluation for other diagnostic aetiologies when CAP is not responding to therapy. In addition, the possibility of an atypical pathogen increases the utility of agents such as the macrolides – particularly as part of combination regimens with β-lactams (which lack effective activity against these organisms).

1.2 Antibacterial Resistance

The emergence of multi-drug resistant strains of *S. pneumoniae* (DRSP) and other respiratory pathogens is becoming a significant problem in the US as well as other countries worldwide. Recent multicentre studies of *S. pneumoniae* isolates obtained in the US indicate that penicillin-non-susceptible rates approximate 30–40%, with high level resistance rates approximating 10–20%.[16,17] Resistance to other commonly used agents (cephalosporins, macrolides, doxycycline, trimethoprim/sulfamethoxazole) is increasing as well. Although there is compelling evidence that drug-resistant pneumococci affect clinical outcomes in patients with meningitis and otitis media, the clinical relevance of resistance in the therapy of pneumonia remains controversial.[18,19]

Much of the controversy relates to the interpretation of the breakpoint classification of the pneumococcus for susceptibility and resistance. The

National Committee for Clinical Laboratory Standards (NCCLS) currently defines the susceptibility of pneumococcus isolates to penicillin as: susceptible <0.06 μg/ml; intermediate 0.1–1 μg/ml; and resistant >2 μg/ml.[20] The results of several studies suggest that penicillins remain effective for pneumonia when the pneumococcus has a minimum inhibitory concentration (MIC) of ≤2 μg/ml, presumably because the pharmacokinetic and pharmacodynamic parameters associated with current dose administration regimens are still sufficient for such strains.[19] However, when the penicillin MIC is ≥4 μg/ml, increased rates of mortality (for patients who survive the first 4 days of hospitalisation) may occur.[21] Currently, 3.5–7.8% of *S. pneumoniae* clinical isolates have penicillin MICs that fall in this latter class but these rates may rise in the future.[19] The clinical relevance of macrolide resistance is specifically discussed in section 2.

2. Macrolides: Characteristics for CAP

Erythromycin is a natural antibiotic isolated from *Saccharapolyspora erythrea* and consists of a 14-membered lactone ring with two attached sugar groups.[22] Erythromycin has been modified in numerous ways to improve its properties. Another of the 14-membered, semisynthetic macrolides, clarithromycin, is produced by addition of a methoxy group at position C6 of erythromycin. These modifications increase the drug stability in gastric acid, thus improving absorption by the oral route. Other 14-membered macrolides include dirithromycin and roxithromycin.[22] Azithromycin results from a rearrangement of the macrolide-giving rise to a 15-membered molecule, also known as azalide.

Table III. Aetiology of community-acquired pneumonia requiring hospitalisation. Data from four studies

Aetiological agent	Patients with aetiology (%)			
	USA[10] (n = 2776)[a]	Japan[11] (n = 200)	Spain[13] (n = 90)[b]	Argentina[12] (n = 346)
Streptococcus pneumoniae	12.6 (5.5)	20.5	30	10
Mycoplasma pneumoniae	32.5 (5.4)	9.5	22	5
Chlamydia pneumoniae	8.9 (2.4)	7.5	13	3
Haemophilus influenzae	6.6 (0.4)	11	7	6
Staphylococcus aureus	3.4 (0.4)	5.0		2
Moraxella catarrhalis	0.76 (0)	3.0		2
Legionella spp.	3.0 (2.4)	1.0		1
Enterobacteriaceae	2.8 (0.7)	2.5	1	3
Pseudomonas spp.	1.7 (0.1)	2.0	0	2
Anaerobes	NR	4.0		NR
Virus	12.7[c]	3.0	6	7
Pneumocystis sp.	1.4	NR	8	1
Mycobacterium tuberculosis	1.4	NR	4	2
C. psittaci	NR	1.0	1	1
C. burnetii	NR	0.5	1	1
Other	0.5	2.0[d]	1	3
Unknown		41.5		48

a Figures in brackets represent % of patients with definite diagnosis based on diagnostic criteria.

b Used conventional testing plus transthoracic needle aspiration.

c During respiratory virus season (Nov-March).

d *S. milleri.*

NR = not reported.

2.1 Spectrum of Activity of the Macrolides (Including Azalides)

Macrolides exert their antibacterial activity by binding to the ribosome and blocking protein synthesis.[21] They target several positions within the 23S ribosomal RNA bacterial ribosome and interfere with the linking of amino acids to the growing peptide chain during the synthesis of new proteins.

The *in vitro* activity of the most commonly used macrolides against the key respiratory pathogens is listed in table IV.[23-33] In general, the macrolides have activity against the key pathogens associated with CAP including *S. pneumoniae*, *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae* and *Legionella* sp. Whereas erythromycin and dirithromycin have little activity against *H. influenzae*, clarithromycin and azithromycin are more active, with azithromycin being most active. The activity of clarithromycin against *H. influenzae* is enhanced because of a synergistic effect of its 14 OH metabolite. Activity against *S. aureus* is intermediate and macrolides are inactive against enteric, Gram-negative bacilli.

2.2 Macrolide-Resistant Streptococcus Pneumoniae (MRSP)

An important factor concerning the use of macrolides for CAP is the emerging resistance of *S. pneumoniae*. There are two common mechanisms for macrolide-resistant *S. pneumoniae* (MRSP): ribosomal methylation and macrolide efflux.[22] The first mechanism, which is encoded by the *ermB* gene, involves the methylation of a ribosomal target site of the macrolides. Phenotypically, there is a wide range of MICs in *ermB* strains, with most isolates having an MIC >16 μg/ml for erythromycin.[22] The second mechanism is an energy-dependent efflux of 14- and 15-membered macrolides via a cell membrane protein transporter, encoded by *mefA*. *S. pneumoniae* strains with *mef* are resistant to macrolides but at a lower level (with an MIC of erythromycin generally between 1–16 μg/ml) but are susceptible to clindamycin (MIC <0.50 μg/ml).[22] Another mechanism of resistance, which is unrelated to either *erm* or *mef* and is due to L ribosomal protein mutations, has rarely been reported.[34]

As a result of increased use of the macrolides over the past decade, there are an increasing number

Table IV. *In vitro* activity of macrolides (μg/ml) [reproduced from Mülazimoglu and Periti,[22] with permission; a compilation of several studies references[23-33]]

Bacterial	Erythromycin		Dirithromycin		Clarithromycin		Azithromycin		Roxithromycin	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (penicillin susceptible)	0.25	0.25	0.25	1	0.25	0.25	0.25	0.25	0.50	1
S. pneumoniae (penicillin resistant)	0.25	32	0.25	1	0.25	16	0.25	>32	1	2
Haemophilus influenzae (β-lactamase negative)	4	16	4	8	8	16	1	2	4	8
H. influenzae (β-lactamase positive)	4	8	8	16	8	16	1	2	8	16
Morexella catarrhalis (β-lactamase negative)	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.25	0.125	0.125
M. catarrhalis (β-lactamase positive)	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.25	0.125	0.125
Legionella pneumophila	0.5	NR	NR	NR	0.25	NR	0.5	NR	0.0625	NR
Chlamydia pneumoniae	0.06	0.125	NR	NR	0.015	0.03	0.06	0.125	0.05	0.0125
Mycoplasma pneumoniae	0.0078	0.0156	0.1	0.1	0.0039	0.0078	0.0001	0.0002	0.015	0.03

MIC_{50} = minimum concentration to inhibit growth of 50% of isolates; **MIC_{90}** = minimum concentration to inhibit growth of 90% of isolates; **NR** = not reported.

of reports describing MRSP.[35-37] Several of the large-scale, multicentre surveillance studies, which have demonstrated an increase in resistance of *S. pneumoniae* to the penicillin, have also shown increasing resistance to the macrolides. A study by Doern et al. of 845 respiratory tract isolates of *S. pneumoniae* from 27 US medical centres demonstrated that 14.3% were resistant by NCCLS standards to erythromycin, clarithromycin and azithromycin.[17] When isolates with varying penicillin sensitivities were studied, it was demonstrated that the rates of macrolide sensitivity in these strains had also decreased. Of all isolates susceptible to penicillin, 97.2% were sensitive to erythromycin; for intermediate penicillin-susceptible isolates, 83.5% were susceptible to erythromycin; and for penicillin resistant isolates, only 52% were susceptible to erythromycin. In a study by Thornsberry et al. of over 4000 *S. pneumoniae* isolates from 1998 to 1999 in the US, 14.4 and 22.5% of isolates were considered resistant to penicillin and clarithromycin, respectively.[16] Fifty percent of isolates were resistant to clarithromycin for all penicillin-intermediate resistant strains and 74% were resistant to clarithromycin if isolates had penicillin MICs of >2.0 μg/ml. A population-based surveillance study by Gay et al. investigated erythromycin resistance over a 6-year period from 1994–1999 in Atlanta, Georgia, evaluating 4148 *S. pneumoniae* isolates from sterile body sites.[38] Using a category of 'high level resistance' for isolates with MICs ≥4 μg/ml, the prevalence of high level resistance increased from 13% in 1994 to 31% in 1999. The rate of penicillin co-resistance was high with 84% of erythromycin-resistant isolates having a penicillin MIC ≥0.12 μg/ml and 66% with a penicillin MIC >1 μg/ml. The percentage of resistant isolates with resistance due to *ermA* was unchanged throughout the 6-year study; however, *mef*-associated resistance increased from 9% of all isolates in 1994 to 26% in 1999.

Although the majority of resistant isolates were associated with the *mefA* mechanism, the prevalence of isolates with erythromycin MIC ≥16 μg/ml was 22% in 1999. This indicates that some of the strains resistant by the efflux mechanism may have MICs associated with levels not easily achieved by the newer macrolides. Moreover, a subsequent report by Hyde et al. of the susceptibility of invasive strains of *S. pneumoniae* in the US has shown a 2-fold increase in the median MIC for the *mef*-mediated resistant strains from 4 μg/ml to 8 μg/ml.[39] This study evaluated strains from 1993 to 1999. During that time macrolide use increased 13% (32% among children younger than 5 years). Macrolide resistance increased from 10.6% in 1995 to 20.4% in 1999. *Mef* phenotype isolates increased from 7.4 to 16.5%, while the proportion with macrolide/lincosamide/streptogramin (MLS) [i.e., *erm*-mediated] phenotype was stable at 3–4%. In 1999, *Mef* phenotypes were more often from children than persons 5 years or older and from whites than blacks. The authors suggested the increasing frequency of macrolide resistance among pneumococci and increasing MICs among resistant strains may require treatment recommendations for empirical therapy of CAP in the US to be re-evaluated.

Table V. *Streptococcus pneumoniae* macrolide resistance-type prevalence by country

Genotype	USA[17]	Canada[42]	Europe[43]	Japan[44]
	1999–2000	1998–1999	1997–2001	1995
	n = 395	n = 215	n = 120	n = 62
Erm	32%	47%	82.5%	40%
Mef	66%	49%	17.5%	43%
Mef + *erm*	<1%	3%		16%
Erm-/mef-	1.5%	1.9%		0%

n = no. of isolates; % indicates percentage of isolates.

The increase of MRSP has been observed worldwide as well with rates of resistance at other locations being highly variable (i.e. Hong Kong, 68.2%; Mexico City, 31.4%; Saudi Arabia, 3.7%; Brazil, 32%)[40] Currently *mef*-associated resistance predominates in North America, while *erm* predominates in Europe (table V). The prevalence of erythromycin resistance varies with age. It is higher in children <2 years old (35%) than in those 3–12 years old (25%) and >13 years old (20%).[16] These data are similar to the data for the prevalence

of penicillin-resistant *S. pneumoniae* (PRSP) in children.[41] The epidemiology of erythromycin-resistant *S. pneumoniae* in North America has been characterised by the following: an increase in prevalence during the 1990s (as well as a trend in higher MICs in the *mef*-associated-resistant strains); a regional (more in the Southeast) and age variation; and correlation with penicillin resistance *in vitro*.

2.3 Clinical Relevance of MRSP for CAP

There are no prospective trials of the clinical efficacy of macrolides in the therapy of patients with infections caused by MRSP. Thus, data for the clinical relevance of MRSP are derived mostly from anecdotal case reports.

2.3.1 Published Macrolide Failures

Lonks and Medeiros[45] describe a previously well 32-year-old male with CAP who worsened after taking oral erythromycin for 3 days. Cultures of the patient's blood grew *S. pneumoniae* resistant to erythromycin (MIC = 64 μg/ml) and the patient improved when he was treated with parenteral penicillin.

Moreno et al.,[46] in Spain evaluated the incidence and significance of resistance to erythromycin among clinical isolates of *S. pneumoniae*. They identified 27 patients with clinically significant erythromycin-resistant *S. pneumoniae* infection among whom 20 had pneumonia. Most strains (94%) showed resistance to multiple antibacterials, including other macrolides. Risk factors associated with erythromycin-resistant strains included the prior use of antibacterials, age under 5 years and nosocomial acquisition of the infection. The mortality of the patients with erythromycin-resistant isolates and erythromycin-susceptible isolates was 18 and 14%, respectively (not significantly different). The authors further analysed the outcomes for the 20 patients with pneumonia caused by erythromycin-resistant pneumococci according to the therapy they received. Of six patients who received erythromycin as their only therapy, four recovered while therapy failed for the other two. Three of the four who recovered were bacteraemic; one of the strains in a recovered patient had an MIC >128 μg/ml, while the other three had MICs of 16 μg/ml. One of the patients who failed therapy with erythromycin was subsequently treated successfully with cefotaxime. Severity of underlying disease in patients who were cured was not different from those who failed. Although the authors did not observe significant differences in cure rates among patients with erythromycin-resistant strains compared to those with erythromycin-sensitive strains, they did suggest that caution be used in the administration of erythromycin for treatment of severe pulmonary infections caused by erythromycin-resistant pneumococci.

Since 2000 there have been several anecdotal reports of clinical failure caused by MRSP in patients who received azithromycin or clarithromycin. Fogarty et al.[47] describe three healthy, non-smoking, middle-aged adults with CAP who failed to respond to 3–5 days of appropriately administered azithromycin. All were found to be bacteraemic with strains of *S. pneumoniae* that were non-susceptible to penicillin, cefotaxime/ceftriaxone and erythromycin/macrolides (erythromycin MICs were 8 and 128 μg/ml). They all responded promptly and completely to levofloxacin, administered orally to two patients and orally after single intravenous dose to the third. Kelley et al.[48] report four cases of macrolide-resistant *S. pneumoniae* bacteraemia requiring hospitalisation after outpatient therapy (failure) with an oral macrolide, three with azithromycin and one with clarithromycin. The erythromycin MICs were 8 and 16 μg/ml. Waterer and Wunderink report a fatal case of bacteraemic pneumococcal CAP treated initially with azithromycin where the clinical failure was at least partially attributable to macrolide resistance (the MIC of erythromycin was 16 μg/ml).[49] Musher et al. report a fatal case of *S. pneumoniae* pneumonia (isolated from sputum culture) treated with intravenous azithromycin (initial MIC to azithromycin of 0.008 μg/ml).[50] The patient initially improved clinically but subsequently deteriorated and repeat sputum culture as well as pleural fluid culture showed the same strain (by pulsed field gel electrophoresis [PFGE] and typing) which had become

resistant to erythromycin, azithromycin and quinupristin/dalfopristin (MIC 2–4 μg/ml for all three agents). It is noteworthy that all but one of the patients in these recent reports had infection caused by strains with an MIC ≥8 μg/ml for erythromycin suggesting that lower levels of *in vitro* resistance (<8 μg/ml) may not be as clinically relevant for these newer agents.

2.3.2 Discrepancy Between In Vitro Resistance and Clinical Experience

The number of published clinical failures due to macrolide resistance appears to be relatively few given the several million numbers of prescriptions written yearly to treat outpatient pneumonia. Several possible explanations have been suggested to explain this apparent discrepancy between *in vitro* and *in vivo* results.[51-53] Possibly in those countries where the macrolide resistance and use is frequent, failures are not observed because low-level resistance predominates. Certainly this is the case in North America where the macrolide resistance in *S. pneumoniae* is predominantly caused by efflux. The present breakpoint for macrolide susceptibility for *S. pneumoniae* is: resistance ≥1 μg/ml for erythromycin and clarithromycin, and ≥2 μg/ml for azithromycin.[20] Since the overwhelming majority of recent reports of macrolide failure had infection due to strains with an MIC ≥8 μg/ml for erythromycin, it is possible that lower levels of *in vitro* resistance (<8 μg/ml) may not be as clinically relevant for these newer agents. Perhaps more likely factors as explanations for a possible discrepancy between *in vitro* resistance and clinical response in ambulatory pneumonia include: (i) most patients are treated empirically and neither true bacterial infection nor resistance is documented; (ii) most infections are mild in severity and the overwhelming percentage of such patients will improve (although perhaps not as rapidly) with less active antimicrobial therapy; (iii) and the pharmacokinetic/pharmacodynamic properties of the newer macrolides may be associated with good outcomes for infections caused by strains with low-level resistance.

The efficacy of the newer macrolides, clarithromycin and azithromycin, can in part be related to their active accumulation into tissue fluids and macrophages.[54] The serum/plasma concentrations of erythromycin and azithromycin are rather low, while those of clarithromycin are higher. However, studies show that their concentration in lung tissue, are at least 10 times that in serum, while those in alveolar macrophages (AM) exceed serum concentrations by 100-fold. These concentrations render clarithromycin and azithromycin effective against most common respiratory pathogens, including those where such efficacy might not normally be expected if based only on serum concentrations. What this means is that susceptibility to clarithromycin and azithromycin, as defined by the usual breakpoints, might be expected to predict clinical success against bacteraemia. However, breakpoints may be moved to a higher level for pathogens localised to the pulmonary tissue or epithelial lining fluid (ELF). ELF and AM have recently been viewed as potential sites of CAP and intercellular pathogens.

Rodvold et al. studied the steady-state concentrations of clarithromycin and azithromycin in plasma with concomitant concentration ELF and AM obtained in intrapulmonary samples during bronchoscopy (table VI).[55] During the period of 24 hours after drug administration, both azithromycin and clarithromycin achieved mean concentrations in ELF and AM that were much higher than the concomitant concentrations in plasma. Since *S. pneumoniae* are extracellular pathogens, ELF may be as clinically important in the treatment of pneumonia as plasma concentrations in nonbacteraemic infections. However, at present, there is no substantial clinical data available to support or disprove this premise. In addition, concerns are noted by some authorities of the marginal serum concentrations achievable with oral azithromycin.[56]

Application of pharmacokinetic and pharmacodynamic principles may also assist in understanding the relationship between drug concentrations at the infection site and *in vitro* activity

Table VI. Concentrations of clarithromycin (CLA) and azithromycin (AZI) in plasma, endothelial lining fluid and alveolar macrophages (reproduced from Rodvold et al.,[55] with permission)

Time (h) between drug administration and sample collection	Mean (±SD) drug concentration (μg/ml) in:					
	plasma		endothelial lining fluid		alveolar macrophages	
	CLA	AZI	CLA	AZI	CLA	AZI
4	2.00 ± 0.6	0.08 ± 0.05	34.5 ± 29	1.0 ± 0.45	480 ± 533	42.7 ± 28.7
8	1.55 ± 0.4	0.09 ± 0.04	26.1 ± 7.2	2.2 ± 0.25	220 ± 86	57 ± 46
12	1.2 ± 0.35	0.04 ± 0.02	15.1 ± 11	0.95 ± 0.40	181 ± 79	40.4 ± 17
24	0.23 ± 0.11	0.05 ± 0.03	4.6 ± 3.7	1.22 ± 0.59	99.4 ± 50	41.7 ± 12

against a specific pathogen. The ratio of serum area under the curve (AUC) to MIC (AUC/MIC) has been shown to correlate with outcome with azithromycin, whereas the proportion of the dose administration interval in which serum concentrations exceed the MIC (T>MIC) is most closely linked to the outcome with clarithromycin.[57] Data suggest that the azithromycin AUC/MIC ratio should be between 25 and 50, and the clarithromycin T>MIC should be between 40 and 50% of the dose administration interval.[57] In a recent study, Kays and Denys used serum and ELF concentrations after standard dose administration to calculate the proportion of 307 isolates of *S. pneumoniae* against which it would be possible to obtain a ratio of azithromycin AUC/MIC >25 and clarithromycin concentrations that exceeded the MIC for >40% of the dose administration interval.[58] Over all 25.4% of isolates were resistant (MIC ≥2 μg/ml) to azithromycin and 25.1% were resistant to clarithromycin (MIC ≥1 μg/ml). On the basis of serum concentrations, clarithromycin achieved its pharmacodynamic target for 76.9% of isolates compared with 59.9% for azithromycin. On the basis of ELF concentrations, clarithromycin achieved its pharmacodynamic target for 93.5% of isolates compared with 74.6% for azithromycin. Further clinical studies in patients are needed to determine the clinical correlation of these findings.

While the documented failure rate of empirical therapy with macrolides for outpatients with CAP is low, there certainly is great concern that macrolide resistance will increase associated with continued use of these agents. Furthermore, the recent data that even the *mef*-mediated resistance is becoming associated with a higher MIC (from a median of 4–8 μg/ml) is of concern. In addition, since the likelihood of macrolide resistance is greater if an isolate of *S. pneumoniae* is penicillin-resistant, it is reasonable to consider alternative therapy if risk factors for PRSP or macrolide-resistance are present. Included among such factors are recent antibacterial usage, recent hospitalisation and day care centre exposure. One recently reported study of patients admitted to one of several hospitals in the US or Spain found that taking an oral macrolide at the time of admission was a risk factor for bacteraemia due to MRSP.[59]

2.4 Immunomodulating Effects of Macrolides

In addition to direct antibacterial effects, the macrolides also have some immunomodulating properties.[60-62] Such properties may be beneficial to the host response during respiratory infections.

The macrolides can inhibit the inflammatory response by a variety of effects.[60] Several of the macrolides, including azithromycin and clarithromycin, have been shown to inhibit oxygen generation and chemotaxis of neutrophils. Oxygen species produced during the 'respiratory burst' within neutrophils can be damaging not only to bacteria but also to the host tissue if generated in excess. Attenuation of oxidative burst capability by macrolides can, therefore, be beneficial in reducing the inflammatory process. In addition, macrolides inhibit synthesis and/or secretion of pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF)-α, and interferon from human monocytes. Inhibition of these

cytokines prevents excessive local and systemic inflammation. While a reduction in the inflammatory response may not directly contribute to bacterial cure, it promotes more rapid resolution of symptoms. In addition, erythromycin has been shown to reduce the chemotactic activity and the IL-8 release from eosinophils. These results could provide an explanation for the beneficial effects of macrolide treatment in allergic airway disorders.

Macrolides reduce bacterial infectivity in other ways as well without invoking either the immune system or antibacterial mechanisms. Specifically, they reduce the ability of pathogens to adhere to internal surfaces and they interfere with expression of virulence factors.[60] In addition, clarithromycin has been shown to reduce both sputum production and sputum elasticity, as well as decreasing mucus production in purulent rhinitis.[63] Neurally induced contraction of airway smooth muscles is similarly attenuated.[16] All these effects tend to reduce the severity of respiratory symptoms, and the reductions in sputum and mucus production may render the environment less hospitable to bacterial growth.

Erythromycin, clarithromycin and azithromycin have already been used as anti-inflammatory drugs, especially for the treatment of diffuse panbronchiolitis, an endemic chronic airway disease characterised by massive infiltration and excessive activation of neutrophils in lungs.[64,65] When used for low-dose, long-term treatment, these macrolides have resulted in a very good improvement. The probable basis for benefit is inhibition of mucus and water secretion from epithelial cells, and a reduction in IL-8 and IL-1 concentrations from neutrophils. Macrolide therapy was beneficial even for patients infected with macrolide-resistant *Pseudomonas aeruginosa*.[65] This improvement was not associated with the disappearance of the organism, and it may in part be related to the efficacy of the 14-membered macrolides in reducing bacterial biofilm.[66]

2.5 Clinical Trials with Macrolides

A large number of clinical trials have evaluated the efficacy of the macrolides in the treatment of CAP (table VII).[67-86] Earlier studies evaluating monotherapy with macrolides have involved ambulatory patients. In general, these studies have demonstrated equal clinical efficacy for the newer macrolides compared with β-lactams, other macrolides and the fluoroquinolones. However, most of these were licensing trials designed to show equivalence, did not include severely ill patients and were generally not large enough to determine small differences. Table VII summarises the clinical and bacteriological response for isolated pathogens in recent representative trials. Since most studies of CAP, which have evaluated 'atypical pathogens', have identified these pathogens by serological tests, it is difficult to assess bacteriological response for these agents.

2.6 Effect of Macrolides on Outcome: Observational Studies

In addition to prospective clinical trials, several observational studies have evaluated the efficacy of macrolides in patients with CAP.

Gleason et al. evaluated the therapies and outcomes of 864 outpatients with CAP from the Patients Outcomes Research Trial database.[87] Most patients were treated with an oral macrolide, including older patients and those with comorbid conditions. Medical outcomes were good in this group. The authors found that monotherapy with the macrolide was as effective as combination therapy and monotherapy was more cost effective. In contrast to these findings, Mundy et al., in a study of 385 consecutive patients hospitalised[88] with CAP in the Johns Hopkins Hospital, Baltimore, Maryland, USA, found that infection with *M. pneumoniae*, *C. pneumoniae* or *Legionella* spp. could be documented in only 7.5% of the patients; and among these patients only 14% received a macrolide or tetracycline for ≥7 days. Despite this, there are now preliminary data available that suggest that the addition of a macrolide to a β-lactam

Table VII. Randomised, clinical trials of the use of macrolides in patients with community-acquired pneumonia

Study	Drug regimen	No. patients[a]	Clinical success rate (%)[b]
Oral (PO)			
Kinasewitz and Wood, 1991[67]	Azithromycin 250mg po od	53	94
	Cefaclor 500mg po tid	66	100
Chien et al., 1993[68]	Clarithromycin 250mg po bid	92	97
	Erythromycin 500mg qid	81	96
Schönwald et al., 1994[69]	Roxithromycin[a] 150mg po bid (x10d)	60	94.3
	Azithromycin[a] 500mg po od (x3d)	90	98.9
Bohte et al., 1995[70]	Azithromycin 500mg po od	54	81
	Benzyl penicillin 1MU po qid	50	70
Lode et al., 1995[71]	Erythromycin 1g po bid	208	85
	Amoxicillin/clavulanic acid 500/125mg po bid	199	80
	Sparfloxacin 200mg po od	401	87
Rizzato et al., 1995[72]	Clarithromycin 250mg po bid (x10d)	20	85
	Azithromycin 500mg po od (x3d)	20	100
Laurent, 1996[73]	Azithromycin 500mg od (x3d)	99	92
	Roxithromyicn 150mg bid (x10d)	94	87
Ortqvist et al., 1996[74]	Roxithromycin 150mg po bid	150	79
	Sparfloxacin 200mg po od	154	94
Genne et al., 1997[75]	Clarithromycin 500mg IV bid	56	86
	Amoxicillin/clavulanic acid 1.2g IV qid	56	84
Patel et al., 1997[76]	Clarithromycin 250mg po bid	248	89
	Grepafloxacin 600mg po od	246	83
Sullivan et al., 1997[77]	Clarithromycin 500mg po bid	180	86
	Trovafloxacin 200mg po od	179	89
Moola et al., 1998[78]	Clarithromycin 250mg po bid	253	89
	Grepafloxacin 600mg po od	251	92
O'Doherty and Muller, 1998[79]	Clarithromycin 250mg po bid (x10d)	101	95
	Azithromycin 500mg po od (x3d)	102	94
Ramirez et al., 1999[80]	Clarithromycin 250mg po bid	175	89
	Sparfloxacin 200mg po od	167	89
Fogarty et al., 1999[81]	Clarithromycin 500mg po bid	188	95
	Moxifloxacin 400mg po od	194	95
Ramirez et al., 1999[82]	Gatifloxacin 400mg od	184	95
	Clarithromycin 500mg bid	188	93
Sokol et al., 2002[86]	Clarithromycin, extended release, 1g od	85	87
	Trovalfloxacin 200mg	66	95
Hoeffken et al., 2001[85]	Clarithromycin, 500mg bid	174	92.2
	Moxifloxacin 200mg od	180	90.7
	Moxifloxacin 400mg od	179	92.8
Intravenous (IV)			
Plouffe et al., 2000[83]	Azithromycin 500mg IV to po od (7–10d)	202	77
	Cefuroxime ± erythromycin	201	74
Vergis et al., 2000[84]	Azithromycin 500mg IV to po od	67	91
	Cefuroxime IV q8h to po bid + erythromycin IV to po	78	91

a No. patients refers to total patients enrolled.

b Success rate refers to those clinically evaluable at follow-up.

bid = twice a day; **od** = once daily; **q8h** = every 8 hours; **qid** = 4 times daily; **tid** = 3 times daily.

antibiotic beneficially enhances the outcome of patients with CAP who require hospitalisation.[89-92]

Several observational studies have found that use of macrolides as part of an initial combination (with a β-lactam agent) therapy of CAP appears to be associated with decreased mortality and shorter length of stay (LOS) for patients who require hospitalisation. Stahl et al. prospectively evaluated 100 patients hospitalised with CAP.[89] Patients were stratified according to the antibacterial they received. Patients who received macrolides (usually intravenous erythromycin or oral clarithromycin) within the first 24 hours of admission had a markedly shorter LOS (2.8 days) than those not so treated. The investigators speculate that the direct antibacterial effect against 'atypical' pathogens as well as a beneficial immunological or anti-inflammatory effect may be responsible for the advantage seen with the macrolides.

In a study of 12 945 Medicare patients (≥65 years of age), Gleason and colleagues found the addition of a macrolide to a second- or third-generation cephalosporin resulted in a significantly reduced 30-day mortality for elderly patients hospitalised with pneumonia.[90] The authors suggest this finding of better outcome may be related to the better activity for the common 'typical' and 'atypical' bacterial pathogens. Dudas et al. in an observational study of 3035 patients hospitalised with pneumonia in one of 72 non-teaching hospitals within a national group purchasing organisation, found the addition of a macrolide to either a second- or third-generation cephalosporin or a β-lactam/β-lactamase inhibitor was associated with decrease mortality and reduced LOS.[91] Houck et al. examined the risk for mortality during the 30 days after admission to the hospital of 10 069 Medicare patients in three time periods: 1993, 1995 and 1997.[92] In 1993, therapy with a macrolide plus a β-lactam was associated with significantly lower mortality than therapy with either a β-lactam alone or other regimens that did not include a macrolide, β-lactam or fluoroquinolone. This association was not observed in 1995 or 1997. The authors speculate this may be a result of a temporal variation in the incidence of atypical pathogen pneumonia.

Two additional studies have found a benefit of adding a macrolide to a β-lactam in patients with bacteraemic pneumococcal pneumonia.[93,94] A study of 225 patients treated within a healthcare system (three tertiary, two secondary and eight rural hospitals) in Tennessee, USA, from 1996 to 2000 observed that dual antibacterial therapy initiated within 24 hours of presentation resulted in a lower 15-day mortality rate compared with monotherapy (6.9 vs 18.2%).[94] A cephalosporin plus a macrolide was the most common combination used, while the most common single therapy was a newer fluoroquinolone. The study excluded patients with immunodeficiency and infections due to non-susceptible strains. A regression analysis that included antibacterial therapy and multiple risk factors for mortality indicated that monotherapy was an independent risk factor for death (adjusted odds ratio 6.4; 95% CI 1.9–21.7). The authors also found that participants given antibacterial coverage for 'atypical organisms' (i.e., *Mycoplasma*, *Chlamydia*, *Legionella* spp.) had a lower mortality rate (9.9%) than those treated without atypical coverage (22.6%, $p = 0.02$); however, this was not significant in a multivariate regression model ($p = 0.17$). The authors speculate that many potential mechanisms may explain this effect: (i) antibacterial synergism; (ii) antibacterial tolerance; (iii) the effect of macrolides on reducing cytokine production or adherence by pneumococci to respiratory epithelial cells; or (iv) the coexistence of atypical pathogens (for which an evaluation was not included in the group of patients). In addition to being retrospective, there are several limitations of this study. The authors were unable to control for time, duration or change after 24 hours of antibacterial therapy, and there was a wide range of antibacterial combinations used. In addition, while the authors controlled for deaths during the first 48 hours, they did not control for deaths within the first 4 days (earlier studies have implied that antibacterials within the first 5 days

had no effect on early mortality [Austrian and Gold, 1964[95]]).

Mufson and Stanek performed an additional evaluation of antibacterial response during a 20-year surveillance in West Virginia, USA, from 1978 to 1997.[94] The authors analysed the case-fatality rate by antibacterial regimen among individuals 50 years of age and older; they observed a macrolide in combination with a penicillin or cephalosporin provided the most effective outcome compared with a penicillin or cephalosporin alone or with any other combination of antibacterials without a macrolide. However, the findings were not controlled for early deaths or other risk factors; and the time period would not have included an assessment during the use of the newer fluoroquinolones. These observations are presently difficult to explain and may reflect confounding variables reflective of retrospective studies.

The above-mentioned studies showed that macrolide monotherapy is effective in the therapy of CAP in the majority of ambulatory patients. However, most of these studies were performed during the early to middle part of the 1990s at a time when macrolide resistance was just becoming significant. Of concern, will be the utility of macrolides for *S. pneumoniae* as higher rates of resistance occur. Data for monotherapy in hospitalised patients are limited to two studies comparing intravenous azithromycin to intravenous cefuroxime plus intravenous erythromycin in relatively less ill patients.[83,84]

3. Guidelines for Management

Guidelines for the initial management of adults with CAP have been developed by numerous international professional organisations. Most associations have relied on prospectively performed studies of patients with CAP on which to base recommendations. Published data and expert opinion have served as major influences in the formulation of these documents. Recent recommendations for empirical antibacterial therapy from representative international guidelines (i.e., North America, Latin America, Europe, South Africa and Asia/Pacific countries) are summarised in table VIII.[96-109] There is clearly a variation in healthcare practices and policies in these different geographical locations as well as in local antibacterial susceptibilities which influence specific recommendations. Although the different guidelines vary in their emphasis of the importance of defining the aetiological agents so that directed-therapy can be implemented, it is acknowledged that the majority of patients will be treated empirically. This is particularly the case for outpatients where diagnostic testing is not cost efficient and is not emphasised. Moreover, even at tertiary level university centres where multiple diagnostic testing methods are used for patients who require hospitalisation, an aetiologic agent is found in only 50% (approximately) of cases.[4]

The selection of specific antibacterial regimens for empirical therapy in the guidelines is based largely on the most likely pathogens (aided by knowledge of commonly encountered pathogens in one's own geographical area and an appreciation of their usual susceptibility patterns), and clinical studies. Other factors for consideration of specific antibacterials, which are mentioned in some of the guidelines, include tolerance (adverse effects), ease of administration and cost. Epidemiological information that may indicate the likelihood of a particular pathogen (such as recent epidemics of influenza, recent travel, and recent exposure to animals or other patients with specific infections) and disease severity (i.e. outpatient vs inpatient) also significantly influences therapeutic choices. Major issues, which seem to be fundamental regarding the use of the macrolides in the various guidelines, include the importance of providing therapy for atypical pathogens, the clinical significance of drug-resistant *S. pneumoniae* and various risk stratification strategies.

3.1 Importance of 'Atypical Pathogens'

A significant difference amongst the guidelines is the emphasis placed on the role of the macrolides for empirical treatment of the atypical pathogens (especially for outpatients). The role of atypical

pathogens is controversial because the frequency with which these organisms are found is largely dependent on the reliability of diagnostic tests and criteria used. The relative proportion rates from studies vary depending upon the strictness of criteria for diagnosis, age group, geographical location and whether an epidemic is occurring at the time of evaluation. In clinical practice, a specific aetiological diagnosis for *M. pneumoniae*, *C. pneumoniae*, or *Legionella* spp. is established in only a minority of patients. Therefore, patients with atypical infections tend to be under diagnosed.

The most common method for diagnosis of chlamydial or mycoplasma infection is by serology; however, these tests have major drawbacks because of variable sensitivity and specificity, and a requirement of convalescent sera for accurate interpretation. In addition, the atypical pathogens, particularly *C. pneumoniae*, are often implicated as part of a mixed infection (such as with *S. pneumoniae*). In most patients this is based on serological diagnosis of the atypical pathogen and microbiological isolation of *S. pneumoniae*. It is uncertain whether these infections represent true concomitant, co-infection or, more likely, an initial infection with the atypical organism which then predisposes to secondary bacterial infection.[13,17,28]

Finally, the importance of therapy for mycoplasma and chlamydial infections has been the subject of some conjecture. A common view is that, especially for mild infections, it really does not matter whether antibacterials are given for most of these infections because the mortality rate is low, these infections are often self-limiting and there are the confounding effects of mixed infection.

Nevertheless, studies from the 1960s indicate that treatment for mild *M. pneumoniae* infections reduces the morbidity of pneumonia and shortens the duration of symptoms.[9] In such studies therapy with a macrolide or a tetracycline was better than penicillin.

The North American guidelines place a significant emphasis on the potential role of the atypical organisms. The rationale is that these organisms are becoming more commonly recognised in recent studies as the aetiology of CAP; and in the several observational studies of therapy for patients who require hospitalisation (as reviewed previously), antibacterial regimens that have activity against the atypical pathogens have been associated with better outcomes. Thus, for both outpatients and inpatients, the option of using a macrolide, either as monotherapy in otherwise healthy individuals or as part of a combination regimen in patients with comorbid illness, is one of the recommendations invariably included in the North American recommendations.

The macrolides are attractive agents for empirical therapy of CAP based on the rationale that they provide appropriate coverage for the most likely bacterial causes of CAP[97,98] – particularly those associated with outpatients, that is, *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae* and *H. influenzae* (if *H. influenzae* is a consideration, such as with chronic inflammatory lung disorder, those agents with activity against this organism, clarithromycin or azithromycin, would be most appropriate). The prominent role of the macrolides is based on the relative frequency of atypical pathogens and the concept that it is difficult to differentiate the aetiology (i.e., atypical vs *S. pneumoniae*) from the clinical and radiographic findings at presentation.

Although certain features of illness have been described for CAP caused by various pathogens, it is recognised that clinical features are not sufficient to be of diagnostic value.[97-99] This concept is generally expressed in most of the guidelines. Although the French statement does differentiate based on a likelihood of atypical pneumonia (for patients under age 40 years presenting with an 'atypical aspect'), the most notable exception is in the Japanese guidelines, which recommend distinguishing whether a patient seems to have 'bacterial' or atypical pneumonia at the time of initial evaluation. The nine criteria from the Japanese

Table VIII. Comparison of recommendations of recently published ìinternational guidelines for empirical antimicrobial therapy of community-acquired pneumonia in adults

Guideline	Outpatient[a]	General ward[a]	ICU/severe[a]
North America			
CDC – Drug Resistant *Streptococcus pneumoniae* Therapeutic Working Group (2000)[96]	*Favoured*: macrolide[b] **or** doxycycline. *Also listed*: (i) β-lactams (i.e., cefuroxime, amoxicillin, amoxicillin/clavulanate) not effective for 'atypical' pathogens[c] **or** (ii) anti-pneumococcal FQ[d] (not first-line because of concerns for emerging resistance)	β-lactam[e] *plus* macrolide; or anti-pneumococcal FQ[d] (not first-line because of concerns for emerging resistance)	IV β-lactam[e] *plus* IV macrolide; **or** IV β-lactam *plus* anti-pneumococcal FQ[d]
Canadian Infectious Disease Society/ Canadian Thoracic Society [2000][97]	*Without modifying factors*: (i) macrolide; (ii) doxycycline. *With modifying factors*: COLD (no recent antibacterials or corticosteroids) – (i) new macrolide;[f] (ii) doxycycline. COLD (recent antibacterials or corticosteroids) – (i) anti-pneumococcal FQ;[d] (ii) (amoxicillin/clavulanate or 2-G ceph) and macrolide	(i) Anti-pneumococcal FQ;[d] (ii) 2-G, 3-G or 4-G ceph *plus* macrolide	*Pseudomonas aeruginosa not suspected:* (i) IV anti-pneumococcal FQ *plus* cefotaxime, ceftriaxone or β-lactam/β lactamase inhibitor; (ii) IV macrolide plus cefotaxime, ceftriaxone or β-lactam/β lactamase inhibitor. *P. aeruginosa suspected:* (i) anti-pseudomonal FQ (eg. ciprofloxacin) *plus* anti-pseudomonal β-lactam[g] or aminoglycoside; (ii) triple therapy with anti-pseudomonal β-lactam[g] *plus* aminoglycoside *plus* macrolide
Infectious Diseases Society of America (2000)[98]	Doxycycline; **or** macrolide; **or** anti-pneumococcal FQ.[d] Selection considerations: choice should be influenced by regional antibacterial susceptibility patterns for *S. pneumoniae* and the presence of risk factors for PRSP. For older patients or those with underlying disease, anti-pneumococcal FQ may be preferred; some authorities prefer to reserve FQs for such patients	Macrolide *plus* cefotaxime, ceftriaxone or a β-lactam/β-lactamase inhibitor (ampicillin-sulbactam **or** piperacillin-tazobactam); **or** anti-pneumococcal FQ	(IV anti-pneumococcal FQ or IV macrolide) *plus* (cefotaxime, ceftriaxone or a β-lactam/β-lactamase inhibitor [ampicillin/sulbactam or piperacillin/tazobactam]). *If structural lung disease:* anti-pseudomonal agents with activity for *S. pneumoniae* (i.e. cefepime, imipenem, meropenem, piperacillin) *plus* a FQ (including ciprofloxacin)
American Thoracic Society (2001)[99]	*No cardiopulmonary disease, no modifying factors*:[h] azithromycin or clarithromycin (doxycycline if allergic or intolerant of macrolides). *Modifying factors*:[h] β-lactam (cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate or parenteral ceftriaxone followed by PO cefpodoxime) *plus* macrolide or doxycycline; **or** anti-pneumococcal FQ[d]	*No modifying factors*:[h] IV azithromycin or doxycycline *plus* a β-lactam; **or** monotherapy with an anti-pneumococcal FQ.[d] *Modifying factors*:[h] IV β-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) *plus* IV or PO macrolide or doxycycline; **or** IV anti-pneumococcal FQ[d]	*No risks for P. aeruginosa*: IV β-lactam (cefotaxime, ceftriaxone) *plus* (IV macrolide [azithromycin] or IV anti-pneumococcal FQ). *Risks for P. aeruginosa*: IV anti-pseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) *plus* IV anti-pseudomonal FQ (ciprofloxacin) **or** IV anti-pseudomonal β-lactam *plus* IV aminoglycoside *plus* either IV azithromycin or IV non-pseudomonal FQ
Latin America			
ALAT (2001)[100]	*Without risk factors for PRSP*: macrolide (use clarithromycin or azithromycin if smoker to cover *Haemophilus influenzae*); **or** doxycycline; **or** anti-pneumococcal FQ.[d] *Risk of PRSP* (i.e., age >65y, β-lactam within 3m, alcoholism, co-morbidities,): anti-pneumococcal FQ;[d] **or** amoxicillin *plus* macrolide	(i) Anti-pneumococcal FQ; **or** (ii) 3-G ceph *plus* macrolide (if suspicion of anaerobic infection, clindamycin can be substitute; if using a FQ with anaerobic activity, such as moxifloxacin, it is not necessary)	(i) 3-G ceph *plus* macrolide; **or** (ii) anti-pneumococcal FQ.[d] *If suspicions for Pseudomonas*: ciprofloxacin *plus* (piperacillin/ tazobactam or imipenem or cefepime). *If suspicion of anaerobes*: add ampicillin/sulbactam **or** clindamycin

South Africa			
South African Pulmonary Society and the Antibiotic Study Group (1996)[101]	IM penicillin followed by amoxicillin; **or** macrolide/azalide; **or** tetracycline(doxycycline)	*Age < 60y, no comorbidity*: penicillin G **or** amoxicillin; (alternative: macrolide/azalide; or tetracycline/doxycycline). *Age > 60y, co-morbidity*: 2-G ceph **or** amoxicillin/clavulanate ± macrolide/azalide	(2-G ceph or amoxicillin/clavulanate) *plus* aminoglycoside *plus* macrolide
Europe			
Spanish Thoracic Society (1997)[102]	*No modifying factors*: amoxicillin (1g q8h PO); **or** cefuroxime (1g q12h PO); or procaine penicillin IM. *If 'atypical syndrome'*: macrolide or tetracycline. *If cause indeterminate*: macrolide. *Modifying factors* (elderly, comorbidities, prior antibacterials): amoxicillin/clavulanate 1000/125mg q8h; **or** cefuroxime (PO or IM) [if suspicion for atypical aetiology, add macrolide]	Cefotaxime **or** ceftriaxone or amoxicillin/clavulanate IV (add erythromycin if suspicion for *Legionella* sp.)	Defined as very serious infection: (cefotaxime or ceftriaxone) *plus* erythromycin *plus* rifampin
German Respiratory Society/Paul Erlich Society (2000)[103]	Defined as mild to moderate pneumonia. *<65y and no underlying disease*: cephalosporins; **or** macrolides; **or** aminopenicillin/β-lactamase inhibitor; **or** anti-pneumococcal FQ. *>60 years or with concomitant disease*: 2-G ceph (cefuroxime, cefotiam, cefamandole, loracarbef) or 3-G ceph (cefotaxime, ceftriaxone, ceftizoxime, cefmenoxine, cefodizime); **or** aminopenicillin/β-lactamase inhibitor; **or** anti-pneumococcal FQ	Defined as severe pneumonia treated on an inpatient basis. (3-G ceph [cefotaxime, ceftriaxone, ceftizoxime, cefmenoxine, cefodizime] or aminopenicillin/β-lactamase inhibitor) *plus* (macrolide or anti-pneumococcal FQ); *alternatively*, carbapenem ± macrolide; **or** (ciprofloxacin or ofloxacin) *plus* clindamycin	(Acylaminopenicillin/β-lactamase inhibitor, carbapenem or 3-G ceph) *plus* macrolide. *Alternatively*, FQ (including ciprofloxacin) *plus* clindamycin
British Thoracic Society (2001)[104]	Amoxicillin 500–1000mg tid (alternatively, erythromycin or clarithromycin)	*If admitted for non-clinical reasons or previously untreated in the community*: amoxicillin (macrolide as alternative). *If admitted for pneumonia and oral therapy appropriate*: amoxicillin *plus* (erythromycin or clarithromycin); [*alternatively*, anti-pneumococcal FQ]. *If parenteral appropriate*: (ampicillin or benzylpenicillin) *plus* (erythromycin or clarithromycin) [*alternatively*, IV levofloxacin]	Defined as severe. Amoxicillin/clavulanate **or** 2/3-G ceph *plus* (IV erythromycin or clarithromycin, ± rifampin) [FQ with enhanced pneumococcal activity *plus* benzylpenicillin as alternative]
Infectious Diseases French Society (2001)[105]	*No comorbidity*: *>40y* – amoxicillin (1g tid); if no improvement in 48h add or substitute a macrolide or change to anti-pneumococcal FQ monotherapy. *<40y and presenting an 'atypical aspect'* – macrolide (except azithromycin); if no improvement in 48h add or substitute amoxicillin or change to anti-pneumococcal FQ as monotherapy. *With comorbidity (not specifically defined)*: amoxicillin/clavulanate 1g tid (*alternative*-ceftriaxone 1g od); *if suspicion of intracellular pathogens* – amoxicillin/clavulanate *plus* macrolide; **or** amoxicillin *plus* ofloxacin (*alternatively:* ceftriaxone *plus* macrolide; **or** anti-pneumococcal FQ); *if suspicion of aspiration pneumonia* – amoxicillin/clavulanate IV (*alternative*: 3-G ceph IV *plus* metronidazole)	Amoxicillin/clavulanate 1g tid PO (*alternative* – ceftriaxone); *if suspicion for intracellular pathogens or aspiration* – same as for outpatients	(Amoxicillin/clavulanate IV or 3-G ceph [ceftriaxone or cefotaxime]) *plus* (parenteral macrolide or FQ [including ciprofloxacin]). *Add* rifampin if *Legionella* spp. suspected

Continued next page

Table VIII. Contd

Guideline	Outpatient[a]	General ward[a]	ICU/severe[a]
Asia-Pacific			
Japanese Respiratory Society (2000)[106]	Specified as 'mild or moderate' pneumonia. *When bacterial pneumonia suspected*: a penicillin type (with a β-lactamase inhibitor) PO, or penicillin type (injection); **or** cephem type drug. *When atypical pneumonia suspected*: macrolide or tetracycline	Specified as 'severe' pneumonia. *For younger patients without underlying illness*: injection use FQ. *For elderly or underlying illness*: carbapenem *plus* (tetracycline or macrolide); **or** 3-G ceph *plus* clindamycin *plus* (tetracycline or macrolide)	Not specified. Consider as for inpatients, for elderly or underlying illness
Philippine Society for Microbiology and Infectious Diseases (1998)[107]	*'Young' adult*: amoxicillin; **or** extended macrolide (clarithromycin or azithromycin); **or** co-trimoxazole. *With comorbid illness or 'elderly'*: co-trimoxazole; **or** amoxicillin/clavulanate or ampicillin/sulbactam; **or** 2-G ceph; **or** extended macrolide	β-lactam ± erythromycin; **or** levofloxacin	Anti-pseudomonal β-lactam ± (aminoglycoside or ciprofloxacin) *plus* erythromycin (rationale to include *Pseudomonas* spp. and *S. aureus*)
Hong Kong – Hong Kong University and Hong Kong Authority (2001)[108]	(Amoxicillin/clavulanate or ampicillin/sulbactam) +/- macrolide; **or** amoxicillin *plus* newer macrolide	(IV or PO amoxicillin/clavulanate or ampicillin/sulbactam) ± macrolide; **or** (cefotaxime or ceftriaxone) ± macrolide	(IV piperacillin/tazobactam or cefotaxime or ceftriaxone) *plus* macrolide
Singapore – Physicians Academy of Medicine Singapore (2000)[110]	*<60y and no comorbidity*: macrolide **or** tetracycline/doxycycline. *>60y or <60y with comorbidity*: macrolide **or** cefuroxime or amoxicillin/clavulanate **or** ampicillin/sulbactam	Penicillin (>10 MU/day) ± metronidazole; **or** 3-G ceph ± macrolide; **or** amoxicillin/clavulanate, ampicillin/sulbactam ± macrolide; **or** anti-pneumococcal FQ	Macrolide *plus* ceftazidime (for possible *Burkholderia* sp.) ± (cloxacillin or clindamycin or vancomycin); **or** anti-pneumococcal FQ *plus* ceftazidime
Australia (2000)[109] [recommendations being revised]	Defined as mild to moderate and oral therapy. Amoxicillin 1g q8h; **or** doxycycline; **or** roxithromycin	Defined as mild to moderate and parenteral therapy required). Benzylpenicillin; **or** procaine penicillin; **or** 1-G ceph IV	Defined as severe. *Nontropical Australia*: erythromycin *plus* benzylpenicillin *plus* gentamicin (discontinue if no Gram-negative pathogen); **or** erythromycin *plus* (cefotaxime or ceftriaxone). *Topical Australia* (concern for *B. pseudomallei* and *A. baumannii*): gentamicin *plus* (ticarcillin/clavulanate or ceftriaxone)

a While the classification of site of care is clear in most of the statements, some, such as the Spanish, German and Japanese recommendations, are less definitive and classify patients as 'mild-to-moderately ill' (implying most can be treated as outpatients) and 'severe' (implying requiring admission to the hospital).

b Erythromycin, clarithromycin or azithromycin.

c Cefuroxime axetil, amoxicillin, amoxicillin/clavulanate, cefpodoxime, cefprozil; does not cover atypical pathogens.

d Anti-pneumococcal fluoroquinolone = levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin.

e Ceftriaxone, cefotaxime, cefuroxime or ampicillin/sulbactam.

f Clarithromycin, azithromycin.

g For example, ceftazidime, piperacillin/tazobactam, imipenem, meropenem.

h Risks for drug-resistant *S. pneumoniae* (includes antibacterial therapy within past 3 months, recent hospitalisation, multiple co-morbidities, elderly, exposure to day care centre) or cardiopulmonary disease.

1-G, 2-G, 3-G, 4-G = first-, second-, third-, or fourth-generation cephalosporins; **ALAT** = Asociacion Latinoamericana del Torax; **bid** = twice daily; **CDC** = Centers for Disease Control and Prevention; **COLD** = chronic obstructive lung disease; **FQ** = fluoroquinolone; **ICU** = intensive care unit; **IM** = intramuscularly; **IV** = intravenous; **od** = once daily; **PO** = orally; **PRSP** = penicillin-resistant *S. pneumoniae*; **qxh** = every x hours; **tid** = three times daily.

guidelines for differentiating the aetiology of CAP are listed in table IX.

The British Thoracic Society (BTS) guidelines do not recommend the use of the term 'atypical' pneumonia; however, they do refer to infections caused by *M. pneumoniae*, *C. pneumoniae*, *C. psittaci* and *C. burnetii* in the phrase, atypical. Furthermore, they suggest that since *M. pneumoniae* exhibits epidemic periodicity every 4–5 years and largely affects younger individuals, a policy for initial empirical therapy that aimed always to cover this pathogen was unnecessary.

Table IX. Nine criteria from the Japanese guidelines for differentiating the aetiology of Community-acquired pneumonia[a]

Symptoms/signs	1. Age >60y
	2. Absence of underlying conditions
	3. Pneumonia epidemic in the community or family
	4. Stubborn cough
	5. Relatively slow pulse
	6. Few physical chest findings
Test results	7. Normal white blood count
	8. Interstitial infiltrate on chest radiograph
	9. Gram stain reveals no likely pathogen

a Patients exhibiting five out of the above nine items and three out of the five symptoms/signs were classified as *Mycoplasma* or *Chlamydia* and prescribed macrolides or tetracycline.[106]

3.2 Importance of MRSP

The clinical relevance of MRSP is another significant issue which influences empirical therapy in the guidelines. The rationale for positioning the macrolides as prominent first-line agents in the North American guidelines is partly based on the perception that the newer macrolides (azithromycin or clarithromycin) can be effective against MRSP strains in which lower-level resistance results from increased drug efflux with resulting MICs of 1–8 μg/ml. This partly explains the difference in the North American and European positioning of macrolides since the majority of resistance in North America is efflux (often with MIC <16 μg/ml), whereas it is ribosomal (with MICs >32 μg/ml) in most locations within Europe. In addition, at the time of the development of the North American guidelines, macrolide failure in outpatients, especially in patients without associated risks for DRSP, had been infrequent. However, the trend in increasing MICs of the efflux-associated resistant strains in the US is of significant concern. As these strains become more prominent, additional treatment failures can be expected and reconsideration of the North American recommendations may be required.

3.3 Risk-Stratification

All the guidelines listed give differing recommendations for empirical antibacterial therapy based on severity of disease. Most classify patients according to site of care (i.e. outpatient vs inpatient). While this classification is clear in most of the statements, some, such as the German and Japanese recommendations, are less definitive and classify patients as 'mild-to-moderately ill' (implying most can be treated as outpatients) and 'severe' (implying requiring admission to the hospital). The Canadian consensus group and the Infectious Diseases Society of America (IDSA) advocate the pneumonia prediction rule for helping to determine the severity of illness and, subsequently, site of care; the others variably recommend other clinical parameters to assist with this decision.

In addition, there are various stratification strategies using factors such as age, underlying conditions, and epidemiological risks for drug-resistant strains as influencing specific antibacterial choices. Such factors have some influence on the likely causative pathogens and consequently the choice of empirical therapy in some circumstances. As an example, the American Thoracic Society (ATS) statement divides patients into four groups (with two additional subgroups) on the basis: (i) of place of therapy (outpatient, hospital ward or intensive care unit [ICU]); (ii) the presence of co-existing cardiopulmonary disease (chronic obstructive pulmonary disease [COPD], congestive heart failure); and (iii) the presence of 'modifying factors' which included the presence of risk factors for drug-resistant pneumococcus, the presence of risk factors

for Gram-negative infection (including nursing home residence) and the presence of risk factors for *P. aeruginosa* (specifically in patients requiring ICU admission) [table VII].[15,19,27] Predominant pathogens according to this classification as listed in the ATS guidelines is as follows.

I. Outpatients with no history of cardiopulmonary disease, and no modifying factors: *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae* (alone or as mixed infection), *H. influenzae*, respiratory viruses and miscellaneous (*Legionella* sp., *Mycobacterium tuberculosis*, endemic fungi).

II. Outpatients with cardiopulmonary disease (congestive heart failure or COPD) and/or other modifying factors (risk factors for DRSP or Gram-negative bacteria): *S. pneumoniae* (including DRSP), *M. pneumoniae*, *C. pneumoniae*, mixed infection (bacteria plus atypical pathogen or virus), *H. influenzae*, enteric Gram-negatives, respiratory viruses and miscellaneous (*Moraxella catarrhalis*, *Legionella* sp., aspiration [anaerobes], *M. tuberculosis* or endemic fungi).

III. Inpatients, not admitted to the ICU, who have:

- cardiopulmonary disease, and/or other modifying factors (including from a nursing home): *S. pneumoniae* (including DRSP), *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric Gram-negatives, aspiration (anaerobes), viruses, *Legionella* sp. and miscellaneous *(M. tuberculosis*, endemic fungi, *Pneumocystis carinii*)
- no cardiopulmonary disease and no other modifying factors: *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), viruses, *Legionella* sp. and miscellaneous (*M. tuberculosis*, endemic fungi, *Pneumocystis carinii*)

IV. ICU admitted patients who have:

- no risks for *P. aeruginosa*: *S. pneumoniae* (including DRSP), *Legionella* sp., *H. influenzae*, enteric Gram-negative bacilli, *S. aureus*, *M. pneumoniae*, respiratory viruses and miscellaneous (*C. pneumoniae*, *M. tuberculosis*, endemic fungi)
- risks for *P. aeruginosa*: all of the above pathogens plus *P. aeruginosa*.

3.4 Recommendations for Empirical Therapy of CAP: Outpatients

All of the new North American guidelines variably recommend macrolides, doxycycline or an anti-pneumococcal fluoroquinolone (i.e., levofloxacin, gatifloxacin or moxifloxacin) as treatment options for patients who are mildly ill and can be treated as outpatients. In general, the North American guidelines recommend a macrolide as first-line treatment for outpatients with no comorbidity or risk factors for DRSP.

In the Canadian statement, outpatients are stratified into those without modifying factors, for whom a macrolide may be used, and those with modifying factors (such as chronic obstructive lung disease or recent use of antibacterials or corticosteroids, which may result in a greater likelihood of DRSP) for whom fluoroquinolones are considered more appropriate as first-line empirical therapy.

The IDSA statement indicates that the selection considerations among the three options should be influenced by regional antibacterial susceptibility patterns for *S. pneumoniae* and the presence of risk factors for DRSP (such as the use of antibacterial agents within the previous 3 months). The statement further indicates that 'for older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients.' Thus, implying macrolide as first-line therapy for those patients without comorbidity or risk factors for DRSP.

Although the Centers for Disease Control and Prevention (CDC) statement lists β-lactams (i.e. cefuroxime, amoxicillin or amoxicillin/clavulanate) as options for outpatients, their recommendation favours the use of a macrolide or doxycycline because of their broad coverage of atypical pathogens (particularly *M. pneumoniae*). Furthermore, the CDC recommendation is that fluoroquinolones should be reserved for cases associated with fail-

ure, allergy to other agents or due to documented DRSP. The rationale is that fear of widespread use may lead to the development of fluoroquinolone resistance among the respiratory pathogens (as well as other pathogens colonising the treated patients).

Similar to the Canadian statement, the revised ATS guidelines recommend stratifying outpatients into two categories (table VII) with macrolides being recommended as first-line therapy for patients with no cardiopulmonary disease, and no risks for DRSP, aspiration or enteric Gram-negatives. Doxycycline is a second choice (because of less reliable activity against *S. pneumoniae*) if patients are intolerant of, or allergic to, macrolides. The statement indicates that if *H. influenzae* is not likely, any macrolide could be used, including erythromycin. For more complex outpatients the ATS statement recommends either a β-lactam/macrolide combination or monotherapy with an anti-pneumococcal fluoroquinolone. The rationale is the concern for likely DRSP and the possibility of clinical failure if the macrolides are used alone.

In contrast, the primary agents recommended in the European, Asia/Pacific and South African statements are β-lactams, basically penicillins, and not macrolides. The rationale is that these agents are effective against *S. pneumoniae*; and when given in high doses are even effective for most strains with decreased sensitivity to penicillin. Therefore, both the French and Spanish statements recommend 'high-dose' amoxicillin (1g three times daily orally) and the BTS guideline lists this dosage as an option. Since most of the macrolide-resistance in Europe is *erm*-mediated, high-level resistance, the macrolides are not regarded as optimal first-line empirical agents to treat this pathogen if *S. pneumoniae* is considered likely.

Since the Japanese statement emphasises early distinction on clinical grounds as to suspected bacterial or atypical aetiology, this statement promotes a syndromic approach in an attempt to differentiate an aetiological category based on clinical parameters. On the basis of this distinction, the Japanese group recommends a penicillin-type drug (with a β-lactamase blocking agent) or (by injection) a penicillin-type or a cephem-type drug when bacterial pneumonia is suspected and there is no microbiological data available to indicate a specific organism. When atypical pneumonia is suspected, a macrolide or tetracycline type drug is recommended.

3.5 Recommendations for Empirical Therapy of CAP: Inpatients

All of the North American guidelines recommend treatment with a β-lactam plus a macrolide or monotherapy with a fluoroquinolone for patients admitted to the general ward. The rationale for recommending these regimens is based on studies showing these regimens were associated with a significant reduction in mortality compared with that associated with administration of a cephalosporin alone.[8,9] These studies did not have a sufficient number of patients treated only with macrolides to justify conclusions about that category as monotherapy, although recent studies suggest intravenous azithromycin monotherapy is equivalent to a β-lactam (cefuroxime) plus erythromycin. The recommendations in the BTS guidelines are fairly similar for patients requiring parenteral therapy, except a penicillin is listed the preferred β-lactam. The Japanese statement stratifies patients on the basis of age and presence of underlying illness with an 'injection use fluoroquinolone' recommended for the first category and a combination regimen for the second category.

For patients with severe CAP who require admission to an ICU all guidelines recommend comprehensive antimicrobial therapy to cover *S. pneumoniae* (including DRSP), *Legionella* spp. and the possibility of pseudomonas in selected cases. For this group of patients with severe disease, azithromycin is the preferred macrolide over erythromycin by the ATS statement because of difficulties in administration and tolerance with erythromycin (parenteral clarithromycin is not available in the US). Also, reflecting local issues concerning likely pathogens, certain Asian/Australian recommendations for empirical therapy characterise patients

from non-tropical or tropical areas to differentiate for the greater possibility of *Burholderia pseudomallei*.

4. Conclusion

In summary, clinicians are now presented with several sets of new guidelines for the same clinical entity. These guidelines are intended to provide clinicians with general principles of disease management, and it is envisaged that these will be adapted to suit regional circumstances, local hospital practices and individual patient characteristics.

In terms of recommendations for empirical therapy, they are more similar than they are different. Differences are in part related to variance in local epidemiology and the clinical relevance of antimicrobial resistance. Presently, the macrolides are more prominently recommended in the North American guidelines than in other parts of the world. The difference in the emphasis placed on the importance of the atypical pathogens as well as the expression of MRSP in North America compared with Europe partly explains this variance.

All of the guideline statements reflect thoughtful consideration by a panel of experts and should be viewed as recommendations for strategies of care and not definite step-wise rules of care. Indeed, clinicians must interpret such statements in the context that these recommendations cannot apply to all hypothetical settings. Rather, these statements represent general state-of-the-art documents which require continuing change because of the changes in our understanding of this important infection.

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