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Efficacy of a three day course of azithromycin in moderately severe community-acquired pneumonia

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Efficacy of a three-day course of azithromycin in moderately severe community-acquired pneumonia. G. Rizzato, L. Montemurro, P. Fraioli, G. Montanari, D. Fanti, R. Pozzoli, E. Magliano. ©ERS Journals Ltd 1995.

ABSTRACT: This study was designed to evaluate the efficacy of a 3 day course of azithromycin in low to moderately severe community-acquired pneumonia.

Forty patients with low to moderately severe community-acquired pneumonia (29 males, 11 females, mean age 46±17 yrs; 20 pretreated with betalactams for 2–10 days with no results before admission to hospital; 18 with evidence of co-morbidity) were enrolled in an open, randomized study with azithromycin, 500 mg *q.d.* oral therapy for 3 days, *versus* clarithromycin, 250 mg *b.i.d.* oral therapy for 10±2 days.

The aetiology of pneumonia was identified in 18 patients by serology (nine *Mycoplasma pneumoniae*, four *Chlamydia pneumoniae*, five *Legionella pneumophila*; one patient with chlamydial infection also had *Klebsiella pneumoniae* bacteraemia). A presumptive aetiological diagnosis was obtained with sputum culture in three other patients (one *Haemophilus influenzae*, two *Haemophilus parainfluenzae)*, all strains were sole isolates with 10^8 Colony forming units (CFU), and with Gram stain in one patient with *Streptococcus pneumoniae*. All patients in the azithromycin group (one after a second 3 day course), and all but two (of those available for evaluation) of the clarithromycin group were cured. Defervescence occurred after 2.6±1.6 days, and chest roentgenogram cleared after 8.9±3.3 days, with no difference between the two groups. Tolerance was good, and there were no withdrawals from therapy.

Azithromycin, as well as clarithromycin, may be a good first choice approach for the treatment of low to moderately severe community-acquired pneumonia, but a 3 day course of azithromycin may increase patient compliance.

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Community-acquired pneumonia (CAP) is caused in most cases by *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* or *Chlamydia pneumoniae*. Some studies have also shown a number of cases due to *Haemophilus influenzae* or *Moraxella catarrhalis*. Macrolides cover most of the above spectra. Thus, many authors suggest a macrolide as the first choice of drug in the treatment of CAP, especially in previously healthy young or middle-aged adults, who are less likely to suffer from enterobacterial infection. Even the recent American Thoracic Society (ATS) guidelines for the treatment of CAP underline that clarithromycin and azithromycin have *in vitro* activity against the major pathogens, thereby providing the option of monotherapy, although more data are required from controlled trials [1].

Azithromycin shows a good penetration into lung tissue [2], and a good persistence at the infected tissue sites for an additional 4–7 days [3] after drug withdrawal. The proposed standard dosage regimen of 500 mg daily *per os* results in tissue concentrations exceeding the minimal inhibitory concentrations (MICs) of relevant respiratory pathogens [4]. Its very long half-life, up to 72 h, allows for clinical use with a new unorthodox dosage of 5 or even 3 days only, thereby improving patient compliance.

In several clinical studies on lower respiratory tract infections (LRTI) (sometimes including a few cases of pneumonia), azithromycin, in a single daily dose over a 3 or 5 day period, proved as effective as a 7–10 day course of other commonly used antibiotics, such as amoxycillin/clavulanic acid, erythromycin, clarithromycin or cefaclor [5–9]. In spite of the vast literature available, the studies with azithromycin in CAP have so far been very limited. Two studies [10, 11] have shown good results following a 5 day azithromycin course in comparison to josamycin or cefaclor. In 1991, SCHONWALD *et al.* [12] compared a 3 or 5 day regimen in patients with atypical pneumonia, treated with a total oral dose of 1.5 g azithromycin; all patients were clinically cured. The 3 day regimen group was given 500 mg once daily for three days, and the 5 day regimen group was given 500 mg on day 1, followed by 250 mg on days 2–5. In two other noncomparative studies [13, 14], azithromycin produced good results when given for 3 days to patients with CAP.

As far as we know, the 3 day course of azithromycin has never been compared to other drugs in the treatment

of CAP. The aim of this study was to evaluate the efficacy and safety of azithromycin, given for 3 days, in comparison to clarithromycin (given for 8 days or more) in the treatment of low to moderately severe CAP.

Methods and patients

Study design

In hospitalized patients with CAP, the mortality rate is around 10%, and the population at risk is mostly over 65 yrs of age. The pharmacokinetics of azithromycin ensures that the drug remains active for an additional 4–7 days after withdrawal, but this may not be reflected in clinical studies. Thus, for ethical reasons, in a pilot study treating CAP with only a 3 day regimen, we chose to exclude patients at higher risk, according to the following exclusion criteria: 1) pneumonia in more than one lobe, as shown by posteroanterior and lateral chest roentgenogram; 2) over 75 yrs of age; 3) white blood cell count (WBC) $<3\times10^{9}\cdot l^{-1}$; 4) arterial oxygen tension (Pa_{O_2}) <7.3 kPa (<55 mmHg); and 5) with bacteraemia.

Patients with bacteraemia were excluded, not only because they are at high risk but also because azithromycin reaches very low blood levels, being mostly concentrated in macrophages and in tissues (this criterion was over-ridden in one case that is discussed later, see Results).

Pretreatment with other antibiotics was not an exclusion criterion: the failure of the previous antibiotic was ascertained from a clinical point of view, and in each case a minimum of 24 h elapsed between the last dose and enrolment.

A diagnosis of pneumonia was made on the basis of significant clinical manifestations and pulmonary opacity on the chest roentgenogram. According to the above exclusion criteria, all patients with CAP, admitted to Vergani Department from October 1, 1992 and willing to participate, were enrolled into the study, in order to reach the total number of 40 patients. Of 112 consecutive CAP patients screened, 72 were excluded due to one or more exclusion criteria (age over 75 yrs in most), and the remaining 40 patients gave their informed consent. The first patient was enrolled on October 2, 1992, and the last on August 24, 1993. The seasonal distribution was homogenous, with 12 patients enrolled in October–December 1992, 11 in January–March, 9 in April–June, and 8 in July–August 1993. The patients were divided into two groups by simple open randomization; 20 patients were given azithromycin (AZ group), 500 mg oral therapy in a single daily dose for 3 days, and 20 patients clarithromycin (CL group), 250 mg *b.i.d.* oral therapy for at least 8 days. Clarithromycin could be continued even after the eighth day, if necessary.

Work-up

All patients underwent the following work-up. Chest roentgenograms were taken on entry, on day 5 or 6 and, if necessary, on day 10, 11 or 12.

Arterial blood samples for blood gases (Pa_{O_2} and arterial carbon dioxide tension (Pa_{CO_2})) were obtained on entry, and during follow-up, if necessary. Three or more blood samples, taken before starting antibiotic therapy, were collected for cultures (carried out with automated instrument Bactec NR) and Kirby Bauer. In pretreated patients, liquid media with resins were used to counteract the residual antibiotic activity.

Sputum Gram stain and culture were performed on entry and at the end of the study, when available: 19 samples were sent on entry, 9 at the end of the study; all the samples were suitable according to Bartlett's criteria.

Serum samples were obtained on entry, and on day 10 and 30, for *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae* antibodies. The indirect fluorescent antibody technique was used to test for *L. pneumophila* serogroups 1–6. The indirect agglutination technique (Serodia-Myco II, Fujirebio Inc, Tokyo) was used to test for *M. pneumoniae* antibodies. *C. pneumoniae* antibodies were detected by microimmunofluorescence using TWAR antigen (Washington Research Foundation, Seattle, USA), as described previously [15].

Biochemical profile included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, γ-glutamyl-transpeptidase (γ–GT), alkaline phosphatase, blood urea nitrogen, creatinine, glucose, erythrocyte sedimentation rate (ESR), C reactive protein, haemoglobin, red blood cell (RBC) count, WBC total and differential count. Blood was taken at the beginning of the study and after 5 or 6 days; further blood samples were taken when necessary during follow-up.

Therapy with the randomized macrolide started within 24 h of hospitalization, after conclusion of the initial work-up.

Aetiological diagnosis

A fourfold antibody titre rise was accepted as evidence of infection due to *M. pneumoniae* or *L. pneumoniae*. For *M. pneumoniae*, when only convalescent serum was available, a titre >1:40 was also considered diagnostic. As regards *C. pneumoniae*, one or more of the following three criteria was accepted as evidence of recent infection [15]: 1) immunoglobin M (IgM) titre >1:16; 2) fourfold increase of immunoglobin G (IgG) titre; and 3) IgG titre >1:512.

Microscopic (Gram stain) and bacteriological examination of the sputum were carried out whenever possible, but only strains that were sole isolates with colony forming units (CFU) $>10^{7}$ were considered [16].

Therapeutic efficacy and safety

Therapeutic efficacy was evaluated according to the following assessments made on entry, during and at the end of the study: fever, cough, volume and appearance of the sputum, physical examination, chest roentgenogram, ESR, C reactive protein, and total and differential WBC count. To investigate bacteriological outcome, a second sputum specimen was taken, when possible, at the end of the trial.

Safety was evaluated both clinically and on the basis of the biochemical profile described above.

Patient population

Patients required hospitalization because of the failure of the prescribed antibiotic therapy in half the cases;

Table 1. – Patients population: demographic features, co-morbidity, previous chemotherapy, fever and pleural effusion at presentation

	AZ group n=20	CL group n=20
Age† yrs	48±13	44±19
Gender M/F	13/7	16/4
Smokers n	9	8
Excessive alcohol intake n	2	2
Parenteral drug abusers n	0	0
Underlying diseases		
Diabetes	1	1
COPD	-	3
Asthma	1	1
Small-cell lung cancer	-	1
Liver disease	1	2
Heart disease	2	4
Anaemia	1	-
Pretreatment*	8	12
Fever >37°C	17	14
Pleural effusion	1	3

†: mean±SD; *: for 2–10 days with betalactam antibiotics in 19 cases and with ciprofloxacin in one case; the time interval elapsed between the last dose of the previous antibiotic and the enrolment was 24 h in one case and 48 h or more in all the others. AZ: azithromycin; CL: clarithromycin; M: male; F: female; COPD: chronic obstructive pulmonary disease.

furthermore, many had evidence of co-morbidity and/or absence of a responsible caregiver in a stable home situation.

Table 1 describes the patient population: there were no differences between the AZ and the CL groups. The three cases of liver disease were due to hepatitis B and C (two patients), and to unknown aetiology (one). A previous antibiotic had been administered unsuccessfully in 20 cases.

Results

Table 2 shows the results on defervescence, chest roentgenogram clearance, period of hospitalization and clinical and bacteriological outcome. In four cases, we observed isolates in the sputum during or at the end of the study. However, no signs of infection accompanied this result, so that we cannot conclude that a superinfection was present, but simply a colonization. *Alcaligenes faecalis*, very rarely pathogenic in the respiratory tract, was probably acquired in hospital, where it is less rare than in the community [17].

In one patient (male, 44 yrs of age, pretreated with amoxycillin for 3 days, with a 5 day history of fever before admission) the fever was still over 38°C after the 3 day course of azithromycin, but both symptoms and clinical signs were improving, and the fever had decreased from the initial 41°C; chest roentgenogram was only partially improved on day 5; the fever disappeared on day 6; he was cured and discharged on day 11. One patient needed a second course of azithromycin on days 14, 15 and 16, because chest roentgenogram resolution was still incomplete after 12 days. In nine patients, clarithromycin was given for more than 8 days, as judged necessary according to clinical signs or chest roentgenogram. In the entire group, clarithromycin was given for 10±2 days (range 8–15 days).

There were two failures in the CL group. One male, 55 yrs of age, pretreated at home with piperacillin with no result, had a left inferior lobe pneumonia, with wide pleural effusion. After 5 days of persistent fever, the therapy was changed to a combination of a cephalosporin plus an aminoglycoside. He had a slowly resolving pneumonia, and was cured. A serum sample taken on the fifth day of hospitalization showed anti-chlamydia antibodies (IgM 1:64; IgG 1:1024) suggesting, at least at the beginning, a clarithromycin resistant *C. pneumoniae* infection. The same titres were seen on the 12th day.

The other failure occurred in a 68 year old male, who was also randomized to clarithromycin after unsuccessful therapy with ceftriaxone. He had an undiagnosed small-cell lung cancer, and the pneumonia (right inferior lobe) was later cured with ciprofloxacin. Aetiology remained undetermined.

Side-effects were mild: one patient had a rash, probably related to clarithromycin; many patients (eight in the AZ group, nine in the CL group) had a transient rise of ALT and/or AST. No statistically significant differences were found between the two groups with regard to the mean rise of ALT or AST. In 12 patients (seven AZ group, five CL group) the therapy was started in spite of higher than normal basal AST or ALT (as may frequently happen in pneumonia); in most of these, we observed a fall to normal or near-normal values at the end of the follow-up.

Table 3 shows that a serological diagnosis could be reached in 18 patients, while sputum permitted a presumptive diagnosis in four patients. Five patients had a *L. pneumophila* pneumonia; all of these had a good outcome. In four of them spirometry was normal at the time of discharge, or within one month later; in the fifth patient, spirometry was not performed. Serology supported *C. pneumoniae* infection in four cases; in one of them, randomized to AZ, *Klebsiella pneumoniae* was cultured in the blood and urine, so that the patient probably had a double aetiology; on the basis of the result of blood culture, it was necessary to exclude him. However, by the time the result became available, fever,

Table 2. – Results on fever, chest roentgenogram, time of stay in hospital and clinical and bacteriological outcome

	AZ group n=20	CL group n=20
Defervescence		
Patients with fever n	17	14
Time of defervescence days	2.6±1.4	2.7±1.7
No defervescence n	0	2
Chest X-ray clearance days	8.7±2.7	9.2±3.9
Mean stay in hospital days	12.7±5.7	14.3±7.6
Clinical outcome		
Failures	0	2
Cured	20	17
Not evaluable		1
Bacteriological outcome n		
Reinfections	0	0
Superinfection	0	0
Colonization	2*	2**

Results are expressed as n or mean±SD as shown. *: *H. parainfluenzae* in both (10^5 and 10^8 CFU, respectively); **: one *H. parainfluenzae* (10^8 CFU), one *A. faecalis* (10^7 CFU). AZ: azithromycin; CL: clarithromycin; CFU: colony forming units.

Table 3. – Aetiology derived from serology and sputum

	AZ group n=20 (8)	CL group n=20 (12)
Serological diagnosis		
Mycoplasma pneumoniae	4 (3)	5 (5)
Legionella pneumophila	4 (2)	1
Chlamydia pneumoniae		3 (2)
C. pneumoniae + *K. pneumoniae*	1*	
Presumptive diagnosis on sputum		
Haemophilus influenzae 10^8 CFU		1
Haemophilus parainfluenzae 10^8 CFU	1 (1)	1
Pneumococcus Sp. (Gram stain)	1	
No aetiology found	9 (2)	9 (5)

*: *Klebsiella pneumoniae* isolated in blood and urine cultures. The number of pretreated patients is shown in parenthesis. For abbreviations see legend to table 2.

cough and dyspnoea had already disappeared, and the 3 day course of azithromycin had already been completed.

Discussion

Our results show that a 3 day course of azithromycin may be a good approach for the therapy of moderately severe CAP. This is possible due to the unusual pharmacokinetics of azithromycin, described in the introduction [2–4]. Azithromycin does not cure pneumonia in 3 days; indeed we have observed the same time of defervescence, chest roentgenogram clearance, and hospitalization as with clarithromycin, or other antibiotics, as described in many reports. But azithromycin ensures equally good results with a 3 day course only, thereby improving the compliance of the patients.

An important limitation to our results is the small number of patients studied. The recent European Guidelines for the Clinical Evaluation of Anti-infective Drug Products, state that the estimation of sample sizes must allow a power of at least 80%, and the test level desired should usually be 5% [18]. Accordingly, all clinical studies should cover at least 80 available patients in each treatment arm. Neither our work, nor other studies so far published on CAP therapy with azithromycin [10–14] have reached this level. Thus, our results cannot exclude a type II error, and should be regarded as a pilot study that may open the door to larger trials. The demonstration of any difference in therapeutic efficacy between the two drugs, which is extremely difficult with only 40 patients, was not the aim of our work and needs to be studied further. Nevertheless, in our experience, the two antibiotics appear of equal efficacy, in agreement with the results from a larger trial on 510 patients with LRTI (including eight with pneumonia) [8].

Another important limitation is that, according to our exclusion criteria, we have studied a selected population of patients. The epidemiology of our institute, where over 100 CAP patients are examined every year, shows that we have the same 10% mortality as described in the literature. However, in this study, there were no mortalities. We enrolled 35% of the screened CAP patients. They were not mild cases, because most mild patients are not referred, or not admitted to hospital; but they had low to moderately severe CAP, according to our exclusion criteria. Thus, the usefulness of azithromycin in more severe cases has yet to be demonstrated.

Finally, the study should be seen in the light of the Italian situation: the wide and unusual use of cephalosporins, that had failed in 50% of our CAPs, had probably selected a population where Legionella, Chlamydia or Mycoplasma are most likely to occur. For this reason, and also probably because all our patients had antibody determined after 30 days, we found a high percentage of cases of *L. pneumophila* (12.5%) and of *M. pneumoniae* (22.5%). However, our percentages are still at the upper limit of the range described in CAP literature, where Legionella ranges 1–27%, with a most consistently reported figure of about 6% [19], and *M. pneumoniae* ranges 11–17% in most cases [20].

S. pneumoniae appeared to be the aetiological agent in one case only. Again, the wide use of cephalosporins together with the rarity of penicillin resistant strains of *S. pneumoniae* in Italy, may explain this result. Moreover, whilst bacteria present in concentrations exceeding 10^6 organisms per ml of the original specimen have been considered significant [21], in the light of current criticism [22], we used more restrictive criteria (sole isolate, $>10^7$ CFU) for considering a sputum isolate as pathogenic [16]. As a result, we reached a presumptive diagnosis on sputum cultures in three patients only (one with *H. influenzae* and two with *H. parainfluenzae*). *H. parainfluenzae* is emerging as an important pathogen of the respiratory tract [23], even if the question of real pathogenicity is still open [24]. Concerning *S. pneumoniae*, it is well-known that it is a delicate organism [25], and that the number of cases of pneumococcal infection is proportional to the number of tests performed [26]. Some of the 18 patients of table 3, in which no aetiology was found for CAP, could perhaps have been ascribed to *S. pneumoniae*, if the research of pneumococcal antigen had been available for our study.

In all five patients with legionellosis, the diagnosis became known when the patient was already cured, and in some cases discharged. Treatment of legionnaires' disease with a macrolide, erythromycin in most cases, is usually suggested for 21 days [27], and we would probably not have given azithromycin for only 3 days if we had known the aetiology. However, all five patients were cured, and no fibrosis was seen on chest roentgenogram or spirometry at the end of the study, in spite of the frequency (up to 25%) of this risk [28]. Also, the eight patients with legionnaires' disease, described by MYBURGH *et al.* [14] had a good outcome with the same therapy.

The diagnosis of *C. pneumoniae* infection, using the TWAR antigen, has recently been criticized [29]. However, our results are in line with most published data: 10% of our patients had *C. pneumoniae* pneumonia, a rate in agreement with the 6–33% given in the literature [22]. One patient with Chlamydial infection failed to respond to clarithromycin, in spite of a usually very low minimal concentration of clarithromycin needed to produce 90% inhibition (MIC_{90}) *versus C. pneumoniae* [30]. However, BATES [30] described two failures in six patients with chlamydial CAP treated with clarithromycin.

The outcome of the patient with *K. pneumoniae* sepsis was surprisingly good. Azithromycin is not very active against *K. pneumoniae*, with MIC_{90} in the range 8–64 $\mu g \cdot ml^{-1}$ [31], and the good result could be due, at least in part, to the postantibiotic effect of azithromycin on *K. pneumoniae* [32].

In conclusion, azithromycin appears to be a promising approach to treatment of CAP. We observed a good activity in the moderately severe patients, but larger double-blind trials are needed. The usefulness in elderly patients and more severe cases has yet to be demonstrated.

References

1. Niederman MS, Bass JB, Campbell DG, *et al.* Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Official Statement of the American Thoracic Society. *Am Rev Respir Dis* 1993; 148: 1418–1426.
2. Baldwin D, Wise R, Andrews J, Ashby J, Honeybourne D. Azithromycin concentrations at the sites of pulmonary infections. *Eur Respir J* 1990; 3: 886–890.
3. Schentag J, Ballow C. Tissue-directed pharmacokinetics. *Am J Med* 1991; 91 (Suppl. 3A): 5s–11s.
4. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. *J Antimicrob Chemother* 1990; 25 (Suppl. A): 73–82.
5. Daniel R and European Azithromycin Study Group. Simplified treatment of acute lower respiratory tract infection with azithromycin: a comparison with erythromycin and amoxycillin. *J Intern Med Res* 1991; 19: 373–383.
6. Lode H, Schaberg T. Azithromycin in lower respiratory tract infections. *Scand J Infect Dis* 1992; 83: 26–33.
7. Maertens J, Barneveld P, Asin H, Ligtvoet E, Visser M, Hoepelman M. A double-blind, randomized study comparing the efficacy and safety of a short (3 day) course of azithromycin and a 5 day course of amoxycillin in acute exacerbations of chronic bronchitis. *Antimicrob Agents Chemother* 1992; 36: 1456–1459.
8. Bradbury F. Comparison of azithromycin *versus* clarithromycin in the treatment of patients with lower respiratory tract infection. *J Antimicrob Chemother* 1993; 31 (Suppl. E): 153–162.
9. Hoepelman A, Sips A, van Helmond J, *et al.* A single-blind comparison of three day azithromycin and ten day co-amoxiclav treatment of acute lower respiratory tract infections. *J Antimicrob Chemother* 1993; 31 (Suppl. E): 147–152.
10. APRIM (Association pour la Promotion et la Recherche en Information Médicale), Brion J, Sedallian A, Le Noc P, Briffod J, Micoud M. Azithromycin *versus* josamycin: traitement de quatre-vingt-neuf pneumopathies aigues. *Path Biol* 1990; 38: 521–525.
11. Kinasewitz G, Wood R. Azithromycin *versus* cefaclor treatment of acute bacterial pneumonia. *Eur J Clin Microb Infect Dis* 1991; 10: 872–877.
12. Schonwald S, Skerk V, Petricevic I, Car V, Majerus-Misic L, Gunjaca M. Comparison of three day and five day courses of azithromycin in the treatment of atypical pneumonia. *Eur J Clin Microbiol Infect Dis* 1991; 10: 877–880.
13. Uzun O, Hayran M, Akova M, Gur D, Akalin H. Efficacy of a three day course of azithromycin in the treatment of community-acquired pneumococcal pneumonia: preliminary report. *J Chemother* 1994; 6: 53–57.
14. Myburgh J, Nagel G, Petschel E. The efficacy and tolerance of a three day course of azithromycin in the treatment of community-acquired pneumonia. *J Antimicrob Chemother* 1993; 31 (Suppl. E): 163–169.
15. Blasi F, Legnani D, Lombardo V, *et al. Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Respir J* 1993; 6: 19–22.
16. Mandler F, Peona V. Batteriologia quantitativa nelle infezioni delle vie respiratorie. *La rivista del medico* 1993; 13: 1–3.
17. Rubin S, Granato P, Wasilauskas B. Alcaligenes. *In*: Lennette E, Ballows A, Hausler W, Shadomy H, eds. Manual of Clinical Microbiology. 4th edn. Washington, Am Soc Microb, 1985; pp. 335–338.
18. Beam T, Gilbert D, Kunin C. General Guidelines for the Clinical Evaluation of Anti-Infective Drugs. *In*: Beam T, Gilbert D, Kunin C, eds. European Guidelines for the Clinical Evaluation of Anti-Infective Drug Products. European Society of Microbiology and Infectious Diseases 1993; pp. 1–31
19. Roig J, Domingo C, Morera J. Legionnaires' disease. *Chest* 1994; 105: 1817–1825.
20. Tuazon C, Murray H. Atypical pneumonias. *In*: Pennington J, ed. Respiratory Infections: Diagnosis and Management. New York, Raven Press, 1994; pp. 407–433.
21. Bartlett J, Finegold S. Bacteriology of expectorated sputum with quantitative culture and wash technique compared to transtracheal aspirates. *Am Rev Respir Dis* 1978; 117: 1019–1027.
22. Almirall J, Moratò I, Riera F, *et al.* Incidence of community-acquired pneumonia and *Chlamydia pneumoniae* infection: a prospective multicentre study. *Eur Respir J* 1993; 6: 14–18.
23. Cavan D, Smith E, Ayres J. *Haemophilus parainfluenzae* as a respiratory pathogen. *Thorax* 1990; 45: 821.
24. Foweraker J, Cooke N, Hawkey P. Ecology of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in sputum and saliva and effects of antibiotics on their distribution in patients with lower respiratory tract infections. *Antimicrob Agents Chemother* 1993; 37: 804–809.
25. Woodhead M. Management of pneumonia. *Respir Med* 1992; 86: 459–469.
26. Boersma W, Lowenberg A, Holloway Y, Kutschrutter H, Snijder J, Koeter G. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community-acquired pneumonia. *Thorax* 1991; 46: 902–906.
27. Edelstein P, Meyer R. *Legionella pneumophila*. *In*: Pennington J, ed. Respiratory Infections: Diagnosis and Treatment. New York, Raven Press, 1989; pp. 381–402.
28. Chastre J, Raghu G, Soler P, Brun P, Basset F, Gibert C. Pulmonary fibrosis following pneumonia due to acute Legionnaires' disease. *Chest* 1987; 91: 57–62.
29. Kern D, Neill M, Schachter J. A seroepidemiologic study of *Chlamydia pneumoniae* in Rhode Island. *Chest* 1993; 104: 208–213.
30. Bates J. *Chlamydia pneumoniae* infections. *Medicine* 1991; 8 (Suppl. A): 18–22.
31. Neu H, Chin N, Saha A, Labthavikul P. Comparitive *in vitro* activity of the new oral macrolide azithromycin. *Eur J Clin Microbiol Infect Dis* 1988; 7: 541–544.
32. Debbia E, Molinari G, Paglia P, Schito G. Postantibiotic effect of azithromycin on respiratory tract pathogens. *Drug Exptl Clin Res* 1990; 16: 615–619.