Community-Acquired Pneumonia*

Etiology, Epidemiology, and Outcome at a Teaching Hospital in Argentina

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Objective: **To survey the etiology and epidemiology of community-acquired pneumonia (CAP) in relation to age, comorbidity, and severity and to investigate prognostic factors.**
Design: **Prospective epidemiologic study, single center.**
Setting: **University hospital at Buenos Aires, Argentina.**
Patients: **Outpatients and inpatients fulfilling clinical criteria of CAP.**
Interventions: **Systematic laboratory evaluation for determining the etiology, and clinical evaluation stratifying patients into mild, moderate, and severe CAP (groups 1 to 3), a clinical rule used for hospitalization.**
Results: **During a 12-month period, 343 patients (mean age, 64.4 years; range, 18 to 102 years) were evaluated. We found 167 microorganisms in 144 cases (yield, 42%). *Streptococcus pneumoniae*, the most common pathogen, was isolated in 35 cases (24%). *Mycoplasma pneumoniae*, present in 19 (13%), was second in frequency in group 1; *Haemophilus influenzae*, present in 17 cases (12%), was second in group 2; and *Chlamydia pneumoniae*, present in 12 cases (8%), was second in group 3. Etiology could not be determined on the basis of clinical presentation; identifying the etiology had no impact on mortality. Some findings were associated with specific causative organisms and outcome. A significantly lower number of nonsurvivors received adequate therapy (50% vs 77%).**
Conclusions: **Age, comorbidities, alcohol abuse, and smoking were related with distinct etiologies. Pa_{O_2} to fraction of inspired oxygen ratio < 250, aerobic Gram-negative pathogen, chronic renal failure, Glasgow score < 15, malignant neoplasm, and aspirative pneumonia were associated with mortality by multivariate analysis. Local microbiologic data could be of help in tailoring therapeutic guidelines to the microbiologic reality at different settings. The stratification schema and the clinical rule used for hospitalization were useful.** ***(CHEST 2000; 118:1344–1354)***

Key words: Argentina; comorbidities; community-acquired pneumonia; epidemiology; etiology; guidelines; mortality; outcome; South America; therapy

Abbreviations: CAP = community-acquired pneumonia; CXR = chest radiograph; F_{IO_2} = fraction of inspired oxygen; IFA = immunofluorescent assay; MIC = minimum inhibitory concentration; PMN = polymorphonuclear neutrophil; TB = tuberculosis

Community-acquired pneumonia (CAP) remains a leading cause of death in both developing and developed countries.[1,2] Estimates of annual incidence vary between 1% and 12%.[3–6] Microbiological tests are not performed routinely in clinical practice; indeed, there is little evidence that these tests have any practical impact. Most studies about etiology show that *Streptococcus pneumoniae* remains the primary cause of CAP. The incidence of other microbial pathogens varies both seasonally and geographically.[7–12] *Legionella pneumophila*,[8] Klebsiella organisms,[10] and *Haemophilus influenzae*[9] were reported as the next most common cause in several settings. Viruses and *Chlamydia pneumoniae* have been reported more frequently than *S pneumoniae*, especially in series focusing on outpatients.[11,13]

Currently, the practice is to prescribe antibiotics empirically. Several clinical practice guidelines have stratified patients by age, comorbidities, and severity of illness to prescribe the best empirical regimen.[1,2,7]

We conducted a prospective study to survey the

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etiology and epidemiology of CAP, to confirm the relationships among age, comorbidity, severity, and microbiology, and to investigate prognostic factors of CAP at a teaching hospital in Buenos Aires, Argentina.

Materials and Methods

Between October 1, 1997, and September 30, 1998, we prospectively studied all adults > 17 years of age who came to the hospital with a clinical diagnosis of CAP. Our institution is a public hospital of the University of Buenos Aires that serves as both a referral center and a primary-care hospital. The population studied was drawn from the Social Security System and included a predominantly elderly and severely ill population.

Patients were recruited in the emergency department, but outpatients with CAP seen in the Pulmonary Division clinic were also included. Occasionally, patients admitted with another presumptive illness in whom a diagnosis of CAP was made during the 24 h after hospitalization were also included.

All patients fulfilling the criteria of CAP described by Fang et al[14] were eligible for the study. Criteria included (1) > 17 years of age with a putative diagnosis of pneumonia, (2) a new infiltrate observed on chest radiograph (CXR), and (3) acutely presenting clinical findings of either one major criteria (axillary temperature > 37.8°C, cough, or expectoration) or at least two minor criteria (pleuritic chest pain, dyspnea, leukocytosis [WBC count, > 12,000/mL] altered mental status, or lung consolidation by clinical examination). Exclusion criteria included patients transferred from another hospital or hospitalized within the last 2 weeks, lung cancer postobstructive pneumonia, or immunocompromise (≥ 40 mg/d of methylprednisolone or equivalent dose of other steroid; AIDS or HIV positive with a CD4+ count < 200; granulocytopenia < 500/mm^3). Also, patients with clinical or CXR evidence indisputably suggestive of tuberculosis (TB) were excluded. Nonetheless, patients in whom other etiologies besides TB were considered and those diagnosed as HIV positive during their hospitalization were included. On entry into the study, a clinical research form was filled out. Other variables recorded were age, sex, place of residence, travels, symptoms, criteria for pneumonia, prior antimicrobial therapy for any indication, past medical history, alcohol and smoking history, contact with people with TB, contact with animals and pets, and admission for CAP during the past year. Presenting CXR pattern and extension (number of lobes involved, bilaterality) and physical examination (respiratory rate; heart rate; BP; axillary or rectal temperature; and respiratory signs such as consolidation, rales, reduced breath sounds, rhonchi, or evidence of pleuritis or effusion) were recorded. Routine tests obtained initially included CXR, and microbiological evaluation. Most of the outpatients and all those hospitalized had a CBC count with differential, serum electrolytes, BUN, blood glucose, and urine examination. Blood gas analysis (Pa_{O_2}, Pa_{CO_2}, pH, and oxygen saturation) and measurements of serum aspartate aminotransferase, alanine aminotransferase, bilirubin, and alkaline phosphatase were performed in a large number of patients, especially in those who were hospitalized. CXRs were classified according to their patterns of airspace pneumonia, interstitial infiltrate, bronchopneumonia, pleural effusion, cavitation, and atelectasis.

A clinical rule was used in deciding hospitalization (Table 1).[1] At entry, cases were classified as either "typical" or "atypical" pneumonia on the basis of the physician's initial clinical impression. ICU admission and therapy for inpatients were decided by the attending physician, but clinical criteria of severe CAP (Table 1) and the adequacy of prescribed antimicrobial agents to the recommendations of a guideline for empiric therapy (Table 2) were recorded.

Table 1—*Hospitalization Criteria and Criteria of Severity According to the Guideline

Clinical Rule for Admission (if any of the following 9 criteria is present)
1. Association (2 or more) of the following: age > 65 yr, chronic lung disease (including severe asthma), chronic heart disease (excluding hypertension), chronic renal failure, chronic hepatic disease, alcoholism, malignancy, diabetes, prior hospitalization for pneumonia during the last year
2. Tachypnea > 30/min
3. Arterial hypotension (systolic < 90 mm Hg, diastolic < 60 mm Hg)
4. Severe alteration in blood analyses: Pa_{O_2} < 60 mm Hg; Pa_{CO_2} > 50 mm Hg with acidosis; leukopenia < 4,000 leukocytes/mm^3; BUN < 25 mg/100 mL; hematocrit < 30%.
5. Altered consciousness.
6. Severe swallowing alteration suggesting gross aspiration
7. Suppurative complications (pericarditis, arthritis, meningitis)
8. Radiographic severity criteria (compromise of more than one lobe, cavitation, increase in size of infiltrate > 50% compared with prior radiograph)
9. Noncompliant patient or social reasons

Severe CAP ICU Admission (if any of the following 6 criteria is present)
1. Sustained hypotension (requiring vasopressors > 4 h and/or hemodynamic monitoring); shock; sepsis; or SIRS
2. Multiorgan (more than one organ, nonsevere) failure (respiratory, renal, neurologic, cardiac, hepatic)
3. Severe tachypnea (> 35/min), diaphragmatic fatigue (abdominal paradox) or use of accessory muscles for breathing
4. Acute severe hypoxemia (Pa_{O_2}/F_{IO_2} < 250) or acute hypercapnia with acidosis (Pa_{CO_2} > 50 mm Hg) [in chronic respiratory failure, worsening hypoxemia, or hypercapnia] and/or need of mechanical ventilation
5. Extrapulmonary infection (meningitis, pericarditis, etc.) if severe
6. Severe acute decompensation of preexisting diseases and/or organ failure (COPD, diabetes, cardiac failure, hepatic failure, renal failure requiring dialysis)

*SIRS = systemic inflammatory response syndrome.

All charts and CXRs were reviewed by four different investigators (C.M.L., A.J.V., F.J.N., and A.D.F.) and defined as "no pneumonia" if review of CXR did not reveal a new infiltrate or if the infiltrates were noninfectious (malignancy, pulmonary edema, atelectasis). Prior antibiotic use was defined as any antimicrobial agent used at the time of inclusion or for any period of time during the 10 days before the date of entry. The Joint Committee on Clinical Investigation and Ethics of the hospital approved the study.

Guideline

Patients were stratified according to their age, presence of comorbidities, and severity of their illness into the following three groups: group 1, mild pneumonia; group 2, moderate pneumonia; and group 3, severe pneumonia (Table 2). A clinical rule for hospitalization was formulated to help physicians to decide whether to admit the patient to either the hospital or the ICU (Table 1). Each group had some target microorganisms and recommended therapy. All group 3 patients had at least one criteria of severity.

Table 2—*Stratification and Guideline for Empiric Therapy

Group 1 (healthy, < 65 yr)
Target microorganisms: *S pneumoniae*, *M pneumoniae*
Initial empiric therapy†: Macrolide
Alternative: Amoxicillin 3 g/d if age > 40–50 yr
Outpatients or inpatients‡
Group 2 (with comorbidity or ≥ 65 yr)
Target microorganisms: *S pneumoniae*, *H influenzae*, *S aureus*, aerobic Gram-negative organisms, atypical microorganisms
Initial empiric therapy†: β-lactam + β-lactamase inhibitor or ceftriaxone/cefotaxime§ ± macrolide
Outpatients or inpatients‡
Group 3 (severe CAP in the ICU)
Target microorganisms: *S pneumoniae*, *H influenzae*, *S aureus*, aerobic Gram-negative organisms, *P aeruginosa*, atypical organisms
Recommended empiric therapy: Macrolide IV + one of the following
Carbapenem
Ciprofloxacin + ceftriaxone/cefotaxime§
Ceftazidime + vancomycin§

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†For outpatients, use oral or intramuscular route. For inpatients, prefer IV administration.

‡According to the admission criteria displayed in Table 1.

§If there is suspicion of aspiration, use β-lactam plus β-lactamase inhibitor or add clindamycin or an imidazole (metronidazole/ornidazole).

Etiologic Diagnosis Workup

On entry, microbiological specimens were obtained. The full evaluation included sputum examination, nasopharyngeal aspiration, two sets of blood cultures and culture of any other respiratory or nonrespiratory specimen when available, and urinary antigen detection for Legionella organisms. Blood was drawn for performing serologic tests at the time of inclusion and repeated after 30 to 40 days.

Microbiological Processing

Cytologic screening was performed looking for the presence of < 10 epithelial cells and > 25 polymorphonuclear neutrophils (PMNs) per low-power field. Sputum specimens were qualified as "high quality" if both PMN and epithelial cell criteria were present, "intermediate quality" if only the PMN criterion was present, and "low quality" if the PMN criterion was not met. Gram's, Ziehl-Neelsen, Kinyoun carbolfuchsin, and Giemsa stains were performed. Only high-quality and intermediate-quality specimens were submitted for bacterial cultures. Standard bacterial cultures were inoculated onto blood, chocolate, and MacConkey agar. All respiratory specimens were submitted for other types of cultures. A mycobacteria detection system (Bactec 460TB; Becton Dickinson; Franklin Lakes, NJ) and Löwenstein-Jensen slants were used for mycobacterial culture. Culture for Legionella spp was performed using trypticase soy broth agar with 5% sheep blood, chocolate agar, buffered charcoal yeast extract differential agar, and buffered charcoal yeast extract selective agar. Sputum culture for fungus was performed on Mycosal and Sabouraud dextrose agar. Blood cultures were performed using an automated system (Bact-Alert; Organon Teknika, Durham, NC).

Serologic Studies

Acute and convalescent serum samples were collected. Indirect immunofluorescent assay (IFA) for detection of human IgG antibodies against influenza virus types A and B, parainfluenza virus types 1 through 3, respiratory syncytial virus, adenovirus (all from Bion Enterprises; Des Plaines, IL), *L pneumophila* serotypes 1 through 6 (Scimedx Corp; Denville, NJ), and *Coxiella burnetii* (MRL Diagnostics; Cypress, CA) were tested. IgG and IgM antibodies were tested for *Mycoplasma pneumoniae* (Bion Enterprises). IgG antibodies for *C pneumoniae* and *Chlamydia psittaci* were tested by micro-IFA (MRL Diagnostics). To determine the IgG antibody titers, the serum screening dilution was 1/16 in phosphate buffer for all samples. For *M pneumoniae*, the screening dilution was 1/10 using absorbent for IgM.

Antigen Detection

Detection of respiratory viruses (influenza A and B; parainfluenza 1, 2, and 3; respiratory syncytial virus, and adenovirus) in nasopharyngeal aspirate was performed using monoclonal antibody and anti-mouse IgG–fluorescein isothiocyanate conjugate, (Chemicon International; Temecula, CA). Cryptococcal antigen was studied on the serum obtained during the first visit by latex agglutination (IMMY; Immuno Mycologics Inc; Norman, OK). False-positive results were ruled out by checking the rheumatoid factor. Determination of Legionella antigen in urine by enzyme-linked immunosorbent assay was performed on a sample of urine retrieved at the time of the first visit (Biotest AG; Dreieich, Germany).

Other Techniques

Fiberoptic bronchoscopy with BAL was performed in seven patients admitted to the ICU during the first 24 h after the clinical diagnosis of CAP. Bronchoscopy and BAL were performed and processed as described elsewhere.[15] Estimates of the number of bacteria originally in the fluid were made by colony counts and expressed as colony-forming units per milliliter. Other microbiologic techniques for staining and culture were also applied for BAL fluid study.

Criteria for Determination of Microbial Etiology

The etiology of CAP was classified as (1) definitive, (2) probable, (3) aspiration, and (4) unknown.

Criteria for definitive diagnosis were the following: (1) blood culture or pleural fluid yielding at least one bacterial pathogen (excluding *Staphylococcus epidermidis*), *Mycobacterium tuberculosis*, or fungi; (2) sputum or BAL revealing *Pneumocystis carinii, Histoplasma capsulatum, Paracoccidioides brasiliensis, Coccidioides immitis, Cryptococcus neoformans, M tuberculosis, Mycobacterium kansasii*, or *Mycobacterium avium-intracellulare*; (3) BAL culture showing ≥ 10^4 cfu/mL of at least one bacterial species; (4) open-lung biopsy (cultures, stains, histopathology) yielding a pathogen; (5) fourfold rise in *M pneumoniae* IFA test; (6) isolation of Legionella spp from respiratory tract samples, positive urinary *L pneumophila* antigen (serogroup 1), or fourfold rise in IFA *L pneumophila* antibody titer (serogroups 1 through 6); (7) antigen detection in nasopharyngeal aspirate or fourfold rise in IFA antibody titer for respiratory viruses; (8) fourfold rise in IFA antibody titer to *C burnetii*; and (9) fourfold rise in micro-IFA antibody titer for *C pneumoniae* or *C psittaci* or single acute titer ≥ 1/512 for *C pneumoniae*.

Criteria for probable diagnosis were the following: (1) two blood cultures positive for *S epidermidis*, obtained at separate

sites and times, as set out by the Centers for Disease Control and Prevention[16]; (2) growth of a bacterial pathogen on an initial sputum culture obtained within 24 h of admission; (3) bacterium isolated in multiple sputum cultures within 3 days of admission; (4) in the case of multiple potential bacterial pathogens growing in equal magnitude, designation of predominant organism, if observed, seen on Gram's stain that was compatible with one of the isolates, or multiple pathogens if Gram's stain revealed the presence of multiple organisms consistent with those isolated in culture; (5) single IFA antibody titer $\geq$ 1:256 to *L pneumophila*; (6) single IFA antibody titer $\geq$ 1:64 for *M pneumoniae*; (7) single micro-IFA antibody titer $\geq$ 1:32 for *C psittaci*; or (8) the presence of a latex agglutination titer for *C neoformans* $>$ 1/10.

Criteria for a diagnosis of aspiration pneumonia were no microbiologic diagnosis in a patient with an associated condition that predisposed to aspiration (swallowing defects or alteration of consciousness), combined with a new infiltrate in a dependent pulmonary segment.[17]

Criteria for unknown etiology were no specific microbiologic diagnosis and failure to satisfy criteria for aspiration pneumonia.

Therapy and Follow-up

Outpatients were first seen by the research team, the members of which were very familiar with the guideline and the antibiotics prescribed according to it (Table 2). In patients who were admitted to the hospital, their attending physician, in most cases, decided therapy; attending physicians were not always familiar with the guideline. For those reasons, the guideline was not always followed in the hospitalized patients. Adequacy of therapy was evaluated in the following two ways: (1) in all patients according to the adherence to the therapeutic guideline, and (2) in patients with specific etiology, when the prescribed antimicrobials were active against all the isolated pathogens (*ie*, β-lactam for susceptible *S pneumoniae*, macrolide for atypicals) or the pathogen has no specific therapy (*ie*, a virus).

Follow-up was extended for $\geq$ 30 days. Visits for hospitalized patients were conducted daily until their discharge. On the patient's last visit, which occurred between days 30 and 45, a physical examination, a CXR, and a blood sample for the second serologic titer were obtained. Patients who did not return for the last visit were contacted by telephone. Fatal outcome during the 30 days after the date of entry was recorded.

Data Processing and Analysis

Data were reviewed and then entered into a database and subjected to standard verification procedures. Results are expressed as mean ± SD. Data were analyzed using commercially available software packages (Primers for Biostatistics; McGraw Hill; New York, NY; and SPSS; SPSS Inc; Chicago, IL). χ^2 or Fisher's Exact Tests were used for comparisons. Findings potentially related with death were studied by a univariate approach using the χ^2 test. Thereafter, a stepwise forward multiple logistic regression model was applied to the variables found to be significantly associated with death ($p < 0.05$ comparing survivors vs nonsurvivors). The relationship between comorbidities and the five most common etiologies, as well as grouped pathogens (Gram-negatives: enteric aerobic Gram-negative bacilli, *Pseudomonas aeruginosa*, and Acinetobacter spp; and respiratory viruses: influenza, adenovirus, parainfluenza, and measles), was studied by multiple regression. Multiple regression permitted an estimate of the odds ratio of dying or having different etiologies and a calculation of the 95% confidence interval. Probability values were two-tailed. Significance level was set at 5%.

Results

Patient Characteristics

Four hundred eight suspected cases of CAP were enrolled in the study. Sixty-two were excluded because CXR failed to show a new pulmonary infiltrate (8 cases), inclusion clinical criteria were not fulfilled (20 cases), or alternative diagnoses were made (34 cases). Thus, 346 cases (161 men [47%]) constituted the final study group. Three patients were enrolled on two occasions each because of recurrent pneumonia. All 346 cases had a new infiltrate on CXR and at least one major or two minor criteria. A significantly higher number of cases were enrolled in winter (112 patients; $p < 0.05$ by χ^2). Median age was 70 years (mean, 64.4 years; range, 18 to 102 years). There was a positive correlation between the age and the incidence of pneumonia starting from 40 years of age both for the overall group and for inpatients (Fig 1). Forty-eight cases were admitted from nursing homes or convalescent care facilities. Most patients experienced comorbidities including pulmonary (severe asthma, COPD, or bronchiectasis), cardiovascular (congestive heart failure, ischemic cardiopathy, valvular disease, or cardiomyopathy), and other chronic disorders, such as renal failure, hepatic diseases, or diabetes (Table 3). One hundred thirty-nine patients (40%) presented with a smoking history ($>$ 4 pack-years); inpatients were heavier smokers, but most of them had quit by the time they had pneumonia, whereas most of the outpatients were still smoking. The relationships among etiology, age, smoking habits, and comorbidities were evaluated (Table 3).

Etiology

Blood cultures were collected in all 343 patients, yielding at least one pathogen in 34 cases (10%). Sputum was obtained in the 176 patients who could expectorate (51%); the yield of sputum specimen bacteriologic examination was 33% for the isolation of at least one pathogen.

The first serum sample was obtained in all 343 patients. A convalescent sample could not be retrieved in 47% of cases because of death (50 patients), lack of returning on time (59 patients), or loss to follow-up (52 patients). Nasopharyngeal aspirates were obtained in 278 patients; the quality of the aspirate was inadequate for processing because of the scanty amount of cells in 42 samples. Respiratory viruses were detected by monoclonal antibody determination in 5% of cases. In four of nine cases, the same pathogen was diagnosed both in serum and in the nasopharyngeal aspirate.

Overall, 167 microorganisms were found to be the pathogen in 144 cases. Etiology was definitive for 88

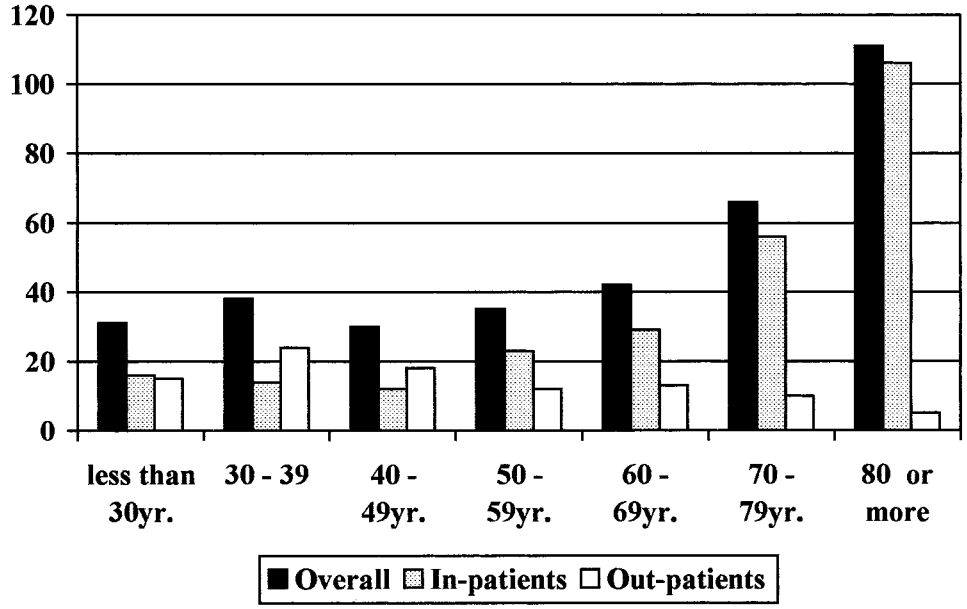

FIGURE 1. Incidence of CAP according to differences in age. Patients are grouped by age in 10-year periods for those ≥ 30 years of age. Frequency was higher as age increased from ≥ 40 years for all patients and for those managed as inpatients, but not for those managed as outpatients.

pathogens and probable for 79. Aspiration pneumonia was present in 35 cases. No pathogen could be isolated in 201 cases (Table 4). The incidence of the different microorganisms varied seasonally, with predominance for *C pneumoniae* and *M pneumoniae* during summer and fall and for *S pneumoniae* and *H influenzae* during winter and spring months.

S pneumoniae accounted for 24% of cases in which

TABLE 3—*Comorbidities, Cigarette Smoking, Alcohol Abuse, and Age at Time of Entry, in Relation to Etiology of CAP**

Comorbidity	Total (n = 346)	Inpatients (groups 2–3; n = 259)	Outpatients: Group 2 (n = 33)	Outpatients: Group 1 (n = 54)	Multivariate Analysis (Stepwise Logistic Regression): Pathogens Associated With Comorbidities	p Value	OR	CI	Mortality (%)
Respiratory	100	87	13	—	*P aeruginosa*	0.0129	7.78	1.53–31.52	14/79 (18)
					Gram-negatives†	0.0088	3.22	1.28–8.09	
					M (Branhamella) catarrhalis	0.0229	13.23	1.41–123.27	
Cardiovascular	98	90	8	—					17/80 (21)
Neurological	31	30	1	—	Aspirative pneumonia	< 0.0001	8.72	3.70–20.75	7/19 (37)
Diabetes	26	24	2	—	*M tuberculosis*	0.0148	12.68	1.65–97.36	4/20 (25)
Malignant neoplasm	21	19	2	—					8/17 (47)
Renal	18	18	0	—					7/14 (50)
Alcohol abuse	12	11	1	—	*M tuberculosis*	0.0302	8.37	1.22–54.66	4/10 (40)
Hepatic	10	9	1	—	*S pneumoniae*	0.0495	4.07	1.12–19.51	1/9 (11)
Age ≥ 65 yr	198	183	15		Aspirative pneumonia	0.0028	6.53	1.21–22.53	40/152 (26)
Age < 65 yr	148	130	18		*M pneumoniae*	0.0451	2.62	0.85–8.22	10/128 (8)
					H influenzae	0.0082	4.66	1.50–14.54	
					C pneumoniae	0.0080	2.81	1.30–6.02	
Current tobacco use	50	29	9	12	*M tuberculosis*	0.0096	11.4	1.80–71.69	3/42 (9)
Tobacco > 4 pack-year	136	103	17	16					17/109 (16)

*Values given as No. of patients, unless otherwise indicated.
†Including enteric aerobic Gram-negative bacilli, *P aeruginosa*, and *Acinetobacter* sp.
OR = odds ratio; CI = confidence interval.

Table 4—*Etiology of CAP**

Pathogen	Definite	Probable	Total (n = 346)	Groups: 1, mild (n = 54)	Groups: 2, moderate (n = 253)	Groups: 3, severe (n = 39)
Streptococcus pneumoniae	10	25	**35**	**7**	**22**	**6**
Haemophilus influenzae	1	16	**17**	1	**15**	1
Pseudomonas aeruginosa	0	8	**8**	1	6	1
Staphylococcus aureus	2	4	**6**	1	3	**2**
Moraxella (Branhamella) catarrhalis	0	5	**5**	0	4	1
Staphylococcus epidermidis	0	5	**5**	0	5	0
Klebsiella pneumoniae	3	1	**4**	0	3	1
Enterobacter cloacae	1	2	**3**	0	3	0
Streptococcus spp	2	0	**2**	0	2	0
Streptococcus viridans	1	1	**2**	0	2	0
Proteus mirabilis	1	1	**2**	0	2	0
Acinetobacter spp	2	0	**2**	0	2	0
Escherichia coli	1	0	**1**	0	1	0
Proteus vulgaris	1	1	**2**	0	2	0
Haemophilus parainfluenzae	1	0	**1**	0	0	1
Campylobacter fetus	1	0	**1**	0	1	0
Salmonella spp	2	0	**0**	0	2	0
Serratia marcescens	0	1	**1**	0	1	0
Mycoplasma pneumoniae	19	0	**19**	**4**	**13**	**2**
Chlamydia pneumoniae	12	0	**12**	**2**	**7**	**3**
Legionella pneumophila	2	2	**4**	0	2	**2**
Chlamydia psittaci	0	1	**1**	0	1	0
Coxiella burnetii	1	0	**1**	1	0	0
Mycobacterium tuberculosis	7	0	**7**	0	**7**	0
Cryptococcus spp	0	3	**3**	**2**	1	0
Candida spp	2	0	**2**	0	2	0
Histoplasma capsulatum	1	0	**1**	0	1	0
Pneumocystis carinii	1	0	**1**	0	0	1
Influenza A	9	0	**9**	**2**	6	1
Adenovirus	9	0	**9**	1	**8**	0
Respiratory syncytial virus	3	0	**3**	0	3	0
Parainfluenza virus	2	0	**2**	0	2	0
Measles	1	0	**1**	0	1	0
More than one pathogen	—	—	**20**	3	12	5
Aspirative	—	—	**34**	0	26	9
Unknown	—	—	**166**	35	115	16

*Bold was used to signify the five or six most frequent etiologies in each group.

a pathogen was isolated. Of 35 strains, 9 were isolated from blood, 2 from pleural fluid, and 26 from respiratory specimens. In two cases, it was isolated simultaneously from two different sources (blood and pleural fluid in one source and blood and sputum in the other). *M pneumoniae* was the second most frequent pathogen (19 cases). *H influenzae* was diagnosed in 17 cases (16 in sputum culture and 1 in blood). The most common pathogens in each group are listed separately in Table 4.

The overall diagnostic yield and the prevalence of multiple etiologies could be properly estimated only for patients who had a thorough diagnostic evaluation including sputum, blood cultures, and complete serology (acute and convalescence samples). All such procedures were available in 98 patients, in whom the diagnostic yield was 57% (55 of 96), 23 of 45 outpatients (51%; groups 1 or 2), and 32 of 51 inpatients (63%; groups 2 or 3). When any of the above-mentioned tests could not be performed, diagnostic yield was 36% (90 of 247 patients; $p < 0.001$). Interestingly, diagnostic yield was not better in cases not receiving prior antibiotics than in cases receiving prior antibiotics 47% (55 of 116 patients) vs 39% (89 of 230 patients; $p = 0.151$). There were 21 positive sputum cultures in the patients receiving prior antimicrobials and 32 in those not receiving prior antimicrobials ($p = 0.388$). Breaking down the data used for definitive diagnosis, we found a trend to highest positivity of blood and pleural fluid cultures in patients not receiving prior antimicrobials (26 of 230 patients [11%]) than in the

rest (7 of 116 patients [6%]; p = 0.167). Interestingly, diagnosis by serology was higher in those patients receiving prior antimicrobials (21 of 116 patients vs 16 of 230 patients; p = 0.003). Multiple pathogens were present in 20 cases (14% of those in which a microorganism was identified). The most frequent pathogens in such cases were *S pneumoniae* in eight cases, *M pneumoniae* in seven cases, *Staphylococcus aureus* in five cases, and *Moraxella (Branhamella) catarrhalis* in four cases. *S pneumoniae* with *M pneumoniae* and *S pneumoniae* with *H influenzae* were the most common associations (three cases each). Some pathogens were more frequently present in association with other microorganisms; 80% of *M (Branhamella) catarrhalis* and 62% of *S aureus* were isolated together with other pathogens. On the other hand, only 1 of 12 isolates of *C pneumoniae* was associated with other pathogens.

Eighteen patients admitted from nursing homes or convalescent-care facilities had at least one pathogen isolated; the most frequent etiologies were Gram-negative bacilli (including *P aeruginosa*) and *S pneumoniae* (five and four cases, respectively). Other common pathogens included *M pneumoniae*, Legionella organisms, and adenovirus (two instances each). Thirteen cases were aspiration pneumonia, and in 17 cases, the etiology was unknown.

Microbial Resistance

For *S pneumoniae*, 28% of the isolates were resistant to penicillin, 19% showed an intermediate degree of resistance (minimum inhibitory concentration [MIC], 0.125 to 1 μg/mL), and 9% showed a high degree of resistance (MIC, > 2 μg/mL) degree of resistance. Twelve percent were resistant to ceftriaxone, 6% of the solates showed an intermediate degree of resistance (MIC, > 1 μg/mL), and 6% showed a high degree of resistance (MIC, > 2 μg/mL). Resistance to macrolides and to ofloxacin was observed in 6% of the cases, to tetracycline in 12%, and to cotrimoxazole in 36%. There were no strains resistant to vancomycin or rifampicin. Only one strain presented multiresistance (simultaneously to penicillin, ceftriaxone, cotrimoxazole, chloramphenicol, tetracycline, and ofloxacin). For *H influenzae*, 41% of strains were β-lactamase producers, 6% were resistant to tetracycline and rifampicin, and 100% were sensitive to amoxicillin plus clavulanate, ampicillin plus sulbactam, cefuroxime, azithromycin, ofloxacin, chloramphenicol, and cotrimoxazole. *M (Branhamella) catarrhalis*, staphylococci, *P aeruginosa*, and other aerobic Gram-negative bacilli showed common sensitivity patterns.

Clinical and Radiographic Presentation

Patients with either only typical (*S pneumoniae* or *H influenzae*) or only atypical (*M pneumoniae, C pneumoniae, L pneumophila*, influenza virus, or adenovirus) pathogens (n = 87) were identified. We compared demographic, clinical, radiologic, and laboratory characteristics in 44 patients with typical microorganisms vs 43 patients with atypical microorganisms, but we could not demonstrate significant differences between pneumonias produced by typical vs atypical pathogens (Table 5). Age (≥ 65 or < 65 years) was associated with specific causative organisms. Patients with other comorbid illnesses, current cigarette smokers, and alcohol abusers also were more likely to have distinct etiologies (Table 3).

Stratification of Patients and Outcome

Group 1 had 54 patients, group 2 had 253 patients, and group 3 had 39 patients. All group 1 patients were managed as outpatients. Two hundred twenty-one group 2 patients had criteria for hospitalization; nonetheless, 47 were managed as outpatients (including 14 patients who had admission criteria but declined to be admitted), whereas group 3 patients were admitted to the ICU. Interestingly, no patient

Table 5—*Demographic, Clinical, Radiologic, and Laboratory Features Comparing Typical vs Atypical Pathogens**

Clinical and Radiographic Findings	Groups		
	Typical Pathogens (n = 44)	Atypical Pathogens (n = 43)	p Value
Age, yr	59 ± 21	56 ± 20	0.495
Dry cough	7	13	0.165
Thoracic pain	18	10	0.145
Purulent sputum	31	23	0.206
Inspiratory rales	17	12	0.449
Inspiratory + expiratory rales	17	17	0.960
Coarse rales	10	10	0.890
Consolidation signs	9	4	0.266
Blood leukocytes, cells/mm^3	11,607 ± 5,525	10,814 ± 5,379	0.497
Airspace pneumonia	39	34	0.507
Interstitial	15	16	0.875
Pleural effusion	4	4	0.762
Cavitation	1	0	0.986
Bilateral involvement	16	9	0.199
Initial impression (typical/atypical)	34/10	28/15	0.310

**S pneumoniae* and *H influenzae* are considered typical and *M pneumoniae*, *C pneumoniae*, *L pneumophila*, *C burnetii*, and respiratory viruses, atypical pathogens for these comparisons.

initially managed as an outpatient was later admitted to the hospital. The thirty-day mortality rate could be ascertained in 280 cases. There were 50 deaths (18%): 0 of 50 (0%) in group 1; 36 of 195 (18%) in group 2; and 14 of 35 (40%) in group 3. Death occurred in 50 of 201 patients (25%) fulfilling the admission criteria and 0 of 79 patients (0%) who did not achieve those criteria. We studied the factors related to mortality and found several prognostic factors associated with higher mortality by univariate analysis (Table 6). However, on multivariate analysis, only a $PaO_2/FIO_2 < 250$, aerobic Gram-negative pathogen, chronic renal failure, Glasgow score < 15, malignant neoplasm, and aspirative pneumonia remained associated with fatal outcome (Table 7).

Antibiotic Therapy

At entry, 34% of patients (117 of 346) were on antimicrobials (more frequently aminopenicillins). Among 84 patients in whom at least one "common" bacteria (nonatypical, nonmycobacterium) was isolated, and outcome was known, the mortality rate was 8% (2 of 24 patients) of those receiving prior antimicrobials, whereas it was 33% (20 of 60 patients) in those not receiving prior antimicrobials. This difference was statistically significant ($p = 0.034$) in the univariate analysis, but multivariate analysis did not confirm that prior antimicrobial therapy independently reduced the mortality.

Table 6—*Prognostic Factors Significantly Associated With Mortality in CAP Patients*

Prognostic Factors	Patients, No.	Deaths, No.	p Value*
Age ≥ 65 yr	152	40	< 0.001
Age < 65 yr	128	10	
$PaO_2/FIO_2 < 250$	64	24	< 0.001
$PaO_2/FIO_2 \geq 250$	216	26	
Not on prior antibiotic therapy	179	39	0.034
Receiving prior antibiotic therapy	101	11	
Prone to aspiration	40	16	< 0.001
Not prone to aspiration	240	34	
Glasgow score < 15	58	21	< 0.001
Glasgow score = 15	222	29	
Renal failure			
Yes	14	7	0.004
No	266	43	
Aspiration pneumonia			
Yes	20	9	0.003
No	260	41	
Malignant neoplasm			
Yes	19	9	0.002
No	261	41	
Aerobic Gram-negative bacilli as a pathogen			
Yes	17	9	< 0.001
No	263	41	

*Univariate analysis, χ^2.

Table 7—*Prognostic Factors Significantly Associated With Mortality in CAP Patients**

Clinical Characteristic	OR	CI	p Value
$PaO_2/FIO_2 < 250$	4.84	2.30–10.19	< 0.0001
Aerobic Gram-negative bacilli as a pathogen	7.30	2.32–22.93	0.0007
Renal failure	7.85	2.22–27.80	0.0014
Glasgow score < 15	3.13	1.44–6.82	0.0040
Malignant neoplasm	4.00	1.34–12.92	0.0207
Aspirative pneumonia	3.64	1.21–10.96	0.0215

*Multivariate analysis, multiple logistic regression. For abbreviations used see Table 3 footnote.

After entry, the most commonly prescribed antimicrobials were ceftriaxone, macrolides, or β-lactam plus β-lactamase inhibitor. One hundred seventy-eight patients (51%) received combination therapy as an initial therapy. They were distributed as follows: 6 of 54 patients (11%) in group 1, 141 of 253 patients (56%) in group 2; and 30 of 39; (77%) in group 3.

There was no difference in adequacy of therapy according to adherence to the therapeutic guideline between survivors and nonsurvivors (64% vs 65%). Nevertheless, in patients with specific etiologies, therapy was adequate in relation to the isolated pathogen in 74 of 96 survivors (77%), but in only 11 of 22 nonsurvivors (50%) ($p = 0.022$).

In 9 of 32 patients with pneumococcal pneumonia, sensitivity to penicillin was reduced (high-degree resistance, 3 patients; and intermediate resistance, 6 patients). In two of three patients in whom the initial empiric therapy did not cover the pathogen, either the dose was increased or a new antibiotic was used according to the sensitivity. There were no deaths among these nine patients.

Discussion

Several studies have reported clinical and epidemiologic data on CAP.[4,5,8,9,14,17–19] Most of these studies were conducted on hospitalized patients.

In the present study, we were able to recognize an etiologic pathogen in only 42% of the cases despite extensive laboratory testing. High frequency of prior antimicrobials and difficulties in obtaining sputum and second sample for serology might explain this low yield. Valid interpretation of positive sputum results is difficult in patients receiving prior antibiotic therapy, in particular for Gram-negative bacilli, *S aureus*, and fungi. In patients with both sputum examination and second serum sample available, the diagnostic yield was 57%, whereas it was 36% in patients for whom neither of these two specimens

were available ($p < 0.001$). Nevertheless, reaching an etiologic diagnosis did not change the outcome, as mortality was 18% for both those in whom a pathogen was found and those with unknown etiology.

Prior antibiotics were received by 34% of cases. In other studies, the use of prior antibiotics oscillated between 16% and 27%.[4,16–20] Fang et al[14] stated that previous antibiotic administration was significantly associated with undetermined etiology; nevertheless, we did not find a lower yield in patients receiving prior antibiotics.

S pneumoniae was the most common pathogen. Susceptibility to penicillin was reduced in 28% of the cases, confirming the trend observed in other studies.[21] Resistance to ceftriaxone was 12%. The high resistance to cotrimoxazole confirms that this antimicrobial should no longer be recommended for patients with CAP.[22] Therapy had to be modified in only two of nine patients with penicillin-resistant pneumococci; there were no deaths among these nine patients. Some authors documented that pneumococci resistant to penicillin are also likely to be resistant to other agents including macrolides. In the present study, susceptibility to macrolides remained high in most cases caused by resistant pneumococci. This does not suggest that cross-resistance with penicillin is common among the Argentinian population as previously stated for other countries.[21,22] *S pneumoniae* was isolated in eight patients receiving prior antimicrobials; in most of these patients, it was resistant to the antibiotic being used. Five patients with *S pneumoniae* died during hospital stay.

Atypical microorganisms were recognized as a pathogen in all three groups, but there were no differences in the clinical presentation between patients with CAP caused by typical vs atypical microorganisms. *M pneumoniae* was the second most frequent pathogen overall, and *C pneumoniae* was the second most frequent pathogen in group 3. There was a trend toward a higher incidence of atypical microorganisms in younger people; nevertheless one of six patients with atypical pathogens was > 80 years of age, and one of three was > 65 years. These findings confirm that atypical pathogens are present in pneumonias of a wide spectrum of severity and age, as stated in a previous study.[23] The low incidence of Legionella spp suggests that it is not a common cause of CAP in Argentina. All four patients with legionellosis were admitted, two of them to the ICU. Three patients were > 70 years of age and had comorbidities, two of whom died at the hospital and one died at home, 45 days after the diagnosis. Although Legionella has been reported among the pathogens of CAP all around the world, the reporting of egionella in most countries of South America, Africa, and Eastern Europe, and in developing countries from Asia remains rare. To some extent, both the low incidence and the lack of previous communications may reflect a geographic variability of the pathogen. Nevertheless, this low incidence in some world areas may be related to insufficient performance of diagnostic tests rather than to an epidemiologic rarity.[24]

H influenzae was frequent, especially in patients with comorbidities; three of these patients died. Resistance caused by the production of β-lactamases was present in 41% of strains and is being reported with increasing frequency.[25] Twenty-four aerobic Gram-negative bacilli were the pathogens in 22 patients, most of whom were hospitalized. *P aeruginosa* was associated with the presence of chronic lung disorders in six of eight patients. Two patients with this pathogen died, without antimicrobial coverage for Pseudomonas. This organism was the most commonly isolated Gram-negative pathogen. This justifies the use of antipseudomonal therapy during the initial empiric treatment of severe CAP in at-risk patients.[2,26]

M tuberculosis was diagnosed in seven patients. Although TB is a chronic pulmonary infection, its clinical presentation can be confused with CAP. Reported incidence varies widely.[4,17,27] TB should be considered among the possible causes in patients with a clinical picture of CAP in areas where TB is endemic.

S epidermidis has been described as one of the pathogens of CAP.[18,19] In the present study, four of five bacteremic patients with *S epidermidis* were > 80 years of age, and they had not undergone invasive procedures that could cause contamination. The fifth patient was a young, previously healthy man; he was later found to be HIV positive. This pathogen is a cause of nosocomial infections (especially bacteremia) in the extremes of age. This organism probably deserves more consideration as a pathogen in other kinds of infections, including CAP. Cryptococcal pneumonia was diagnosed by serum antigen in three immunocompetent patients. *C neoformans* is a cause of CAP, especially in immunocompromised hosts. It also has been described in healthy, immunocompetent hosts.[28,29] Standard confirmatory diagnostic methods include culture of respiratory specimens and stains showing typical organisms on histopathology.[30] These patients were not treated for cryptococcosis; only one of them, age 82 years, died.

In patients receiving prior antimicrobials, the prescription was inadequate in 74 of 116 (64%); in a number of cases, this was because of self-prescription. Self-medication is common in Argentina and other countries of South America, as patients can buy antimicrobials without a prescription. We dem-

onstrated by univariate analysis that prior antimicrobial therapy was associated with lower mortality. This finding coincides with the description of Rello et al[31] of severe CAP.

Some comorbidities predisposing the patient to specific etiologies include the following: respiratory (aerobic Gram-negative bacilli, *P aeruginosa*, and *M [Branhamella] catarrhalis*); neurologic (aspirative pneumonia); hepatic (*S pneumoniae*); and diabetes (*M tuberculosis*). Current tobacco use and alcoholism was also associated with *M tuberculosis*. Age was also related with specific etiologies ($\geq$ 65 years, aspirative pneumonia; $<$ 65 years, *M pneumoniae, C pneumoniae*, and, interestingly, *H influenzae*). These observations confirm the findings reported recently by Ruiz et al.[32]

In the majority of patients, initial therapy was based on the therapeutic guideline. There was no difference in adherence to the guideline when comparing survivors and nonsurvivors (64% vs 65%). Nevertheless, when sensitivity of the pathogens to the therapy, instead of adherence to the guideline, was used for defining adequacy of therapy, adequate therapy was significantly more common in survivors. In severe CAP, adherence to the guideline was poor in survivors and nonsurvivors, as the prescribed regimen was followed strictly in 14% and partially (lack of coverage only for either atypical pathogens or for *P aeruginosa*) in 57% of cases. According to our guideline and other recommendations, therapy in patients with severe CAP should be applied early, and *P aeruginosa*, resistant pneumococci, and atypical microorganisms should be covered.[1,2] Mortality remained high, sometimes in spite of correct antibiotic coverage. In severe CAP, other factors besides the adequacy of therapy may affect outcome. This study suggests that our guideline should be reviewed, taking into account the observed etiology, as adherence to the guideline did not improve the outcome but adequate therapy did. Our data suggest that patients with moderate or severe CAP should be covered for atypical organisms and that for those with severe CAP and severe chronic lung disease, there should be antipseudomonal coverage as well.

None of the patients managed as an outpatient was later hospitalized, which was an unexpected result. However, some of the 45 patients admitted while receiving prior antimicrobials could represent an initial failure of the admission criteria to identify severity or worsening pneumonia, needing further admission.

Stratification criteria and the hospitalization rule were useful as mortality was significantly different among the three groups and was 0% for all patients without hospitalization criteria. These criteria were valid in identifying high-risk and low-risk patients more easily than more complex previously published rules.[33]

We should recognize that one significant limitation of this study is the higher frequency of elderly and hospitalized patients. This does not reflect the reality of CAP in the population; rather, this frequency was determined by a high number of patients with CAP who were referred to the hospital only if they needed hospitalization.

In conclusion, despite elaborate diagnostic studies, microbial etiology was established in less than half of cases. The most frequent pathogens were *S pneumoniae, M pneumoniae*, and *H influenzae.* Clinical presentation was not useful to differentiate typical vs atypical pathogens. Realization that atypical organisms and *P aeruginosa* are common etiologies should affect empiric therapy. Age, comorbidities, and severity were used for stratifying patients and in the decision of hospital admission; different groups have different target microorganisms, and outcome was poorer in group 2 and 3 patients. We corroborate that age, comorbidities, alcohol abuse, and smoking have strong associations with distinct etiologies. $Pao_2/Fio_2 < 250$, aerobic Gram-negative pathogen, chronic renal failure, Glasgow score < 15, malignancy, and aspirative pneumonia were associated with fatality on multivariate analysis. This study supports the proposal that having local data on microbial and resistance patterns would improve the application of guidelines in different settings.

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