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Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: Results of a one-year study

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Summary *Introduction:* Determining the cause of community-acquired pneumonia (CAP) remains problematic. In this observational study, we systematically applied currently approved diagnostic techniques in patients hospitalized for CAP in order to determine the proportion in which an etiological agent could be identified.
Methods: All patients admitted with findings consistent with CAP were included. Sputum and blood cultures, urine tests for pneumococcal and *Legionella* antigens, nasopharyngeal swab for viral PCR, and serum procalcitonin were obtained in nearly every case. Admission-related electronic medical records were reviewed in entirety.
Results: By final clinical diagnosis, 44 patients (17.0%) were uninfected. A causative bacterium was identified in only 60 (23.2%) cases. PCR identified a respiratory virus in 42 (16.2%), 12 with documented bacterial coinfection. In 119 (45.9%), no cause for CAP was found; 69 (26.6%) of these had a syndrome indistinguishable from bacterial pneumonia. Procalcitonin was elevated in patients with bacterial infection and low in uninfected patients or those with viral infection, but with substantial overlap.
Conclusions: Only 23.2% of 259 patients admitted with a CAP syndrome had documented bacterial infection; another 26.6% had no identified bacterial etiology, but findings closely resembled those of bacterial infection. Nevertheless, all 259 received antibacterial therapy.

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Careful attention to the clinical picture may identify uninfected patients or those with viral infection, perhaps with reassurance by a non-elevated procalcitonin. Determining an etiologic diagnosis remains elusive. Better discriminators of bacterial infection are sorely needed.

Introduction

Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality in adults.[1,2] By the late 1980s, changes in host and disease patterns, development of new antibiotics, and a great diversity in approaches to treatment led to the creation of guidelines for initial, often empiric, treatment of CAP.[3] The subsequent demonstration that delaying therapy contributes to a poor outcome[4] further increased the tendency to treat empirically. Recent guidelines[1] recommend that antibiotics be administered empirically at the point of care when the diagnosis of CAP is first made.

The emphasis on immediate treatment of pneumonia has certain disadvantages.[5–7] It has reduced the impetus to determine a causative organism, an unfortunate development at a time that the contribution by *Streptococcus pneumoniae* may have decreased and the range of identifiable potential pathogens has greatly expanded. Empiric therapy has also led to the use of antibiotics in patients who do not have infections[6–8] and has been associated with increases in microbial resistance.[9]

We undertook a prospective observational study of patients admitted to our medical center for a syndrome consistent with CAP. Our hypothesis was that careful collection of clinical and traditional diagnostic microbiologic data together with the use of newer FDA-approved techniques might yield sufficient information to inform decision-making at admission. Our findings show that an etiologic diagnosis in CAP is far more elusive than we had hypothesized.

Methods

Study design

Every patient hospitalized for a syndrome consistent with a diagnosis of CAP at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) between July 5, 2011 and June 30, 2012 was asked to participate. Nearly 95% of patients agreed, signing a consent form approved by the Institutional Review Board of the Baylor College of Medicine. A CAP syndrome was defined as a newly recognized pulmonary infiltrate together with ≥ 2 of the following findings: subjective fever or documented temperature $\geq 99.4\,°F$, increased cough, sputum production, or shortness of breath, pleuritic chest pain, confusion, rales, leukocytosis (white blood count [WBC] $>12,000/mm^3$), or a suppressed WBC count ($<6000/mm^3$).[1,10,11] All patients had CAP as one of the admitting diagnoses, and, in fact, all received antibiotic therapy in the Emergency Department, although this was not required for inclusion in the study. Patients who had been hospitalized in the preceding 4 weeks, who were bed-bound in long-term care facilities or who had known aspiration were excluded.

Data collection and analysis

We recorded patient demographics, comorbid conditions, sick contacts, symptoms of pulmonary disease, vital signs, oxygen saturation, relevant physical findings, WBC count and differential, B-natriuretic protein, radiographic findings, blood culture results and results of sputum Gram stain and culture, specifically noting the adequacy of the sputum sample and the time between antibiotic administration and the time the sputum was collected.[12] Nasopharyngeal swabs were obtained for PCR to detect 15 respiratory viruses (BioFire Diagnostics [formerly Idaho Technology], Salt Lake City, UT); during most of the duration of the present study, this technique was not yet approved to detect *Mycoplasma* or *Chlamydophila*. Urine was studied for *Legionella* and pneumococcus antigens (BinaxNOW, Alere, San Diego, CA). Serum procalcitonin was assayed (Vidas, BioMerieux. Durham NC). PORT scores and a PORT severity index[13] were calculated. Procalcitonin levels were interpreted as follows[14,15]: values $<0.1\ \mu g/ml$ strongly oppose the presence of bacterial infection; ≥ 0.1 and <0.25 oppose bacterial infection; ≥ 0.25 but <0.5 suggest bacterial infection; and ≥ 0.5 strongly favor bacterial infection.

Study design

All clinical, laboratory and radiological data were collected onto spread sheets; viral PCR results and procalcitonin levels were initially masked. At regular intervals, two or three investigators (always including the senior investigator) reviewed tabulated data together with the electronic medical record and agreed on an *initial clinical diagnosis*. Results of viral studies were then unmasked, and cases were reviewed to reach a *final clinical diagnosis*. Only then were procalcitonin levels unmasked in order to determine congruence with the final clinical diagnosis.

Definitions for final diagnoses were designed and refined in stages. The original definitions were designed before the study began. After 78 patients had been enrolled, all data were analyzed and definitions were refined. As further data were accrued, there was minimal further diagnostic refinement. At the end of accrual period, all cases were re-reviewed in light of the final set of definitions, and patients were assigned final clinical diagnoses based on the following criteria.

Uninfected
Patient had a well-documented cause other than infection for the presenting findings together with supporting laboratory data (e.g., elevated B-natriuretic

protein or a documented lung mass on x ray) and had none of the criteria for bacterial or viral infection described below.

Bacterial
Proven: a likely bacterial pathogen was isolated from a normally sterile body site, or the urine assay for pneumococcus or *Legionella* antigen was positive.
Presumptive: a likely bacterial pathogen was observed microscopically as the predominant organism in a good-quality sputum specimen, and culture documented the presence of that organism.

Viral
PCR identified influenza, parainfluenza, respiratory syncytial, human metapneumo-, corona-, rhino- or adenovirus.

Fungal
Pneumocystis jiroveci was detected in bronchial secretions, or there was a strong clinical diagnosis in an appropriate host with response to directed antimicrobial therapy.

Coinfected
Bacterial or fungal infection together with positive viral PCR.

Infected, unknown cause
Patients thought to be infected but with no microbiological cause identified were stratified as follows:

Likely bacterial: ≥3 of the following: absence of upper respiratory symptoms, presence of a biphasic respiratory illness with acute deterioration, hyperacute presentation, presentation with sepsis or shock, WBC count >15,000 or <6000 with increased band forms, dense segmental or lobar consolidation.
Likely nonbacterial: ≥2 of the following: exposure to sick contact(s), upper respiratory symptoms and patchy infiltrates, plus absence of findings suggesting a likely bacterial cause.
Undetermined: failure to fit into either of the above categories.

Statistical analysis

For dichotomous data, the presence or absence of each finding was compared among groups by the chi square test; for small groups, Fisher's exact was used. For continuous variables that were normally distributed, Student's *t* test was used. If results were not normally distributed, ANOVA was used. Significance was set at a *p* value of <0.05.

Results

Demographics

During the year of observation, 259 hospitalized patients with a syndrome that met criteria for CAP agreed to

Table 1 Demographic characteristics of 259 patients admitted to a tertiary care veterans hospital for a syndrome consistent with CAP.

Age (years)	69.8 ± 11.9
Gender (male)	268 (95.7%)
Race	
Caucasian	185 (71.4%)
African American	72 (27.8%)
Other	2 (0.8%)
Ethnicity (Hispanic)	15 (5.7%)
Comorbid conditions	
Chronic lung disease	114 (44.0%)
Heart disease	115 (44.4%)
Diabetes mellitus	92 (35.5%)
Malignancy	60 (23.1%)
Cigarette smoker	
Current	61 (23.6%)
Former	140 (54.0%)
Never	58 (22.4%)
Chronic alcohol use	67 (25.9%)
HIV infection	13 (5.0%)

participate in this study. Demographics and common comorbid conditions are listed in Table 1. All patients received antibiotic treatment at admission; treatment followed accepted guidelines[1] in 234 (90.3%) cases.

Diagnostic studies

Blood was cultured at admission in 253 (97.7%) cases. Urine was assayed for pneumococcal and *Legionella* antigens in 242 (93.4%) and 240 (92.7%) cases, respectively. A sputum sample for Gram stain and culture was obtained in 175 (67.6%) cases, but it was judged inadequate in 53 and obtained >18 h after antibiotics had been begun in 44. Thus, an adequate sputum sample was obtained within 18 h of antibiotic administration in only 78 (30.1%) cases. Viral PCR on a nasopharyngeal swab was done in 253 (97.7%) cases. Serum procalcitonin from admission was assayed in every patient.

Final diagnostic classification

Patients were stratified to one of the following final diagnostic classifications as follows (Table 2).

Uninfected
Forty-four (17.0%) patients were uninfected (24 congestive heart failure/fluid overload, 14 lung cancer, 6 other). When compared to all other patients with CAP (Table 3), these 44 were less likely to have fever (*p* < 0.001) and more likely to have heart disease (*p* < 0.02), consistent with the prevalence of pulmonary edema. Mean WBC count was 11,576, significantly lower than for patients with bacterial pneumonia (*p* < 0.02) and no different from that of patients with

Table 2 Final categorization by disease status in 259 patients with CAP syndrome.

Uninfected	44
CHF/volume overload	24
Lung cancer	14
Pulmonary fibrosis, infarct, other	6
Bacterial	60
Proven	28
Presumptive	32
Viral	42
Fungal	6
Coinfected (virus + bacterium or fungus)	12
Unknown	119
Likely bacterial	69
Likely viral	18
Undetermined	32
Total	259[a]

[a] Total cases = 259. Each coinfected patient is listed in three places: under the individual class of each organism (e.g., bacterial, viral or fungal), and under coinfected.

Table 4 Etiologic agents in 108 CAP patients.[a]

Bacterial	64
Streptococcus pneumoniae	20 (17)[b]
Haemophilus influenzae	12
Staphylococcus aureus	9 (3)
Pseudomonas aeruginosa	6 (1)
Klebsiella pneumoniae	2 (1)
E. coli	2
Mycobacterium avium-intracellulare	2
Nocardia	2 (1)
Moraxella	1
Other bacteria	8 (5)
Viral	44
Rhinovirus	26
Coronavirus	7
Parainfluenza virus	4
Respiratory syncytial virus	3
Human metapneumovirus	3
Influenza virus	1
Fungal (*Pneumocystis jiroveci*)	6

[a] Data are shown as the numbers of potential etiologic agents identified. The total number exceeds the number of infected patients because of cases in which multiple organisms were identified.
[b] Under bacterial, numbers of patients with proven infection (isolation of organism from a normally sterile site) are shown in parentheses.

viral pneumonia, but the WBC count exceeded 11,500 in 21 of 44 (47.7%) cases. Mean serum procalcitonin in this group was 0.55 ± 1.10 (median = 0.09); the level was ≥0.25 (elevated) in 14 (31.9%), <0.25 but ≥0.1 (indeterminate) in 4 (9.1%), and <0.1 (normal) in 26 (59.1%). If higher cutoff points for procalcitonin were used to suggest infection, 12 had levels >0.5 and 8 had levels >1.0. If a procalcitonin level <0.25 were used to determine treatment, antibiotics might have been withheld in two-thirds of 44 patients who presented with a CAP syndrome but who were judged to be uninfected.

Infected, bacterial

Sixty (23.2%) patients had bacterial pneumonia, 28 proven and 32 presumptive. Etiologic agents are shown in Table 4; numbers of patients with proven infection are shown in parentheses. The proportions with cough, sputum production, shortness of breath, pleuritic chest pain, confusion

Table 3 Clinical features of patients presenting with a syndrome of community-acquired pneumonia.[a]

	n	Cough	Sputum	Dyspnea	Pleuritic chest pain	Altered mental status	⇓ O$_2$ saturation	Fever and/or chills[b]	WBC (mean)	Procal (mean)	Procal (median)
Uninfected	44	37 (84%)	27 (61%)	37 (84%)	6 (14%)	9 (20%)	21 (48%)	17 (39%)	13,180	0.55	0.09
Bacterial (all)	60	56 (93%)	48 (80%)	51 (85%)	13 (22%)	16 (27%)	34 (57%)	49 (82%)	15,576	3.52	0.90
Proven	28	25 (89%)	21 (75%)	22 (80%)	5 (18%)	8 (29%)	11 (39%)	21 (75%)	16,814	5.57	2.48
Presumpt	32	31 (97%)	27 (84%)	29 (91%)	8 (25%)	8 (25%)	23 (72%)	28 (88%)	14,341	1.53	0.36
Fungal	6	6 (100%)	2 (33%)	5 (83%)	2 (33%)	0 (0%)	2 (33%)	3 (50%)	7100	0.14	0.12
Viral	30	30 (100%)	21 (70%)	25 (83%)	2 (7%)	5 (17%)	14 (47%)	19 (63%)	10,527	0.81	0.09
Unknown (all)	119	103 (87%)	71 (60%)	92 (78%)	18 (15%)	23 (19%)	47 (40%)	89 (75%)	12,791	2.11	0.23
Likely Bacterial	69	58 (84%)	45 (65%)	50 (72%)	14 (20%)	12 (17%)	25 (36%)	55 (80%)	14,990	3.41	0.73
Likely Viral	18	16 (89%)	12 (67%)	15 (83%)	2 (11%)	3 (17%)	7 (39%)	11 (61%)	7700	0.17	0.03
Uncertain	32	31 (91%)	15 (44%)	28 (82%)	2 (6%)	10 (29%)	15 (47%)	16 (47%)	10,981	0.44	0.07
All CAP patients	259	232 (90%)	169 (65%)	210 (81%)	41 (16%)	53 (21%)	117 (45%)	169 (65%)	13,120	2.18	0.2

[a] Data shown as number of subjects in each group with the finding (percentage in parentheses). Patients with presumed or proven bacterial infection who also had a virus identified by PCR are included in bacterial infection; the same applies to a single patient with fungal infection (see Methods).
[b] Patients with subjective findings of fever or chills plus those with documented fever or hypothermia at admission.

and O_2 desaturation were similar when compared to other groups of infected patients (Table 3; $p > 0.05$ for all comparisons). Although 49 of these 60 (81.7%) patients had had evidence of fever by history or examination, only 31 (51.7%) had documented fever (temperature $\geq 99.4\ °F$) or hypothermia (temperature $< 96\ °F$) during the first 24 h in the hospital.

S. pneumoniae was the most frequently implicated bacterial cause (20 of 60 [33.3%] cases), but this represented only 7.7% of the 259 cases of CAP. Twelve patients had Haemophilus influenzae in their sputum, six of these together with pneumococcus (1 of whom had bacteremic pneumococcal pneumonia). Staphylococcus aureus, and Pseudomonas aeruginosa were the next most frequent bacterial isolates. A coinfecting virus was identified by PCR in 11 of 60 (18.3%) patients who had bacterial pneumonia — rhinovirus in 10 cases and respiratory syncytial virus (RSV) in 1.

Mean WBC count in 60 patients with bacterial pneumonia was $15,495 \pm 9276$, with no difference between proven and presumptive infections ($p = 0.5$; Table 3). Eight patients had suppressed WBC responses (WBC < 6000), and 11 had "normal" WBC counts (between 6000 and 11,500). Mean procalcitonin was 3.52 ± 6.13; values were higher (5.57) in patients with proven than those with presumptive (1.53) bacterial infection ($p = 0.03$). In 19 of 60 (31.7%) cases of bacterial infection (6 proven and 13 presumptive), procalcitonin was < 0.25, and in 14 of 60 (23.3%) cases (3 proven and 11 presumptive) procalcitonin was ≤ 0.1. Of patients with bacterial infection and procalcitonin ≤ 0.25, 13 were in the PORT risk group 4 (PORT score index [PSI] 4)[1]; 9 of these had procalcitonin < 0.1, although none had PSI of 5. These results indicate that a low procalcitonin level at the time of admission cannot be relied upon to exclude the likelihood of serious bacterial infection.

Infected, viral

PCR identified a total of 44 respiratory viruses in 42 (16.2%) patients with CAP — as the only pathogen detected in 30 and together with a bacterial or fungal pathogen in 12. Only 1 patient had influenza virus infection, consistent with the high uptake of influenza vaccine in our population and the absence of a major influenza outbreak during the year of this study. Fever, cough, sputum production, myalgias, chest pain, confusion, and hypoxia were present in proportions similar to those of patients with bacterial pneumonia (Table 3). Mean WBC count was 10,526, and mean procalcitonin was 0.81, significantly lower than in patients with bacterial infection ($p < 0.001$ and $p < 0.002$, respectively). Nevertheless, procalcitonin was ≥ 0.25 in 23.3% of patients and > 0.1 in 46.7% of patients with viral infection, showing that an elevated level does not exclude the diagnosis of viral pneumonia. Three of the 30 patients had clinical characteristics suggestive of bacterial pneumonia (biphasic illness, WBC count $> 15,000$, dense infiltrate), but no bacterium was recovered; if these three are removed, the average WBC count in patients who had viral pneumonia was 9881 and the average procalcitonin was 0.64.

Infected, fungal

Six (2.3%) patients, all with untreated or inadequately treated HIV infection, had P. jiroveci pneumonia. One was coinfected with rhinovirus. In these subjects, mean WBC count was 7140, and mean procalcitonin was 0.14.

Unknown CAP

One hundred and nineteen (45.9%) patients were thought to have an infectious cause for their CAP syndrome, largely by exclusion of noninfectious causes, but no etiologic agent was identified. Using definitions stated in Methods, these patients were stratified as follows.

Likely bacterial: 69 (57.9%) were judged to have a likely bacterial infection, in accord with criteria specified in the Methods section. In these patients, mean WBC was 14,990, and mean procalcitonin was 3.41, with procalcitonin < 0.25 in 22 (33.3%) cases and < 0.1 in 13 (19.7%) cases, results nearly identical to those for patients with documented bacterial pneumonia. The predominant reading of the Gram-stained sputum and culture was "mixed respiratory flora."

Likely nonbacterial: 18 (15.1%) patients were thought, on clinical grounds, to have nonbacterial (viral) infection. The mean WBC count was 7965, and mean procalcitonin 0.17 ($p < 0.001$ vs. results for patients with unknown, likely bacterial infection or those with proven bacterial infection). In 14 (77.8%) patients, procalcitonin was < 0.25, and in 12 of 18 (66.7%) < 0.1.

Undetermined: in 32 (26.9%) cases, no clear clinical suspicion could be reached because symptoms and signs from each of the above categories were present.

Discussion

This prospective observational study systematically applied currently available FDA-approved diagnostic techniques to study 259 patients hospitalized for CAP in a tertiary care veterans' hospital during a 12- month period. Forty-four patients (17.0%) were judged to have no infection although diagnosed with CAP and treated with antibiotics. Of 215 who were thought to be infected, a bacterial cause was identified in 60 (27.9%), a viral cause in 42 (19.5%) (11 had a documented bacterial coinfection), and P. jiroveci infection in 6 (2.8%). Thus, in the majority of patients who were thought to be infected (119 of 215, 55.3%), no etiologic diagnosis was ever determined. The clinical syndromes and laboratory findings suggested bacterial infection in 69 of these, viral infection in 18, and were indeterminate in the remaining 32.

Pneumococcus caused 20 of 60 (33.3%) cases for which a bacterial infectious etiology was established, representing only 9.3% of the 215 infected patients, remarkably different from the 90—95% that was found in the preantibiotic era.[16] Other studies have found S. pneumoniae in 7—48% of CAP.[11,17—21] European studies with the highest reported yields for pneumococcus have utilized nontraditional techniques that are not fully validated.[18,19,22] Using lung puncture, Ruiz-Gonzalez et al.,[23] attributed only 25% of CAP to pneumococcus. Quantitative PCR on nasal washings[24] detected S. pneumoniae in 27% of African AIDS patients with pneumonia, still a substantially lower percentage than might have been expected in that patient population.

One possible explanation for the low rate of diagnosis of pneumococcal pneumonia is failure to detect the organism. Only 80 (37.2%) infected patients provided an adequate sputum sample within 18 h of initiation of antibiotics; the yield of pneumococci falls off greatly after that time.[12] Routine use of nebulization to induce sputum in the emergency department might increase this yield. In preliminary studies (unpublished), we have found that the use of DNA hybridization (Accuprobe, Genprobe, San Diego, CA) on whole sputum or on a sputum culture plate may identify pneumococci in a small proportion of these cases. In contrast, the pneumococcal antigen detection system (Binax®) cannot be used because of the high proportion of false positives (C. Stager and D. Musher, unpublished observations).

Other results, however, support the low frequency of pneumococcal infection in CAP. Only 5 of 254 (2.4%) blood cultures and 13 of 242 (5.4%) urine tests for pneumococcal antigen were positive. If, by conservative estimate, 15% of cases of pneumococcal pneumonia are bacteremic,[16] and if the test for detecting cell wall polysaccharide is positive in about 70% of bacteremic cases and 50% of nonbacteremic cases,[25] pneumococcal infections would still not have exceeded 19% of all infected patients. Use of multiplex PCR for pneumococcal capsular polysaccharide on urine might have slightly increased this yield.[26,27]

Secular trends[21] may have led to a reduction in the prevalence of S. pneumoniae as a cause of pneumonia. Widespread use of pneumococcal polysaccharide vaccine in our population (about 85% of eligible patients served by MED-VAMC have been vaccinated) and conjugate vaccine in children in Houston (about 95% uptake in infants and toddlers) has certainly reduced the frequency of pneumococcal disease in adults by direct and indirect effects.[28] Pneumococcal colonies may be difficult to detect on blood agar plates because of the prevalence of other alpha-hemolytic streptococci. In contrast, laboratory identification of other potential pulmonary pathogens — e.g. S. aureus, H. influenzae, or Gram negative bacilli — is relatively easy. If pneumococci are not responsible for many of the cases of CAP and these other bacteria are not identified, then it is unclear what organisms are responsible. One wonders whether it could be mixed respiratory flora. The Swedish Infectious Disease Society[22] recommends penicillin for treatment of CAP; an observed response would be consistent with either undetected pneumococcus or mixed respiratory flora as causative agents.

PCR identified a respiratory virus in 42 (19.5%) infected patients, a slightly lower proportion than reported in some series,[29–33] but one consistent with the age of our patients[30,34] and a much higher proportion than in healthy adults.[31,34] For two reasons, identifying a virus in a patient with pneumonia does not prove a causal relationship: (1) some asymptomatic adults may carry one of these viruses[31,34]; and (2) viral respiratory illness may predispose to secondary bacterial infection.[35] After exclusion of patients who had documented bacterial coinfection, the significantly lower mean WBC counts and procalcitonin levels in patients with viral PCR-positivity supported the diagnosis of viral pneumonia. Mean PCT was greater in patients with documented viral infection than in those in the unknown, likely viral group. Patients in the latter group were identified clinically and would have been excluded if they had any feature(s) consistent with bacterial pneumonia. In contrast, patients with confirmed viral infection were not selected so restrictively and may also have had bacterial infection, as some were proven to do. Mean PSI scores were nearly identical in coinfected patients and those with bacterial infection only ($p = 0.67$), opposing the recent suggestion[36] that coinfected patients have more severe illness than those with bacterial infection alone.

A major strength of this study is that we included all patients with a syndrome consistent with CAP and did not exclude patients who were subsequently judged to be uninfected. Of patients admitted for CAP, 17% were uninfected; most had congestive heart failure. Pulmonary edema may be difficult to distinguish from pneumonia: (1) symptoms and signs (including WBC counts[37,38]) overlap; (2) pneumonia symptoms in older persons are nonspecific[39]; and (3) fever may not be present in pneumonia (only one-half of our patients with pneumonia had temperature $\geq 99.4\,°F$ in their first 24 h in the hospital). Once unmasked, procalcitonin levels were found to be much lower in uninfected patients than in those with bacterial pneumonia; such a finding might reinforce the willingness to withhold antibiotics in these cases.

Despite intensive efforts to identify etiologic agents, none was found in a 119 of 259 (45.9%) CAP patients in this series. Applying clinical criteria developed during review of the first 79 patients in this series, we determined that 69 of these 119 had clinical and laboratory findings strongly suggesting bacterial infection. Eighteen had a clinical syndrome that closely resembled viral pneumonia. Results of the procalcitonin assay supported the validity of these clinical criteria. No inference could be made regarding the remaining 32 cases.

Consistent with earlier reports,[14,15,40–43] we found clear differences in mean serum procalcitonin levels between patients with bacterial infection and those who were uninfected or who had viral or fungal infection. However, nearly one-third of patients with documented bacterial infection had a procalcitonin below the level generally associated with bacterial infection, and one-third without bacterial infection had levels above those associated with no bacterial infection. This lack of specificity precludes dependence on this test in selecting initial treatment. If careful attention to clinical and laboratory findings suggests that a bacterial infection is not present, a low procalcitonin level might support the withholding of antibiotics. A recent meta-analysis suggested that monitoring procalcitonin levels may allow duration of antibiotic treatment to be reduced by 3–4 days without adversely affecting outcomes[14,44]; however, careful attention to clinical details might do the same.

Our study supports concern that hospitalization for CAP is likely to lead to unnecessary antibiotic therapy.[6,8] In addition to 44 patients who were uninfected, 30 had viral pneumonia, 10 were infected with mycobacterium, Nocardia or Pneumocystis, and 18 had syndromes that, in all regards, suggested a viral infection, although viral PCR was negative. Thus, 102 of 259 (39.4%) patients admitted with a diagnosis of CAP were treated empirically with antibiotics, but had little or no chance of benefiting from them. This finding should stimulate more thoughtful application of guidelines for empiric therapy and provide further impetus to develop better diagnostic studies.

The principal limitation of our research is that it was carried out at a single medical center where a male, middle-aged population predominates. Enrollment at a single medical center, however, offered a potential advantage in the consistency of the data, although there is also a possibility of consistent bias in data collection and analysis. The study was also limited because the PCR technology we used was not yet FDA-approved to detect mycoplasma or Chlamydia, and we chose not to attempt to diagnose these infections serologically.

In conclusion, many problems remain in diagnosing and treating CAP. In our series of cases, 17% of 259 patients admitted with that diagnosis did not even have an infection; in most of these, more careful clinical analysis and better antibiotic stewardship would have led to a correct diagnosis at admission. Another 17% had a viral infection, one-quarter of whom had a secondary bacterial infection. Although, with current PCR technology, it is relatively simple to detect viral infection, it can be much more difficult to exclude the presence of a secondary bacterial infection. Other patients who had fungal, mycobacterial and nocardial infections also were initially diagnosed with CAP, although in many there was good evidence at the time of admission that a bacterial infection was not responsible. Most important is the large group of patients — 45% in this series — in whom no diagnosis could be made. All of these patients received standard antibacterial therapy on admission. Inducing sputum in the emergency department might lead to a correct diagnosis in some proportion of cases, and additional techniques might help to identify pneumococci in sputum. Routine use of an assay for serum procalcitonin level may help in diagnosis, especially by indicating patients who do not have bacterial infection. Our data show clearly that the facile use of guidelines to label all 259 patients with CAP and to treat with antibiotics is problematic. Better discriminators of bacterial infection are sorely needed.

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