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Editorial

New Directions for Future Studies of Community-Acquired Pneumonia: Optimizing Impact on Patient Care

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Community-acquired pneumonia (CAP) has long been an active field of investigation given its relevance, its complexity, and its challenges. In 1989 and 1990, two notable prospective observational studies on community-acquired pneumonia by Marrie et al. [1] and Fang et al. [2] were published. More comprehensive than previous studies, these studies reported that two newly recognized pathogens, *Chlamydia pneumoniae* and *Legionella pneumophila*, were causes of CAP in immunocompetent hosts. Since then, a near avalanche of studies of CAP has been published worldwide. In addition, a series of meta-analyses and rigorous chart review studies from the PORT project have been published by Fine et al. [3]. In this issue, Sopena et al. [4] have conducted yet another observational study of patients with CAP. Their excellent study was labor-intensive and rigorous, but the overall findings were similar to those of numerous previously published studies.

Given this scenario, we offer some guidelines for investigators contemplating future studies of CAP. We reviewed seven prospective studies published between 1995 and 1998 that specifically addressed the etiology or epidemiology of CAP and enrolled at least 100 patients. Other studies that have been omitted for reasons of space can be reviewed elsewhere [3, 5]. A comparison between these seven studies and that of Sopena et al. [4] is shown in Tables 1 and 2. There were, of course, some weaknesses in all studies, but we recommend that the weaknesses addressed below be rectified in future studies of CAP.

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Explicit criteria should be used to define pneumonia [6]. Signs and symptoms are important, but objective evidence of fever, leukocytosis, and pulmonary infiltrate on chest radiograph should be part of the definition. Five of the studies [4, 7–10] used a complete definition of pneumonia that included fever, leukocytosis, signs and symptoms of pneumonia, and a new pulmonary infiltrate on chest radiograph. Two studies [11, 12] used somewhat looser diagnostic criteria based on radiographic evidence and clinical findings.

The rank order of the frequency of occurrence of the most common etiologic agents found in various studies can be used to guide empiric therapy. Studies to date are surprisingly consistent (Table 1). *Streptococcus pneumoniae* is the most common cause of CAP worldwide. *Haemophilus influenzae* ranks second among the "typical" pathogens. The "atypical pathogens" (*Chlamydia pneumoniae, Legionella pneumophila*, and *Mycoplasma pneumoniae*) rank in the top five of the most common causes of CAP in hospitalized patients. *Mycoplasma pneumoniae* is more common in ambulatory patients. Aerobic gram-negative bacilli are uncommon pathogens in the immunocompetent host. An exception was the Verona study [11]; in which the definition of pneumonia was not given, etiologies were not subclassified as to definitive or presumptive, and invalid clinical criteria were used to separate typical from atypical pathogens. Aerobic gram-negative bacilli were found to be the most common etiologic agents and *Streptococcus pneumoniae* was a distant fifth; criteria for the bases of these etiologic diagnoses were not given by the authors.

New etiologic agents of CAP have not been discovered since *Chlamydia pneumoniae* and *Hantavirus*, so recent studies on etiology have essentially been confirmatory rather than groundbreaking. As a result, we discourage any further observational surveys for etiologic agents unless a new microorganism is to be sought, a specific hypothesis is to be tested, or a new diagnostic method

Table 1 Etiologies in selected studies of community-acquired pneumonia that included more than 100 hospitalized patients

Site [reference]	Date	No. of cases diagnosed etiologically	Rank order of etiology (%)					Unknown etiology (%)
			First	Second	Third	Fourth	Fifth	
Barcelona, Spain [3]	1994–96	389	*S. pneumoniae* (24)	*C. pneumoniae* (14)	*Legionella* spp. (13)	*H. influenzae* (2)	*P. aeruginosa* (2)	42
Okayama, Japan [7]	1994–97	326	*S. pneumoniae* (23)	*H. influenzae* (7)	*M. pneumoniae* (5)	*K. pneumoniae* (4)	*S. millerei* (4)	39
Verona, Italy [11]	NA	345	gram-neg. rods (8)	*M. pneumoniae* (4)	*Legionella* spp. (3)	viral (3)	*S. pneumoniae* (2)	NA
Ohio, USA [8]	1991	2776	*M. pneumoniae* (33)	*S. pneumoniae* (13)	*C. pneumoniae* (9)	influenza A (7)	*H. influenzae* (7)	20
Beer-Sheva, Israel [12]	1991–92	346	*S. pneumoniae* (43)	*M. pneumoniae* (29)	*C. pneumoniae* (18)	*Legionella* spp. (16)	viral (10)	19
Murcia, Spain [13]	1991–94	100	*S. pneumoniae* (23)	*C. pneumoniae* (21)	*H. influenzae* (19)	*M. pneumoniae* (11)	*Legionella* spp. (15)	NA
Leiden, the Netherlands [9]	1991–93	334	*S. pneumoniae* (27)	*H. influenzae* (8)	*M. pneumoniae* (6)	*C. pneumoniae* (3)	*Legionella* spp. (2)	45
Four U.S. cities [10]	1994–96	149	*S. pneumoniae* (25)	*Legionella* spp. (14)	*H. influenzae* (13)	*C. pneumoniae* (10)	*M. pneumoniae* (9)	41

gram-neg. rods, aerobic gram-negative rods including *Pseudomonas aeruginosa*; NA, not available

is implemented. If studies of etiology are initiated, comprehensive microbiology testing is obligatory. Specifically, application of specialized laboratory diagnostic tests should be attempted for all patients enrolled. The net effect of selective testing is underestimation for that particular pathogen in the population when the specific test is not obtained or overestimating the virulence of a pathogen when tests are targeted to those patients who are not responding to therapy or who are admitted to the intensive care unit.

Completeness of diagnostic testing varied considerably among the studies by specific test (Table 2). No information was given for one study [13]. The rates of tests completed ranged from (i) 16 to 100% for blood culture; (ii) 13 to 80% for sputum culture; (iii) 64 to 99% for serological testing; (iv) 0 to 80% for *Legionella* sputum culture; and (v) 13 to 99% for detection of *Legionella* urinary antigen. The studies by Sopena et al. [4], Marston et al. [8], Bohte et al. [9], and Vergis et al. [10] not only used explicit criteria for etiologic classification but also provided specific data on the numbers of patients who received each test. The effort by Marston et al. [8] bordered on the heroic in that 2776 patients were enrolled. Interestingly, Sopena et al. [4] found a high incidence of *Legionella* even though diagnostic testing was applied only to a select population.

Given the difficulties in interpretation of results derived only from sputum culture, etiological agents should be classified as definitive or presumptive [6]. (Sopena et al. [4], Marston et al. [8], and Bohte et al. [9] used the term "probable", but we prefer "presumptive", which acknowledges the tentativeness of the criteria.) The "definitive" classification might include the following: (i) a blood or pleural fluid culture yielding a pathogen, (ii) cultures from an open lung biopsy yielding a pathogen, (iii) microscopy of a bronchoalveolar lavage specimen revealing *Pneumocystis carinii*, (iv) sputum cultures yielding *Legionella pneumophila*, and (v) a fourfold rise in antibody titer to *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Coxiella burnetii*, or viral pathogens. It must be conceded that serologic criteria are not as rigorous as isolation of the organism, and etiologies classified as definitive based on the results of serologic tests should be classified explicitly in the Results section. Classification of an etiology as presumptive could be applied to growth of a bacterial pathogen in sputum cultures in which Gram stain revealed a predominant pathogen compatible with the culture result. Use of sputum culture without confirmation of Gram stain is weak, so if Gram stain confirmation is not applied, this weakness must be mentioned in the Methods. Gram stain results were generally not reported in most studies. The outstanding exception was the study by Marston et al. [8], who reported that 79% of patients from whom sputa was collected fulfilled Gram stain criteria for adequacy of sputum.

As our knowledge on the sensitivity and specificity of the available diagnostic tests increases, previous studies can remain useful, since the etiologies might be reclassified based on newer criteria. This is especially pertinent for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, for which gold standards of diagnosis have not been established [14, 15].

Patients with CAP of uncertain or unknown etiology should be characterized. These patients (i) may have received prior antibiotics that masked the identity of the pathogen; (ii) may not have undergone specialized

Table 2 Diagnostic tests performed and patient demographics in studies of community-acquired pneumonia (CAP) that included more than 100 patients

Site [reference]	Explicit diagnostic criteria used[a]	Percentage of patients in which test was performed					In vitro susceptibility of *S. pneumoniae* determined	Patient inclusion		
		Blood Culture	Sputum Culture	Serological test for *Legionella*	Culture for *Legionella*	Urinary antigen detection		Immuno-compromised	HIV+	Nursing home resident
Barcelona, Spain [3]	yes	98	52	64	52	13	no	yes	yes	yes
Okayama, Japan [7]	yes	86	76	91	NA	0	yes	no	no	no
Verona, Italy [11]	no	16	42	90	NA	0	no	no	no	yes
Ohio, USA [8]	yes	76	65	69	25	63	no	NA	NA	no
Beer-Sheva, Israel [12]	yes	40	13	89	0	0	no	NA	no	NA
Murcia, Spain [13]	no	NA	NA	NA	NA	0	yes	no	no	NA
Leiden, the Netherlands [9]	yes	100	61	72	0	0	no	NA	NA	no
Four U.S. cities [10]	yes	99	80	99	80	99	yes	no	no	no

[a] definitive, presumptive, or probable classification for etiology
NA, not available; HIV+, HIV-positive

testing for atypical microorganisms; (iii) may have been unable to produce sputum specimens, or (iv) may have been infected by a pathogen that has yet to be identified. Since the issue of dual etiologies has been raised, the patients fulfilling criteria for CAP due to more than one etiology should be described in detail, especially those who fulfill definitive criteria for two etiologies. Such data may show that serological criteria are less specific than is currently believed.

The prevalence of etiologic agents may show geographic variation. Hemorrhagic fever viruses from tropical areas, *Klebsiella pneumoniae* in South Africa, *Coccidioides immitis* in southwestern USA, *Mycobacterium tuberculosis* in developing countries, and *Pseudomonas pseudomallei* in Asia are some notable examples. Etiologic agents are also dependent on host defense and the clinical setting. It is now becoming clear that in addition to immunocompetent patients, four large demographic groups are also worthy of special study. Specifically, ambulatory patients, immunocompromised patients, especially HIV-positive patients [16], patients admitted to intensive care units [17], and nursing home patients [18] constitute a notable proportion of patients with CAP, with each group affected by CAP of a distinct epidemiology. Although it is reasonable to summarize the data from all patients, as Sopena et al. [4] have done, a separate analysis for ambulatory patients, immunosuppressed patients including HIV-positive patients, and residents of nursing homes should have been made available to the reader (similar to their important Table 4, which shows the etiology among patients admitted to the intensive care unit) [4], since the demographics and epidemiology are different for these distinct patient groups. Five studies [7, 9, 11–13] excluded patients who were immunocompromised or who were admitted from nursing homes. However, most studies [8, 9, 11, 13] did not provide sufficient information about patient exclusions in the above four categories.

The appearance of new diagnostic tests, e.g., detection of pneumococcal urinary antigen or the polymerase chain reaction (PCR), justifies initiating a new study. More precise testing can lessen the pressure for broad-spectrum empiric antibiotic therapy. Defining the sensitivity and specificity of these new tests should be of considerable importance to the practicing clinician. These tests should be compared to established gold standards such as bacteremia. Furthermore, unlike culture, detection of urinary antigen and PCR may be useful diagnostic tests even in patients who received prior antibiotics. Sopena et al. [4] applied a new diagnostic technique: the detection of soluble capsular pneumococcal antigen in urine. This may be a potentially important advance in diagnostic testing for CAP, since sputa are often difficult to obtain. Unfortunately, the test was performed in only 60% of the patients, and information about the impact of prior antibiotic use on the results of this test was not given.

Computed tomography scans are more sensitive and precise in defining pulmonary infiltrates, but their role in the management of CAP has not been defined [19]; a study assessing the role and utility of computed tomography scans is in order.

Comparative studies of antibiotics in which pharmacoeconomic factors are taken into consideration are

important. An attempt should be made to correlate increased antibiotic potency in vitro and improved pharmacodynamics to improved outcome [20]. The new antibiotics to be evaluated should be compared with the current standards as outlined by consensus committees [6]. Monotherapy using beta-lactam agents is not recommended; based on numerous etiological studies, the empiric regimens should cover the atypical pathogens. Certainly, antibiotic trials using monotherapy with beta-lactam agents are seriously flawed if they do not provide the results of routine testing for the atypical pathogens.

All pathogens should be saved for in vitro susceptibility testing. The prevalence of penicillin-resistant *Streptococcus pneumoniae* continues to increase worldwide. Resistance to the cephalosporins, macrolides, and quinolones is likewise increasing among *Streptococcus pneumoniae*. In vitro susceptibility testing of *Streptococcus pneumoniae* isolates should be a key part of all studies of CAP for the next decade (Table 2). In vitro susceptibility testing of *Haemophilus influenzae* should also be considered if undue numbers of treatment failures are seen in these patients. While it is recognized that the prevalence of penicillin-resistant, macrolide-resistant, and quinolone-resistant *Streptococcus pneumoniae* varies geographically [21–23], there are few data on the outcome of patients with pneumonia caused by these strains. Correlation of in vitro susceptibility to clinical outcome is now an important and unresolved issue. For example, in studies with small sample sizes the outcome of patients with pneumonia due to penicillin-resistant or macrolide-resistant *Streptococcus pneumoniae* was shown to be similar to that of patients with pneumonia due to susceptible *Streptococcus pneumoniae* [21, 24].

In this era of cost-containment, socioeconomic studies are pertinent to improve resource allocation and efficiency of health care delivery. Prediction rules for admission based on multivariate analyses of studies with large samples size have been proposed, although such rules are a crude approach for decision-making. They are essentially black and white, while the clinical reality is full of situations with in-between grays. We propose a more practical approach for decisions on hospitalization that would receive greater approval by physicians, be safer for patients, and lead to lower frequency of hospitalization than prediction rules. First, admit selected patients to a holding unit and administer antibiotic therapy. After 24–48 h of observation, a judgment on hospitalization versus immediate discharge with oral antibiotics will then be more precise. Dean et al. [25] has demonstrated that hospitalization can be minimized in selected patients by using daily nursing visits and administering injectable antibiotics.

Large-scale studies in the area of epidemiology and outcomes research are labor-intensive to conduct. Yet most of the results published to date have merely confirmed current clinical impressions based on anecdotal experience. The results are publishable, but the relevance for the practitioner is minimal: "Tell us something we don't already know." We recommend that innovative hypotheses designed to modify clinical practice be incorporated into these observational studies. Meta-analyses of studies of CAP are fraught with pitfalls since the rigor of the studies varies widely and definitions are often absent or imprecise. Observational studies reporting multivariate analyses of risk factors for mortality should be curtailed. It is obvious that abnormal laboratory tests, extensive infiltrates on chest radiograph, the presence of various immunosuppressive conditions, and the severity of vital signs will negatively affect outcome. Informing us that admission to intensive care unit and higher APACHE score are poor prognostic factors is hardly enlightening. The results of many studies can be summarized under the simple rubric "Sick patients die."

With the proliferation of studies of CAP, we are now asymptomatically approaching the plateau for accumulation of useful information. Our suggestions are intended to stimulate thoughtful redesign of future studies of CAP so that innovative hypotheses and increased intensity in data collection will be required. CAP is a dynamic infectious disease syndrome. New antimicrobial therapy, changing patterns of microorganism resistance, and development of new diagnostic tests will render previous studies obsolete. Attention to the points made in this editorial will maintain the vitality of studies of CAP by maximizing the impact of the results for the clinician.

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