MAJOR ARTICLE

Management of Nonsevere Pneumonia in Military Trainees with the Urinary Antigen Test for *Streptococcus pneumoniae:* An Innovative Approach to Targeted Therapy

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Background. The drug of choice for treatment of *Streptococcus pneumoniae* infection is generally a penicillin (including amoxicillin). Targeted therapy is, however, rarely used, because results of definitive diagnostic tests for pneumonia are not available for several days. Thus, broad-spectrum antibiotics are used for empirical treatment of pneumonia to cover both typical and atypical pathogens. Our purpose was to assess the usefulness of a strategy of targeted antimicrobial therapy based on the results of a rapid urinary antigen test for *S. pneumoniae.*

Methods. Military trainees with pneumonia were prospectively assigned to 2 groups: patients with positive urinary antigen test results who were treated with amoxicillin (1000 mg 3 times per day), and patients with negative urinary antigen test results who were treated with clarithromycin (500 mg 2 times per day). The duration of therapy was 5–10 days for both groups.

Results. A total of 219 evaluable patients were enrolled in the study. The most common causes of pneumonia were *S. pneumoniae, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae.* Patients with positive urinary antigen test results had illness of greater severity at the time of study entry. Twenty-two percent of patients had positive urinary antigen test results (i.e., the amoxicillin group), and 78% had negative urinary antigen test results (i.e., the clarithromycin group). The clinical success rates were 94% for the clarithromycin group and 90% for the amoxicillin group (P = not significant). None of the patients who were classified as having treatment failure died. Resolution of clinical manifestations was slower for patients with pneumococcal pneumonia defined by a positive urinary antigen test result.

Conclusions. The urine antigen test allowed targeted use of a penicillin (amoxicillin) for young immunocompetent individuals with nonsevere, community-acquired pneumonia. Clarithromycin was highly effective against both *S. pneumoniae* pneumonia and pneumonia due to atypical pathogens.

Community-acquired pneumonia (CAP) is the leading cause of morbidity in military communities. The mean annual incidence of CAP in the Russian Army is 4.2%; however, in military training camps, the incidence can increase to as high as 20% during outbreaks of CAP [1].

Expectorated sputum is the most common laboratory specimen used for etiological diagnosis of CAP, despite the fact that many studies have documented the relatively poor sensitivity and specificity of sputum culture. In addition, the interpretation of the clinical outcome of sputum cultures is fraught with problems associated with poor-quality specimens, upper-airway contamination, and oropharyngeal colonization [2–5]. Thus, in typical clinical practice, patients generally receive an empirical, broad-spectrum antibiotic regimen rather than a narrow-spectrum antibiotic regimen for targeted individualized therapy.

A new rapid test for diagnosis of pneumococcal

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pneumonia, the urinary antigen test for *Streptococcus pneumoniae* (Binax), is now commercially available. Its sensitivity and specificity are superior to those of sputum culture, and it is more sensitive than blood culture [3–5]. Its sensitivity is also independent of the severity of pneumonia [6]. Therefore, we initiated a prospective, interventional study to assess whether application of the urinary antigen test may allow targeted therapy for CAP at the time of initiation of antibiotic therapy.

METHODS

The Field Military Medical Unit (Korov, Vladmir Region, Russia) has 60 beds in the internal medicine department and is staffed by 3 physicians and 12 nurses. Patients with CAP are placed in this unit and are observed until they are ready to return to their duties. Gram stains, sputum cultures, serologic tests (as described below), complete blood cell counts (CBCs), and chest radiographs were available for all patients. The most common diagnosis for patients in this unit is CAP. Male patients aged 18–24 years were admitted to the study from a military training camp.

Definitions. CAP was defined as radiological evidence of an infiltrate and at least 1 of the following symptoms: fever (temperature, $\geqslant$37.5°C), new onset of cough, sputum production, dyspnea and/or tachypnea (breath rate, >20 breaths/min), pleuritic pain, and auscultatory findings, including rales and/or rhonchi consistent with pulmonary consolidation. Chest radiographs were initially examined by the admitting physicians, and the findings were subsequently confirmed independently by radiologists. The Pneumonia Severity Index (PSI) was used to classify the severity of illness [7]. Because blood urea nitrogen and arterial gas studies were not available, a score of 0 was entered for these parameters. A PSI of 40 was used to define pneumonia of mild severity, and a PSI of 70 was used to define pneumonia of moderate severity.

Study design. This was a prospective, open-labeled, controlled study. The urinary antigen test result for *S. pneumoniae* was used to classify treatment regimens into 2 groups (figure 1). If the test result was positive, 1000 mg of amoxicillin (Hiconcil; KRKA) was administered orally 3 times per day for 5–10 days. If the test result was negative, 500 mg of clarithromycin (Fromilid; KRKA) was administered orally 2 times per day for 5–10 days.

Patients were excluded from the study if they had a history of hypersensitivity to macrolides or penicillins, suspected aspiration pneumonia, or severe infection requiring parenteral therapy or if they had been hospitalized for >48 h before the onset of pneumonia or had previously received >1 dose of an antibiotic with in vitro activity against *S. pneumoniae.* Patients who met the inclusion criteria were given oral antibiotics for at least 5 days. Patients were evaluated at the time of enrollment in the study (visit 0) and after days 3–4 (visit 1), 10–12 (visit 2), 17–21 (visit 3), and 31–45 (visit 4) of treatment. Patients received oral hydration as needed; intravenous fluids were not given. This study was approved by the local institutional review board.

Microbiology. Urine samples were collected at visit 0 for detection of pneumococcal antigen by immunochromatography (BinaxNOW test; Binax). Expectorated sputum specimens were collected for Gram stain and bacteriological culture. Only samples that contained <10 squamous epithelial cells and >25 leukocytes per low-power field were considered to be acceptable for interpretation of the Gram stain [8]. Blood cultures were not performed. Blood samples were obtained for a solid-phase EIA (Thermobiolabsystems OY) for IgG and IgM for *Mycoplasma pneumoniae* and *Chalmydophila (Chlamydia) pneumoniae.* Serum samples were collected at visits 0, 3, and 4 and were stored at −70°C. In vitro susceptibility testing for *S. pneumoniae* was performed for penicillin, amoxicillin, erythromycin, clarithromycin, levofloxacin, trimethoprim-sulfamethoxazole (TMP-SMZ), and tetracycline with the broth microdilution method, in accordance with NCCLS criteria.

S. pneumoniae was determined to be the etiology of CAP on the basis of the following criteria: for a definitive diagnosis, a urinary antigen test positive for *S. pneumoniae* plus growth of *S. pneumoniae* on sputum culture and/or a sputum Gram stain revealing gram-positive diplococci; for a probable diagnosis, a positive urinary antigen test result or gram-positive diplococci on a sputum Gram stain plus *S. pneumoniae* growth on sputum culture; for a possible diagnosis, growth of *S. pneumoniae* on sputum culture or gram-positive diplococci on a sputum Gram stain; and for an unknown diagnosis, commensal flora isolated from respiratory tract cultures, light growth of multiple organisms on culture, or a Gram stain revealing the presence of multiple organisms.

M. pneumoniae and *C. pneumoniae* were designated as the etiology on the basis of the following serologic criteria: (1) a single elevated IgM titer of >1.1:1, or (2) seroconversion, as defined by an increase in the IgG titer of 1.3 or 1.5 for convalescent-phase serum samples when the titer of the acute-phase serum sample was $\geqslant$130 EIU or <130 EIU, respectively.

Analysis of efficacy. Efficacy or failure of treatment was assessed by the investigator in accordance with Infectious Diseases Society of America guidelines on clinical trials of antiinfective drugs (i.e., insufficient lessening of signs and symptoms of infection, such that additional or alternative antimicrobial therapy was required) [9]. Early treatment failures (at visits 1–2) were classified as failures at both visit 3 and visit 4, and treatment failures at visit 3 were also considered to be failures at visit 4. Efficacy was defined as resolution or improvement of acute signs and symptoms related to pneumonia,

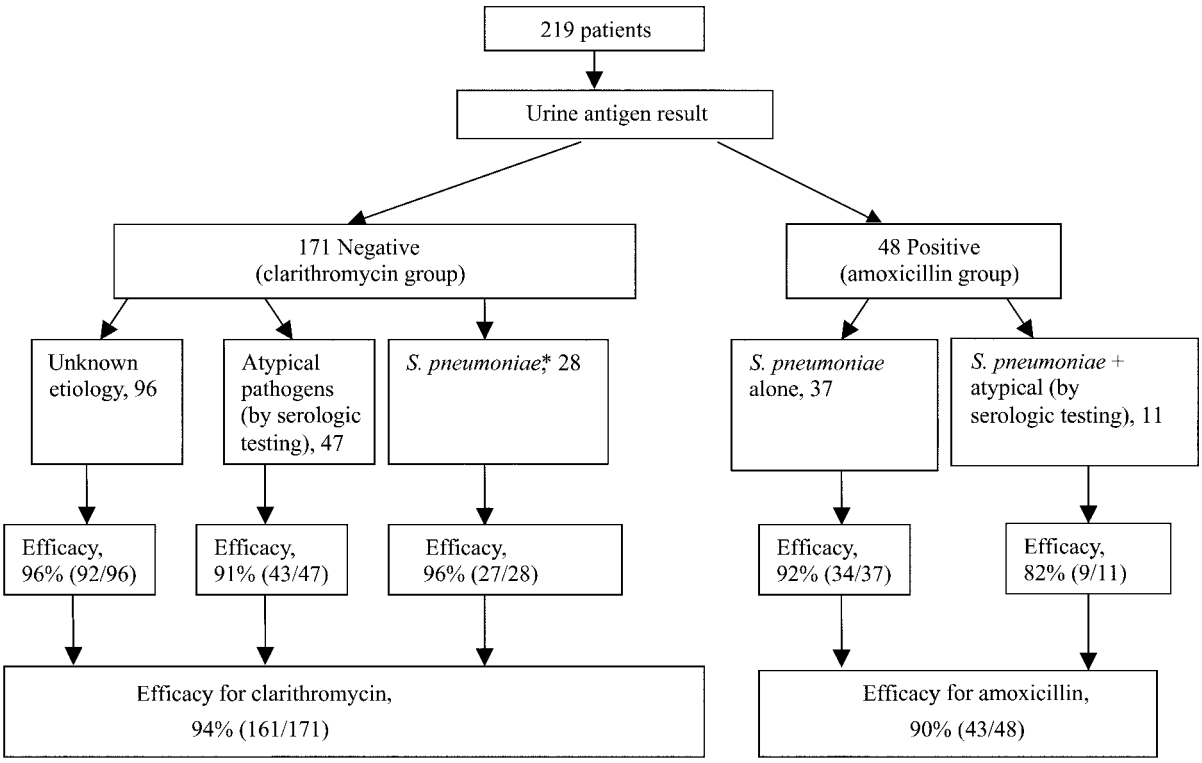

Figure 1. Efficacy of treatment, classified by antibiotic administered. *Of the 28 patients with negative urinary antigen test results, *Streptococcus pneumoniae* was diagnosed by sputum culture and/or Gram stain. Thirteen patients were coinfected with atypical pathogens, as determined by serologic testing; the efficacy rate for clarithromycin in this subgroup was 92% (12 of 13 patients) (table 5). The efficacy rate for *S. pneumoniae* alone was 100% (15 of 15 patients) table 5.

as well as a decrease or resolution of pulmonary infiltrates. Failure was defined as persistence or worsening of signs and symptoms of pneumonia after 72–96 h and/or appearance of new symptoms that required administration of new or additional antimicrobials, as well as infiltrates seen on chest radiographs progressing after 72–96 h or appearance of new infiltrates consistent with pneumonia.

Statistical analysis. Statistical analyses were performed with SAS software, version 8.2 (SAS Institute). The primary efficacy variable was the clinical response at visit 4 (i.e., the late follow-up visit). For comparison of ordered categories, Mantel-Haenszel correlation tests were used. For unordered categories, Fisher's exact test was used. Significance was defined as $P < .05$ on a 2-sided test.

RESULTS

Patients

A total of 220 patients were enrolled in the study. One patient was withdrawn from the study during the first 48 h because of a violation of inclusion criteria, leaving 219 patients evaluable for efficacy analyses. Patients had a significantly higher severity of pneumonia, as defined by the PSI, if the urinary antigen test result was positive ($P < .05$) (table 1). Patients were also significantly more likely to have signs of more-severe pneumonia, as assessed by symptoms, vital signs, and physical examination, if the urinary antigen test result was positive ($P < .05$) (table 2).

Etiology

Ninety-eight (44.7%) of the 219 patients provided sputum samples. Of these, 73 (75%) fulfilled the Murray-Washington Class V criteria [8]. In 37 (51%) of 73 cases, gram-positive diplococci were the predominant microorganisms on Gram stain. *S. pneumoniae* was classified as the etiology in 76 patients (35%) (tables 3 and 4). One hundred fifty-two patients underwent serologic testing for *C. pneumoniae* and *M. pneumoniae*. Atypical pathogens were classified as etiologic agents of pneumonia in 71 patients (32%); 47 (21%) of 219 patients were infected with *C. pneumoniae* and/or *M. pneumoniae,* and 24 (11%) were coinfected by an atypical pathogen plus *S. pneumoniae* (table 4).

Antibiotic Therapy

One hundred seventy-one (78%) of 219 patients received clarithromycin because they had urinary antigen tests that were negative for *S. pneumoniae,* and 48 (22%) received amoxicillin because they had positive urinary antigen test results (figure

Table 1. Demographic characteristics of 219 patients with non-severe community-acquired pneumonia.

Characteristic	Amoxicillin recipients (n = 48)	Clarithromycin recipients (n = 171)	P
Age, mean years ± SD	19.1 ± 1.5	19.0 ± 1.2	NS
Duration of disease before hospitalization, mean days ± SD	2.3 ± 1.7	3.4 ± 2.8	.005
Severity, no. (%) of patients			
Mild	22 (46)	122 (71)	…
Moderate	26 (54)	99 (58)	.005
No. (%) of cigarette smokers	19 (40)	82 (48)	NS

NOTE. Amoxicillin recipients had positive results of urinary antigen tests, and clarithromycin recipients had negative results of urinary antigen tests. NS, not significant.

1). The etiology for 28 patients receiving clarithromycin was *S. pneumoniae*, as defined by positive Gram stain and culture results but negative urinary antigen test results.

Antimicrobial susceptibility was determined for 24 *S. pneumoniae* isolates. All 24 isolates were susceptible to all but 2 antibacterial agents tested; 83% were resistant in vitro to TMP-SMZ, and 38% were resistant in vitro to tetracycline. All were susceptible to penicillins, cephalosporins, macrolides, and quinolones.

Efficacy of Therapy

Therapy was defined as efficacious for 161 (94%) of 171 patients who were treated with clarithromycin and for 43 (90%) of 48 who were treated with amoxicillin (P = not significant [NS]). All patients who were classified as having had treatment failure were ultimately successfully treated with other antibiotics for prolonged durations. No patients died in either treatment group.

Of the 48 patients in the pneumococcal pneumonia group with a positive urinary antigen test result, therapy was effective for 43 (90%). Twenty-eight patients with pneumococcal pneumonia who had negative urinary antigen test results but who received a diagnosis of *S. pneumoniae* pneumonia (on the basis of sputum culture and/or Gram stain) received clarithromycin, as per the study protocol; the efficacy rate was 96% (27 of 28 patients) (table 5 and figure 1). When this group was subclassified further by criteria for diagnosis of *S. pneumoniae* pneumonia, the efficacy rate was 100% (8 of 8 patients) for patients classified as having probable *S. pneumoniae* pneumonia and 95% (19 of 20) for those classified as having possible *S. pneumoniae* pneumonia. Eleven patients who had positive urine antigen test results but who had evidence of atypical infection (by serologic criteria) were treated with amoxicillin; the efficacy rate was 82% (9 of 11 patients) (table 5 and figure 1).

In the patients who had pneumonia due to atypical pathogens with no coinfection with *S. pneumoniae*, the efficacy rate for clarithromycin was 89% (36 of 38 patients); the rates were 67% (6 of 9) for *M. pneumoniae* alone, 100% (27 of 27) for *C. pneumoniae* alone, and 82% (9 of 11) for coinfection with both *C. pneumoniae* and *M. pneumoniae* (table 5). In the patients for whom the etiology was unknown, the rate of efficacy for clarithromycin was 96% (92 of 96 patients).

In 152 patients for whom both serologic tests for atypical pathogens and *S. pneumoniae* tests were performed (i.e., excluding patients for whom serologic tests were not performed), the efficacy rates were 92% (24 of 26) for amoxicillin and 94% (118 of 126) for clarithromycin.

Severity of illness. Patients who had positive urinary antigen test results (i.e., the amoxicillin group) had significantly more-severe disease than did patients with negative urinary antigen test results (i.e., the clarithromycin group; $P < .005$) (table 1). The efficacy rates for clarithromycin therapy for patients classified as having mild and moderate pneumonia (PSI of 40 and 70, respectively) were 96% (117 of 122 patients) and

Table 2. Clinical manifestations of 219 patients with pneumonia at the time of study entry.

Sign or symptom	Amoxicillin recipients (n = 48)	Clarithromycin recipients (n = 171)	P
Malaise	88	76	NS
Weakness	96	76	.002
Cough			
Mild	35	33	NS
Moderate	63	59	
Severe	2	6	
Pleuritic chest pain	85	79	NS
Dyspnea	52	39	NS[a]
Chills	79	73	.02
Temperature, °C			
Mean ± SD	38.8 ± 0.9	38.4 ± 1.0	NS
Median	38.9	38.2	
Range	6.9–41	36.6–41	
Pulse rate, mean beats/min ± SD	100.2 ± 17.1	88.8 ± 14.9	<.01
Systolic blood pressure, mean mm Hg ± SD	101.7 ± 11.8	108.2 ± 10.7	<.01
Rhonchi			
Dry	24	27	NS
Wet	58	49	NS
Diminished breath sounds	68	37	<.01
Egophony	46	19	<.01
Dullness on percussion	61	33	<.01
Sputum finding			
Mucous sputum	23	19	
Purulent sputum	58	60	NS
Hemoptyses	13	6	

NOTE. Data are percentage of subjects, unless otherwise indicated. NS, not significant.

[a] $P = .10$.

Table 3. Laboratory test results for 76 patients classified as having *Streptococcus pneumoniae* pneumonia.

Etiology, laboratory test results	No. (%) of patients
Definite *S. pneumoniae*	
All	16 (21)
Positive UAT, Gram stain, and culture results	10
Positive UAT and culture results	3
Positive UAT and Gram stain results	3
Probable *S. pneumoniae*	
All	40 (53)
Positive UAT results, negative Gram stain and culture results	32
Negative UAT results, positive Gram stain and culture results	8
Possible *S. pneumoniae*	
All	20 (26)
Negative UAT and culture results, positive Gram stain results	16
Negative UAT and Gram stain results, positive culture results	4

NOTE. *S. pneumoniae* was classified as the etiology for 28 patients (8 with probable and 20 with possible *S. pneumonia* pneumonia) on the basis of sputum Gram stain and culture results; however, results of the urinary antigen test (UAT) for *S. pneumoniae* were negative. These patients were allocated to the clarithromycin group.

90% (44 of 49), respectively. Similarly, the efficacy rates for amoxicillin for patients with mild and moderate pneumonia were 86% (19 of 22 patients) and 92% (24 of 36), respectively (P = NS). However, the PSI is not an ideal measurement of severity of illness; when the Curb65 score [10] and a modification of the Pitt bacteremia score [11] were used in place of the PSI score, the results were unchanged (i.e., patients with more-severe illness were in the positive urinary antigen test result group; data not shown).

Response of clinical manifestations. Fever resolved by day 3 in 41 (85%) of 48 patients in the amoxicillin group and in 153 (89%) of 171 patients in the clarithromycin group (P = NS). However, other clinical manifestations resolved more rapidly in patients who had negative urine antigen test results (figure 2); this difference was statistically significant for cough, sputum, and chills. Rhinitis resolved significantly more slowly among patients with negative urinary antigen test results than among those with positive results (data not shown).

DISCUSSION

S. pneumonia is not only the most common bacterial cause of CAP, but it is also the most frequent cause of CAP-related death. Both quinolone and macrolide resistance are now emerging for *S. pneumoniae*.

A urinary antigen test for *S. pneumoniae* is now commercially available. With the availability of this sensitive and presumably specific test, which is rapid (results are available within minutes), easy to perform, and inexpensive, the possibility of targeted antibiotic therapy for *S. pneumoniae* now exists. Therefore, we used this urinary antigen test as the key test for decision-making regarding the selection of antibiotic therapy for immunocompetent patients with nonsevere pneumonia. If the urinary antigen test was positive for *S. pneumoniae*, an oral β-lactam agent (amoxicillin) was administered. If the urinary antigen test result was negative, an oral macrolide (clarithromycin) was administered. The latter selection is consistent with consensus guidelines for empirical antibiotic therapy for CAP from both the American Thoracic Society [12] and the Infectious Diseases Society of America, and these guidelines are based, in part, on local susceptibility data [13].

The etiology of nonsevere CAP in the military trainees in our study was primarily *S. pneumoniae*, followed by atypical pathogens (table 4), which is similar to the results of other studies [8, 14–22]. Both clarithromycin and amoxicillin proved to be efficacious. The rates of efficacy were 94% (161 of 171 patients) for clarithromycin and 90% (43 of 48) for amoxicillin (P = NS). For the subgroup of 28 patients classified as having *S. pneumoniae* pneumonia who received clarithromycin, the rate of efficacy for clarithromycin was 96% (26 of 27 patients), which is similar to that for amoxicillin (43 [90%] of 48; P = NS) (table 5 and figure 1). Eleven patients with urinary antigen tests positive for *S. pneumoniae* had coinfection with atypical pathogens, as determined by serologic criteria; 9 (82%) of these 11 patients were cured with amoxicillin alone. Of all patients classified as having treatment failure, none died. All were successfully treated with antibiotics other than the study antibiotics for prolonged duration.

It should be noted that patients who were allocated to the amoxicillin group were more severely ill before antibiotic administration. Specifically, the severity of illness (as defined by

Table 4. Etiologies of community-acquired pneumonia (CAP) for 219 patients.

Pathogen	No. (%) of patients
Streptococcus pneumoniae	
All cases	76 (35)
S. pneumoniae alone	52
S. pneumoniae plus an atypical pathogen[a]	24
Atypical pathogens	
All cases	47 (21)
Chlamydia pneumoniae alone	27
Mycoplasma pneumoniae alone	9
C. pneumoniae and *M. pneumoniae*	11
Unknown	96 (44)

[a] Thirteen patients had CAP due to *S. pneumoniae* and *M. pneumoniae*, 6 had CAP due to *S. pneumoniae* and *C. pneumoniae*, and 5 had CAP due to *S. pneumoniae*, *M. pneumoniae*, and *C. pneumoniae*.

Table 5. Efficacy of antibiotic regimen, subclassified by etiologic agent, for 219 patients with community-acquired pneumonia.

Etiology	No. of patients cured by treatment/no. with etiology (%)	
	Amoxicillin recipients	Clarithromycin recipients
Streptococcus pneumoniae alone	34/37 (92)	15/15 (100)
S. pneumoniae and *Chlamydia pneumoniae*	2/3 (67)	2/3 (67)
S. pneumoniae and *Mycoplasma pneumoniae*	4/4 (100)	9/9 (100)
S. pneumoniae, M. pneumoniae, and *C. pneumoniae*	3/4 (75)	1/1 (100)
C. pneumoniae alone	NA	27/27 (100)
M. pneumoniae alone	NA	6/9 (67)
C. pneumoniae and *M. pneumoniae*	NA	9/11 (82)
No pathogen identified	NA	92/196 (96)
Total	43/48 (90)	161/171 (94)

NOTE. Twenty-eight patients with *S. pneumoniae* pneumonia were diagnosed by sputum culture plus Gram stain, with negative urine antigen test results; these were assigned to the clarithromycin group. NA, not applicable.

the PSI), abnormal vital signs, and abnormal lung findings at study admission occurred more frequently in the positive urinary antigen test result group (i.e., the amoxicillin group) (tables 1 and 2). No significant difference in treatment efficacy was seen when stratified by etiology (table 5) and severity of pneumonia.

Interestingly, studies from the 1920s to the 1990s showed that *S. pneumoniae* caused a majority of cases of CAP [23–26]. However, in more recent studies, *S. pneumoniae,* while remaining the most common etiology, has accounted for <50% of cases of CAP. One suggested reason for the decrease in the incidence of pneumococcal pneumonia and the increase in the incidence of pneumonia of uncertainty etiology is the lack of emphasis on Gram stains and on obtaining adequate sputum samples [27, 28]. This hypothesis is supported by a 1999 study of the lung aspirate specimens of 55 patients in whom no microbial cause could be identified by conventional microbiologic testing; *S. pneumoniae* was the most common etiology [29]. It is important to note that, in our study, the urine antigen test was the only diagnostic test positive for *S. pneumoniae* for 32 patients. Had this test not been available, these patients would have otherwise received diagnoses of pneumonia due to atypical pathogens or pneumonia of unknown etiology. According to current guidelines, these patients would have received broad-spectrum antibiotic therapy, such as therapy with a third-generation cephalosporin, a quinolone, or a macrolide. However, our study documented that these patients fared just as well receiving a penicillin.

Our study has a number of limitations. It was performed with military trainees who were young (mean age, 19 years) and were generally healthy, with no underlying diseases, so these results cannot necessarily be extrapolated to other populations. A second limitation was the application of serologic test results as the sole criterion for designation of atypical pathogens as etiologic agents for CAP; however, the only modalities currently available to the clinician are serologic tests. There is no gold standard for the diagnosis of *M. pneumoniae* or *C. pneumoniae* pneumonia, and thus, the specificity of serologic testing is uncertain [30]. Complete serologic testing data for *C. pneumoniae* and *M. pneumoniae* were evaluable only for 152 (69%) of 219 patients, because convalescent-phase serum samples were often not obtainable from soldiers discharged from the medical unit. A third limitation was that *Legionella* microbiology testing was not performed; however, the incidence of *Legionella* infection is very low for immunocompetent patients treated for "ambulatory" pneumonia [31]. A fourth limitation was that viral studies were not performed. Thus, the rate of CAP due to these pathogens was probably underestimated. Interestingly, *S. pneumoniae* has been found to be a major cause of pneumonia in children thought to have viral pneumonia [32]. A fifth limitation was that, for 96 (44%) of 219 patients, an etiology could not be determined. (This trend of observational studies of CAP in which the etiology cannot be determined is a focus of an insightful editorial that bemoans the decline in quality of microbiology [27].)

S. pneumoniae was uniformly active in vitro for the study antibiotics, clarithromycin and amoxicillin. No isolates were found to be resistant to penicillin, as defined by NCCLS criteria, but high-level in vitro resistance was seen for TMP-SMZ and tetracycline. These data are similar to those previously published in in vitro studies of *S. pneumoniae* isolated from Russian patients [33]. Thus, it may be claimed that our targeted approach may not be possible in geographic areas where high-level penicillin resistance exists for *S. pneumoniae.* We point

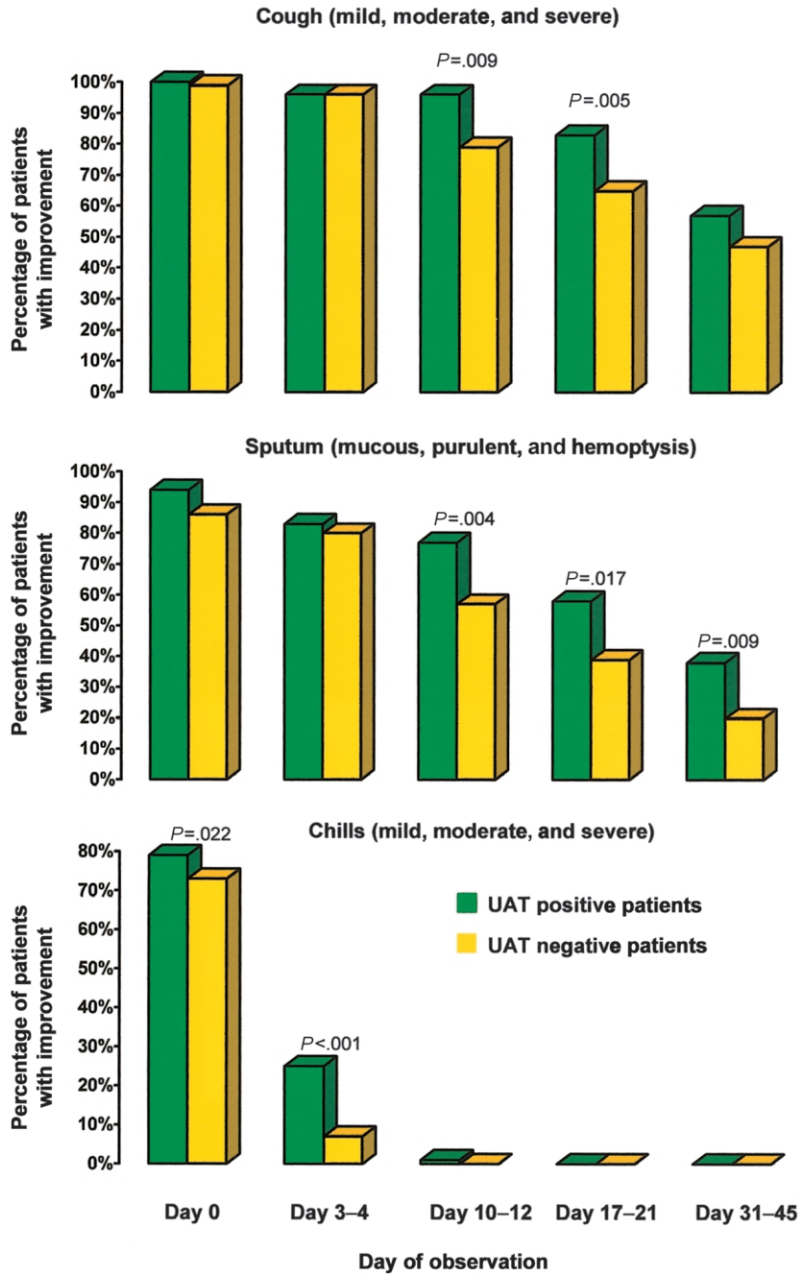

Figure 2. Rates of improvement of clinical manifestations of cough, sputum production, and chills. UAT, urinary antigen test.

out, however, that numerous studies have documented that penicillin resistance, as defined by NCCLS criteria, has little impact on clinical outcome, even when discordant antibiotic therapy is administered [34–37].

We found the routine application of urinary antigen for *S. pneumoniae* in patients with CAP to be useful in at least 2 ways:

1. The results of the urinary antigen test identified patients who were more severely ill (tables 1 and 2). Although the efficacy rate was similar for both urinary antigen–positive and urinary antigen–negative patients, the clinical response was slower for urinary antigen–positive patients (figure 2). Pneumococcal pneumonia is known to be more severe than pneumonia due to *C. pneumoniae* and *M. pneumoniae* and to have a notably higher mortality rate [25, 38]. Thus, the urinary antigen test can be used to identify patients who need more-extensive monitoring and follow-up.

2. Most importantly, the positive results of the urinary antigen test allowed us to administer targeted therapy with an antibiotic of the penicillin class (amoxicillin) rather than broader-spectrum antibiotic therapy (e.g., treatment with a quinolone or a macrolide). The cost of amoxicillin was notably

lower than that of clarithromycin. Thus, broad-spectrum agents, such as macrolides or quinolones, can be reserved for patients whose urinary antigen tests are negative for *S. pneumoniae*. Additional trials of this approach in other patient populations and other clinical settings are warranted.

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References

1. Guchev IA, Gray GC, Klochkov OI. Two regimens of azithromycin prophylaxis against community-acquired respiratory and skin/soft tissue infections among military trainees. Clin Infect Dis **2004**; 38: 1095–101.
2. Davidson M, Tempest B, Palmer DL. Bacteriologic diagnosis of acute pneumonia: comparison of sputum, transtracheal aspirates, and lung aspirates. JAMA **1976**; 235:158–63.
3. Yu VL, Rihs JD, Kellog JA, et al. Evaluation of the Binax urinary gram stain and sputum culture for *Streptococcus pneumoniae* in patients with community-acquired pneumonia [abstract 116]. In: Program and abstracts of the 38th Annual Meeting of the Infectious Diseases Society of America. Alexandria, VA: Infectious Diseases Society of America, **2000**:86.
4. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP, et al. Rapid urinary antigen test for diagnosis of community-acquired pneumococcal pneumonia in adults. Eur Respir J **2003**; 21:209–14.
5. Smith MD, Derrington P, Evans P, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW *Streptococcus pneumoniae* urine antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol **2003**; 41:2810–3.
6. Gutierrez F, Masia M, Rodriguez JC, et al. Evaluation of immunochromataographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis **2003**; 36:286–92.
7. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med **1997**; 336:243–50.
8. Lehtomaki K, Leinonen M, Takala A, Hovi T, Herva E, Koskela M. Etiological diagnosis of pneumonia in military conscripts by combined use of bacterial culture and serological methods. Eur J Clin Microbiol Infect Dis **1988**; 7:348–54.
9. Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS. Evaluation of new anti−infective drugs for the treatment of respiratory tract infections. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis **1992**; 15(Suppl 1):S62–88.
10. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax **2003**; 58:377–82.
11. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med **2004**; 140:26–32.
12. Niederman MS, Mandell MA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Resp Crit Care Med **2001**; 163:1730–54.
13. Mandell LA, Bartlett JG, Dowell SF, File TM, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis **2003**; 37:1405–33.
14. Musher DM, Groover JE, Reichler MR, et al. Emergence of antibody to capsular polysaccharides of *Streptococcus pneumoniae* during outbreaks of pneumonia: association with nasopharyngeal colonization. Clin Infect Dis **1997**; 24:441–6.
15. Crum NF, Wallace MR, Lamb CR, et al. Halting a pneumococcal pneumonia outbreak among United States Marine Corps trainees. Am J Prev Med **2003**; 25:107–11.
16. Vincent JM, Cherry JD, Nauschuetz WF, et al. Prolonged afebrile nonproductive cough illnesses in American soldiers in Korea: a serological search for causation. Clin Infect Dis **2000**; 30:534–50.
17. Csango PA, Haraldstad S, Pedersen JE, Jagars G, Foreland I. Respiratory tract infection to *Chlamydia pneumoniae* in military personnel. Scand J Infect Dis Suppl **1997**; 104:26–9.
18. Feikin DR, Moroney JF, Talkington DF, et al. An outbreak of acute respiratory disease caused by *Mycoplasma pneumoniae* and adenovirus at a federal service training academy: new implications from an old scenario. Clin Infect Dis **1999**; 29:1545–50.
19. Gray GC, Duffy LB, Paver RJ, Putnam SD, Reynolds RJ, Cassell GH. *Mycoplasma pneumoniae:* a frequent cause of pneumonia among US Marines in Southern California. Mil Med **1997**; 162:524–6.
20. Mohamed AR, Evans DA. The spectrum of pneumonia in 1983 at the Riyadh Armed Forces Hospital. J Infect **1987**; 14:31–7.
21. Eckman M-R, Grayston JT, Visakorpy R, et al. An epidemic of infections due to *Chlamydia pneumoniae* in military conscripts. Clin Infect Dis **1993**; 17:420–5.
22. Sanchez JL, Craig SC, Kolavic S, et al. An outbreak of pneumococcal pneumonia among military personnel prophylaxis. Mil Med **2003**; 168: 1–6.
23. Fekety FR, Caldwell J, Gump D. Bacteria, viruses and mycoplasmas in acute pneumonia in adults. Am Rev Respir Dis **1971**; 104:499–507.
24. Vergis EN, Yu VL. New directions for future studies of community-acquired pneumonia optimising impact on patient care. Eur J Clin Microbiol Infect Dis **1999**; 18:847–51.
25. Ramirez JA, Borden J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae.* Arch Intern Med **2001**; 161:848–50.
26. Larsen NP, Cecil RL. Clinical and bacteriologic study of lobar pneumonia. JAMA **1922**; 79:343–9.
27. Bartlett JG. Decline in microbial studies for patients with pulmonary infections. Clin Infect Dis **2004**; 39:170–2.
28. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clin Infect Dis **2004**; 39: 165–9.
29. Ruiz-Gonzalez A, Falguera M, Nogues N, et al. Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology: a microbiologic study of lung aspirates in consecutive patients with community acquired pneumonia. Am J Med **1999**; 106:385–90.
30. File TM, Bartlett JG, Cassell GH, et al. The importance of *Chlamydia pneumoniae* as a pathogen: the 1996 consensus conference of *Chlamydia pneumoniae* infection. Infect Dis Clin Pract **1997**; 6(Suppl 2): S28–31.
31. Marrie TJ, Peeling RW, Fine MJ, Singer DE, Coley CM, Kapoor WN. Ambulataory patients with community-acquired pneumonia; the frequency of atypical agents and clinical course. Am J Med **1996**; 101: 508–15.
32. Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-

associated pneumonia. The Vaccine Trialist Group. Nat Med **2004**; 10: 811–3.
33. Kozlov RS, Bogdanovitch TM, Applebaum PC, et al. Antistreptococcal activity of telithromycin compared with several other drugs in relation to macrolide resistance mechanisms in Russia. Antimicrob Agents Chemother **2002**; 46:2695–8.
34. Yu VL, Chiou CC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis **2003**; 37: 230–7.
35. Aspa J, Rajas O, Rodriguez de Castro F, et al. Drug-resistant pneumococcal pneumonia: clinical relevance and related factors. Clin Infect Dis **2004**; 38:787–98.
36. Song JH, Jung SI, Ki HK, et al. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. Clin Infect Dis **2004**; 38:1570–8.
37. File TM, Lode H, Kurz H, Kozak R, Xie H, Berkowitz E. Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin (2000/125 milligrams) vs. those of amoxicillin-clavulanate (875/125 milligrams) both given twice daily for 7 days in treatment of bacterial community-acquired pneumonia in adults. Antimicrob Agents Chemother **2004**; 48:3323–31.
38. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. Medicine **1990**; 69:307–16.