# Clinical Factors Associated with Negative Urinary Antigen Tests Implemented for the Diagnosis of Community-Acquired Pneumococcal Pneumonia in Adult Patients

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## Abstract

*Objective:* This study investigated clinical factors associated with negative urinary antigen tests (UAT) implemented for the diagnosis of pneumococcal community-acquired pneumonia (CAP) in adult patients. *Subjects and Methods:* We reviewed the medical records of 755 adult patients who completed the UAT in our hospital between 2009 and 2012. Of these, we evaluated 63 patients with bacteriologically confirmed definite pneumococcal CAP (33 were UAT-positive, and 30 were UAT-negative). *Results:* There was no significant difference between the UAT-positive and the UAT-negative patients regarding age, dehydration, respiratory failure, orientation, blood pressure (ADROP) score (the CAP severity score proposed by the Japanese Respiratory Society), gender, white blood cell counts, liver/kidney function tests, or urinalysis. However, serum C-reactive protein (CRP) concentrations were 31% lower in the UAT-negative patients than in the UAT-positive patients (p = 0.02). Furthermore, the prothrombin time-international normalized ratio was 50% higher in the UAT-negative patients than in the UAT-positive patients, although the difference did not reach statistical significance (p = 0.06). The prevalence of comorbidities was similar in both UAT-positive and UAT-negative patients. However, warfarin had been prescribed in 8 (27%) of the UAT-negative patients compared to only 1 (3%) of the UAT-positive patients (odds ratio = 11.6; p = 0.01). *Conclusions:* These results suggested that low serum CRP concentrations and the use of warfarin increased the possibility with which false-negative UAT results occurred in these patients with pneumococcal CAP.

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## Introduction

Community-acquired pneumonia (CAP) is highly prevalent and a major cause of death throughout the world. *Streptococcus pneumoniae*, the most common pathogenic microorganism, accounts for approximately 30% of the causative bacteria in CAP [1]. Due to the widespread use of rapid urine tests for the diagnosis of pneumococcal CAP and the publication of guidelines [2, 3] for CAP treatment with high-dose penicillin, the treatment

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outcomes for CAP has greatly improved. Because of its high sensitivity (77–87%) and specificity (97–100%) [1, 4], the Binax NOW® (Alere, Waltham, Mass., USA) *S. pneumoniae* urinary antigen test (UAT), a simple rapid immunochromatographic test that detects the C-polysaccharide antigen in urine, is widely used in the medical diagnosis of CAP [5]. Compared to conventional microbiologic tests, the Binax UAT detected CAP in an additional 11.4% of patients [6]. CAP of initially unknown cause, as diagnosed with conventional microbiologic tests, has been attributable to *S. pneumoniae* in up to 57% of the cases after the introduction of the UAT [7]. Hence, a number of studies and guidelines have suggested the usefulness of the UAT as a powerful tool for the diagnosis of pneumococcal CAP [4].

In routine clinical practice, however, we often encounter puzzling cases of CAP where *S. pneumoniae* was ultimately judged to be a causative bacterium based on microbiologic examinations, while the UAT result was negative [8]. The presence of such false-negative results imposes a significant limitation on the UAT that compromises its clinical usefulness as a diagnostic tool for CAP [9]. However, the factors that affect the sensitivity of UAT are largely unknown. In the present study, we reviewed the clinical records of patients with pneumococcal pneumonia to identify factors associated with decreased sensitivity of the UAT.

### Subjects and Methods

*Study Population and Protocol*

This retrospective study included patients aged 18 years or older who had undergone the UAT in the Emergency Room or at the Outpatient Clinic of the Tokai University Hachioji Hospital, a 500-bed city teaching hospital serving a population of approximately 560,000 in southwest Tokyo, Japan, from September 2009 to September 2012. This study was conducted in compliance with the requirements and under the authorization of the Tokai University Institutional Review Board (Certification No: 13R-158). The Binax NOW *S. pneumoniae* UAT was performed in 755 patients with suspected pneumonia in the Emergency and Outpatient Departments. It was performed according to the instruction manual attached to the test kit. A total of 683 patients had negative, and 72 patients had positive results. Pneumococci were detected in sputum and/or other biological samples (see below) in 88 patients. A total of 63 of the 88 patients were analyzed, excluding 25 who did not have CAP.

Microbiologic evaluation was performed as described previously [9]. The UAT and various laboratory cultures were also performed simultaneously. Inclusion criteria for the assessment of pathogenic *S. pneumoniae* infection were: detection of Gram-positive diplococci in sputum samples containing ≤10 epithelial cells and ≥25 polymorphonuclear leukocytes per low-power field; iso-lation of ≥$10^7$ colony-forming units/ml *S. pneumoniae* in sputum culture, or the isolation of *S. pneumoniae* in any cultures of blood (two sets), pleural effusion or spinal fluid. Failure to satisfy the assessment criteria resulted in the exclusion from the study. According to the Japanese Respiratory Society's (JRS) diagnostic criteria [2], CAP was defined as an acute illness acquired in the community with the presence of new lung infiltration on a chest X-ray and with at least two of the following criteria: fever, cough, or purulent sputum. Diagnosis of definite pneumococcal CAP (DPnCAP) was made when patients satisfied both criteria for pathogenic *S. pneumoniae* infection and the criteria for CAP. Exclusion criteria were patients with any of the following: previously treated with antibiotics before admission, transferred to another hospital or received inpatient care at another hospital within 3 weeks, received pneumococcal vaccination within 5 days, had other acute conditions such as pulmonary edema, pulmonary embolism and malignancy during follow-up, had severe immunocompromised status with severe neutropenia [peripheral white blood cell (WBC) count <1,000/μl], postorgan/bone marrow transplant, or had a HIV infection.

The susceptibility of penicillin to *S. pneumoniae* was determined using the Clinical and Laboratory Standards Institute (CLSI) penicillin breakpoints M100-S18 [10] (susceptible, ≤2 μg/ml, penicillin-susceptible *S. pneumoniae*; intermediate, 4 μg/ml, penicillin-intermediate *S. pneumoniae*; resistant, ≥8 μg/ml, penicillin-resistant *S. pneumoniae*).

The urine tests were qualitative analyses and expressed a score of 0–3. The details of the standard score of the urine tests were as follows: urinary protein qualitative, 0: <30 mg/dl, 1: 30 to <100 mg/dl, 2: 100 to <300 mg/dl, and 3: >300 mg/dl; urinary sugar qualitative, 0: <100 mg/dl, 1: 100 to <250 mg/dl, 2: 250 to <500 mg/dl, and 3: >500 mg/dl; urinary occult qualitative, 0: <0.06 mg/dl hemoglobin, 1: 0.06 to <0.135 mg/dl hemoglobin, 2: 0.135 to <0.405mg/dl hemoglobin, and 3: >0.405 mg/dl hemoglobin.

*Statistical Considerations*

All statistical analyses were performed with Stat Mate IV (ATMS Co., Ltd., Tokyo, Japan). A descriptive analysis was performed for the demographic and clinical characteristics, and results are presented as means ± standard deviations for quantitative variables and numbers (percentages) for qualitative variables. For comparisons, the Mann-Whitney U test was performed for continuous variables which did not have parametric distributions, and Fisher's exact test was used for categorical variables. All p values were two-sided and considered statistically significant when they were ≤0.05.

### Results

The final analysis included 63 patients with DPnCAP, of whom 33 were UAT-positive and 30 UAT-negative. One of the 5 blood culture-positive cases had positive results in spinal fluid culture, and it was diagnosed as pneumococcal meningitis without CAP. Finally, this case was excluded from the CAP cases of this study (table 1).

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**Table 1.** Details of the UAT in 755 patients

| UAT | Total (n = 755) | Positive (n = 72) | | | | | Negative (n = 683) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | S | N | B | P-E | C-F | S | N | B | P-E | C-F |
| Culture *S. pneumoniae* detection | 88 | 33 | 7 | 5 | 1 | 2 | 31 | 8 | 3 | 0 | 1 |
| Definite pneumococcal CAP | 63 | 29 | 0 | 4 | 1 | 1 | 26 | 0 | 3 | 0 | 1 |

S = Sputum; N = nasal secretion; B = blood; P-E = pleural effusion; C-F = cerebrospinal fluid.

### Resistant/Coexisting Bacteria

The distribution of coexisting pathogens in patients with DPnCAP is shown in table 2. Of the 63 patients with DPnCAP, 17 (27.0%) had a polymicrobial infection; *Staphylococcus aureus* was detected in 5 patients, *Moraxella catarrhalis* in 4 patients, *Klebsiella pneumoniae* in 2 patients, and 7 patients had other infections. However, there was no significant difference in the distribution of coexisting pathogens between the UAT-positive and the UAT-negative patients with DPnCAP. Penicillin-resistant *S. pneumoniae* (at least penicillin intermediate resistant *S. pneumoniae*) was isolated from 17 (27.0%) patients of the 63 patients with DpnCAP, without any significant difference noted between the UAT-positive (9; 27.3%) and the UAT-negative group (8; 26.7%).

### Sex, Age, Severities, and Laboratory Tests

Of the 63 patients with DPnCAP, 42 (%) were male and 21 (%) were female (table 3). The mean age was 64.7 years. There was no significant difference between the UAT-positive and the UAT-negative groups with respect to age, dehydration, respiratory failure, orientation, blood pressure (ADROP score; the CAP severity score proposed by the JRS), gender, blood WBC counts, liver/kidney function tests, or urinalysis (table 3). However, the serum C-reactive protein (CRP) concentration was 31% lower in the UAT-negative patients than in the UAT-positive patients ($p = 0.02$). In contrast, the prothrombin time-international normalized ratio was 50% higher in the UAT-negative patients than in the UAT-positive patients although the difference did not reach statistical significance ($p = 0.06$).

### Initial Antibiotics

A penicillin/β-lactamase inhibitor combination was used in 22 (66.7%) of the 33 UAT-positive patients (66.7%) and in 13 (43%) of the UAT-negative patients (43%). The difference was not statistically different ($p = $

**Table 2.** Distribution of mixed pathogens in patients with definite pneumococcal CAP stratified by the *S. pneumoniae* UAT

| Definite pneumococcal CAP | Total (n = 63) | UAT | |
|---|---|---|---|
| | | positive (n = 33) | negative (n = 30) |
| *S. pneumoniae* alone | 4 (73.0) | 25 (75.8) | 21 (70.0) |
| PSSP:PI-RSP | 46:17 (27.0) | 24:9 (27.3) | 22:8 (26.7) |
| *Haemophilus influenzae* | 1 | 2 | 0 |
| *Klebsiella pneumoniae* | 2 | 0 | 2 |
| *Mycobacterium avium* | 1 | 0 | 1 |
| *Moraxella catarrhalis* | 4 | 3 | 1 |
| *Mycoplasma pneumoniae* | 1 | 1 | 0 |
| *Pseudomonas aeruginosa* | 1 | 0 | 1 |
| *Staphylococcus agalactiae* | 1 | 1 | 0 |
| *Staphylococcus aureus* | 5 | 2 | 3 |
| *Staphylococcus pyogenes* | 1 | 0 | 1 |
| *Haemophilus influenzae* + *Staphylococcus aureus* | 1 | 1 | 0 |
| Influenza virus A | 1 | 0 | 1 |

Figures in parentheses are percentages. PSSP = Penicillin-susceptible *S. pneumoniae*; PI-RSP = penicillin-intermediate or -resistant *S. pneumoniae*.

0.08). Cephem antibiotics were used in 9 (27.3%) UAT-positive patients and in 12 (40.0%) UAT-negative patients. Carbapenem antibiotics were used in 2 (6.1%) UAT-positive patients and in 4 (13.3%) UAT-negative patients.

### Underlying Diseases and Treatment

Of the 63 patients, 51 (81%) with DPnCAP had at least one comorbidity (table 4). The most common underlying disease was cardiovascular disease (11; 17.5%) and diabetes mellitus (11; 17.5%), followed by cerebrovascular disease (8; 12.5%), hypertension (8; 12.5%), liver disease (6;

**Table 3.** The comparison of background factors in positive and negative patients with definite pneumococcal CAP

| Definite pneumococcal CAP | Total (n = 63) | UAT | | p value |
|---|---|---|---|---|
| | | positive (n = 33) | negative (n = 30) | |
| Gender, male/female | 42/21 | 21/12 | 21/9 | |
| PSSP:PI-RSP | 46:17 (27.0) | 24:9 (27.3) | 22:8 (26.7) | |
| Age, years | 64.7±16.4 | 65.1 ± 13.8 | 64.1 ± 19.3 | – |
| ADROP score | 1.0±0.91 | 0.91 ± 0.84 | 1.1 ± 0.95 | – |
| 0 | 21 | 12 | 9 | |
| 1 | 24 | 12 | 12 | |
| 2 | 13 | 7 | 6 | |
| 3 | 5 | 2 | 3 | |
| 4 – 5 | 0 | 0 | 0 | |
| WBC, $10^3/\mu l$ | 12,922±5,540 | 13,003±5,406 | 12,833±5,775 | – |
| CRP, mg/dl | 16.8±10.6 | 19.7±9.8 | 13.5±10.9 | 0.02* |
| Cr, mg/dl | 0.96±0.5 | 0.86±0.40 | 1.07±0.58 | 0.09 |
| AST, IU/l | 34.1±29.0 | 31.5±29.9 | 36.9±28.3 | – |
| ALT, IU/l | 29.3±27.3 | 28.2±29.9 | 30.5±24.5 | 0.13 |
| LDH, IU/l | 253±161 | 224±70 | 284±217 | 0.18 |
| INR | 1.55±0.84 | 1.21±0.16 | 1.81±1.06 | 0.06 |
| Urine-specific gravity | 1.019±0.007 | 1.018±0.008 | 1.020±0.006 | – |
| Urine pH | 6.14±0.85 | 6.25±0.89 | 5.94±0.76 | – |
| Urine protein qualitative, score | 0.90±0.94 | 0.98±1.0 | 0.78±0.86 | – |
| Urine sugar qualitative, score | 0.6±1.33 | 0.79±1.54 | 0.28±0.83 | 0.18 |
| Urine occult qualitative, score | 0.95±1.18 | 0.91±1.15 | 1.0±1.27 | – |

Figures in parentheses are percentages. p > 0.2 shown with –. PSSP = Penicillin-susceptible *S. pneumoniae*; PI-RSP = penicillin-intermediate or -resistant *S. pneumoniae*; Cr = creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; INR = prothrombin time-international normalized ratio. * p < 0.05 for the comparison between UAT-positive and negative patients.

**Table 4.** Comorbidity characteristics of patients with definite pneumococcal CAP

| Definite pneumococcal CAP | Total (n = 63) | UAT | |
|---|---|---|---|
| | | positive (n = 33) | negative (n = 30) |
| Underlying disease | 51 (81) | 27 (81.8) | 24 (80) |
| Bronchial asthma | 4 (6.3) | 2 (6.1) | 2 (6.7) |
| Cardiovascular disease | 11 (17.5) | 4 (12.1) | 7 (23.3) |
| Cerebrovascular disease | 8 (12.7) | 3 (9.1) | 4 (13.3) |
| Collagen disease | 3 (4.8) | 2 (6.1) | 1 (3.3) |
| COPD | 4 (6.3) | 3 (9.1) | 1 (3.3) |
| Diabetes mellitus | 11 (17.5) | 7 (21.2) | 4 (13.3) |
| Hypertension | 8 (12.7) | 4 (12.1) | 4 (13.3) |
| Liver disease | 6 (9.5) | 3 (9.1) | 3 (10) |
| Malignant disease | 3 (4.8) | 1 (3) | 2 (6.7) |
| Pulmonary fibrosis | 4 (6.3) | 3 (9.1) | 1 (3.3) |
| Renal disorder | 2 (3.2) | 1 (3) | 1 (3.3) |
| Other disease | 5 (7.9) | 2 (6.1) | 3 (10) |

Figures in parentheses indicate percentages.

**Table 5.** Treatment of underlying diseases

| Medicine | UAT | |
|---|---|---|
| | positive (n = 33) | negative (n = 30) |
| Antihypertensive agents | 4 | 5 |
| Antiulcer agents | 5 | 4 |
| ICS + LABA | 3 | 2 |
| Oral corticosteroid | 4 | 2 |
| Antidiabetic agents | 7 | 4 |
| Anticoagulants | 2 | 4 |
| Warfarin* | 1 | 8 |
| Hepatoprotective agents | 2 | 2 |
| Others | 2 | 1 |
| No medication | 6 | 6 |

ICS = Inhaled corticosteroid; LABA = long-acting β-agonist. * A significant p value (0.01) for the comparison between UAT-positive and negative patients.

9.5%), bronchial asthma (4; 6.3%), COPD (4; 6.3%) and pulmonary fibrosis (4; 6.3%). There was no significant difference in the prevalence of comorbidities between the UAT-positive and the UAT-negative groups. However, warfarin had been prescribed in 8 (26.7%) UAT-negative patients when compared to only 1 (3.0%) UAT-positive patient (odds ratio = 11.6; p = 0.01), while the prescription of antiplatelets, antihypertensives, antidiabetics, and antiulcer drugs as well as of corticosteroids, bronchodilators, and hepatoprotective drugs were similar in the two groups of patients (table 5).

## Discussion

In this study, the false-negative UAT was associated with lower serum CRP concentrations (p = 0.02) and a greater use rate of warfarin (p = 0.01). The prothrombin time-international normalized ratio was 50% higher in the UAT-negative patients than in the UAT-positive patients although the difference was not statistically significant (p = 0.06). In contrast, the positive or negative rate of UAT was not influenced by age, sex, severity of pneumonia, the presence of penicillin-resistant S. pneumoniae or coexisting bacteria, nor was it influenced by WBC counts, or liver and kidney function tests. These findings suggest that an insufficient increase in CRP concentrations and the current use of warfarin reduced the sensitivity of the UAT as a diagnostic tool for pneumococcal CAP.

The clinical usefulness of the UAT is often compromised by the false-negative result that confuses clinical decisions to select antibiotics. In our study, the false-negative rate of UAT was 47.6% patients with DPnCAP, which is comparable to or somewhat higher than the previously reported value of 19–38% [8, 9, 11]. Bacterial colonization in the airway is known to be a possible cause of negative UAT in patients with a positive sputum culture of S. pneumoniae [6]. To avoid a bias that may result from bacterial colonization, our study included only DPnCAP patients who satisfied the established diagnostic criteria for both CAP and pathologenic S. pneumoniae infection.

In this study, two interesting features that were associated with the false-negative UAT were identified. The first false-negative UAT was associated with lower serum CRP concentrations when compared with positive UAT cases. A probable explanation of this association was that a bacterial load might have been lower in the false-negative UAT patients than in the positive UAT patients. However, this explanation is not supported given that the severity of pneumonia, as determined by the ADROP score, was similar between the two groups of patients. An alternative explanation involved a possible interaction between C-polysaccharide in the pneumococcal capsule [pneumococcal C-polysaccharide (PnC)] and CRP. CRP had been shown to bind with phosphorylcholine residues in PnC, thereby serving as a carrier protein that allows the PnC to circulate in the blood and to be efficiently excreted in urine [12–14]. Because UAT detects the PnC excreted in urine, if serum CRP levels are insufficiently increased, the amount of PnC excreted in urine would be decreased, potentially leading to the false-negative UAT. The second false-negative UAT was also associated with the current use of warfarin. DPnCAP patients treated with warfarin for underlying cerebro- and cardiovascular diseases were 11.6 times more likely to have an opportunity to yield a negative UAT result. In contrast, the positive or negative rate of UAT was not influenced by the prevalence of cerebro- and cardiovascular diseases per se, or by the use of antiplatelets and other medications (table 5). These findings suggest that the use of warfarin may mechanistically be linked to the false-negative result of UAT. However, the reason for the association between the warfarin usage and the negative UAT is currently unclear. We speculate that as one probability, warfarin might have controlled the binding of PnC and CRP through anticoagulation factors and ionic channels thereby leading to both insufficient CRP concentration and internal warfarin that probably produced the false-negative UAT.

The present study has several limitations. First, this is a retrospective study, so some of the sampling biases could have confounded the results. Second, the UAT was implemented only once when patients visited the emergency room or the outpatient clinic. Later timing of the urine sampling (for example, on the day after admission) could have increased the sensitivity of the UAT.

Three cases which had positive blood cultures were UAT-negative in this study. Two of 3 cases which were UAT-negative had received anticoagulation therapy (one of them had taken warfarin). Furthermore, the CRP concentrations of these 2 cases were lower than that of UAT-positive cases. In the last case, which was UAT-negative, there was no influence of medicine, and a high concentration of CRP was observed (25.7 mg/dl). In this case, no reason for the negative UAT results could be found. As described above, the UAT may have shown positive results when checking on the following day.

Finally, as for the selection of the initial antibacterial agent, there was no significant difference to penicillin se-

lection of initial antibacterial agent between the positive UAT group and the negative group (p = 0.08). However, the negative UAT patients who were diagnosed with the complication of atypical pneumonia were treated with the combined therapy of β-lactam antibacterial agent and macrolide. The information of negative UAT might have affected the decision of clinicians to diagnose the complication of atypical pneumonia. In the region where the ratio of the atypical pneumonia especially in CAP is high [15], these results suggested that information from later UAT is valuable for clinical decision-making because empiric antibiotic prescriptions would have already been started.

## Conclusions

The present study suggested that an insufficient increase in CRP concentrations and the current use of warfarin are factors associated with negative UAT results implemented for the diagnosis of CAP in adult patients. While further research needs to be conducted to confirm these results, physicians should make a clinical diagnosis of pneumococcal or nonpneumococcal pneumonia while keeping in mind that patients with relatively low CRP values and those receiving warfarin are prone to be associated with the false-negative UAT results.

## Disclosure Statement

The authors declare that there is no conflict of interest.

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