J Microbiol Immunol Infect.
2008;41:41-47

Original Article

Clinical application of the rapid pneumococcal urinary antigen test in the treatment of severe pneumonia in children

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Received: May 8, 2006 Revised: July 20, 2006 Accepted: August 30, 2006

Background and Purpose: To evaluate the efficacy of the pneumococcal urinary antigen test (PUAT) in severe pediatric pneumonia.

Methods: The study enrolled 245 pediatric patients with severe pneumonia. Patients were divided into four groups; groups 1 and 2 received PUAT, while groups 3 and 4 did not. Additionally, PUAT-positive group 1 patients were treated with penicillin, while PUAT-negative patients received ampicillin-sulbactam or cefuroxime. Group 2 patients were treated empirically without following the group 1 protocol. Group 3 patients were treated following the guideline of the Infectious Diseases Society of Taiwan (IDST), and group 4 patients were treated empirically without following the IDST guideline. Treatment was assessed by the duration of fever.

Results: Treatment was most effective for group 1 and least effective for group 4. Group 2 treatment was superior to group 3 treatment. Multivariate regression analysis of groups 1 and 2 revealed that the use of PUAT (groups 1 and 2) was associated with superior response in comparison with group 4.

Conclusion: Application of PUAT and adequate antimicrobial treatments in the initial stage for pediatric patients with severe pneumonia resulted in improved outcome as assessed by shortening of the duration of fever.

Key words: Antigens, bacterial; Child; Pneumonia, pneumococcal; Predictive value of tests; *Streptococcus pneumoniae*

Introduction

Streptococcus pneumoniae pneumonia is an important cause of morbidity and mortality in children. This form of pneumonia can occur during all seasons, but is most prevalent during the winter and spring months [1]. *S. pneumoniae*-derived pneumonia occurs at any age, but especially in the very young and elderly, and is the most common community-acquired bacterial pneumonia [2]. The choice of initial therapy in children is important, but is usually empirically guided by knowledge of the likely bacterial pathogens in this age group, since examination of sputum or tracheal aspirate is usually uncomfortable and inconvenient in patients younger than school age [1].

In Taiwan, some physicians follow the guideline of therapy of pneumonia in pediatrics from the Infectious Diseases Society of Taiwan (IDST). According to the guideline, broader spectrum antimicrobials such as the second- or third-generation cephalosporins, amoxicillin-clavulanate and ampicillin-sulbactam are recommended for pneumonia in children younger than five years old for the treatment of *S. pneumoniae*, as well as the pathogens that commonly produce beta-lactamase, including *Haemophilus influenzae* and *Moraxella catarrhalis* [3]. However, *S. pneumonia*e, which is not a beta-lactamase-producing pathogen, remains the leading cause of pneumonia in children less than five years old. Thus, the use of the more expensive beta-lactamase inhibitor antimicrobials may

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not be warranted [4-6]. Because of the high incidence of pneumococcal infection, penicillin G is recommended as the first-choice antimicrobial in the IDST guidelines for pneumonia in children older than five years old, with the aforementioned cephalosporins recommended as alternative regimens. Nevertheless, penicillin G is unsatisfactory for the treatment of beta-lactamase-producing pathogens such as *H. influenzae* and *M. catarrhalis,* that are also often found in children older than five years of age. As a result, when beta-lactamase-producing pathogens are encountered in the clinical setting, penicillin G therapy often needs to be substituted by broader spectrum antimicrobials after some days of hospitalization when treatment has been unsatisfactory, thus prolonging hospitalization and increasing the cost of treatment.

To improve the detection of the causative pathogen, reduce the duration of hospitalization, and lower the cost of medication in the treatment of pneumonia in children, we studied the use of the pneumococcal urinary antigen test (PUAT) as a tool for the early detection of *S. pneumoniae* in children with severe pneumonia. In addition, to better understand the clinical efficacy of PUAT in severe pneumonia of children, the present study compared the effect of PUAT on treatment responses (assessed as the duration of fever).

Methods

Pediatric patients less than 18 years old with severe pneumonia who were admitted to Kaohsiung Veterans General Hospital (VGHKS) from January 1 to December 31, 2004 were enrolled in this study. VGHKS is a 1389-bed teaching hospital in southern Taiwan, which provides both primary and tertiary medical care to an average of 6500 patients each year.

The baseline characteristic and demographic data such as age, gender, laboratory tests and chest X-ray (CXR) severity are shown in Table 1. Severe pneumonia was defined as the presentation of a cough and fever, and agreement with the enrolled criteria of severe pneumonia in CXRs. CXR findings were systematically reviewed with consensus of a pediatrician and a thoracic radiologist. The findings were classified into five grades [2,7], as summarized in Table 2. The enrolled criteria of severe pneumonia included cases of grade four or five in this CXR classification scheme, which acted to exclude less severe pneumonia cases from the study.

Patients not receiving a CXR, who were treated using macrolide alone or in whom fever was absent, were excluded from study. Medical records of the remaining cases were collected on a standardized form

Table 1. Baseline characteristics of the four groups of pediatric patients with severe pneumonia

Variable	Group 1 No. (%)	Group 2 No. (%)	Group 3 No. (%)	Group 4 No. (%)	*p*
Age (years)					
<5	105 (80.8)	28 (66.7)	21 (67.7)	40 (95.2)	<0.05
>5	25 (19.2)	14 (33.3)	10 (32.3)	2 (4.8)	
Mean (median)	4.0 (4.0)	6.5 (4.0)	4.8 (2.0)	2.5 (1.0)	<0.05
Gender					
Male	70 (53.8)	19 (45.2)	15 (48.4)	20 (47.6)	0.75
Female	60 (46.2)	23 (54.8)	16 (51.6)	22 (52.4)	
White blood cell count					
5000-15,000	79 (60.8)	22 (52.4)	15 (48.4)	28 (66.7)	0.28
<5000, >15000	51 (39.2)	20 (47.6)	16 (51.6)	14 (33.3)	
Mean (median) [/mL]	12,573 (10,770)	14,855 (12,810)	13,131 (12,500)	12,052 (10,970)	0.31
C-reactive protein					
<10	70.8	73.8	96.8	90.5	<0.05
>10	29.2	26.2	3.2	9.5	
Mean (median) [mg/dL]	10.9 (4.5)	9.7 (7.2)	3.3 (1.8)	4.4 (1.2)	<0.05
Band form of WBC					
<5%	101 (77.7)	31 (73.8)	24 (77.4)	35 (83.3)	0.77
>5%	29 (22.3)	9 (26.2)	7 (22.6)	7 (16.7)	
Mean (median)	4.1 (1.0)	6.0 (2.0)	4.5 (1.0)	3.4 (0.0)	0.43
Chest radiograph (grade)					
4	39 (30.0)	8 (19.0)	14 (45.2)	24 (57.1)	<0.05
5	91 (70.0)	34 (81.0)	17 (54.8)	8 (42.9)	

Abbreviation: WBC = white blood cells

Table 2. Classification of chest X-ray observations in pneumonia

Grade	Classification
1	Normal
2	Mild, diffuse infiltration of lungs including coarse reticular opacity
3	A diffuse reticulonodular pattern often with focal and patchy areas of consolidation when the infection has spread to the alveoli
4	Much more infiltration than grade 3, to the point of air space consolidation
5	Non-segmental, homogenous consolidations, with air bronchogram, of pleural effusion, with thin-wall or thick-wall cavity lesions

and analyzed according to different variables, including PUAT, gender, age, blood profile data and duration of fever. When conducted, PUAT (Binax, Inc., Portland, ME, USA) was performed on patients suspected of having severe pneumonia prior to the start of antibiotic therapy. Those who were not assessed using PUAT were enrolled as study controls.

The patients with severe pneumonia were submitted to different clinical teams in our pediatric department, and different teams were applied to the four study groups. The members of the clinical teams were assigned by the chief resident in the administrative position. A treatment protocol was designed for patients receiving PUAT. PUAT-positive patients were treated with penicillin G, while PUAT-negative patients received ampicillin-sulbactam or cefuroxime, and those with a weakly positive PUAT result were treated according to the guideline of the IDST. Patients who were examined using PUAT and who were treated according to the aforementioned protocol represented group 1. Patients examined using PUAT, but who were not treated according to the protocol represented group 2. Patients not assessed using PUAT and who were treated following the IDST guideline for pediatric pneumonia represented group 3. Finally, patients who were not assessed using PUAT and who were not treated using the IDST guideline represented group 4. For group 2, antimicrobials were: ceftriaxone, oxacillin, cefazolin, piperacillin, gentamicin, cefepime, ampicillin, vancomycin, ampicillin-sulbactam, clindamycin, and meropenem. The antimicrobials used in group 4 were: penicillin, cefotaxime, amikacin, ampicillin, gentamicin, piperacillin, vancomycin, cefepime, ceftizoxime, cefazolin, amoxicillin-clavulanate, cefixime, ticarcillin-clavulanate and macrolide combined with any of the other antibiotics listed.

With the exception of PUAT and the treatment protocol, all other treatment regimens and management decisions, including duration of hospitalization, were determined by the primary caregivers, and were unaffected by the study protocol. The clinical outcomes of the four groups were evaluated according to the duration of fever; a shorter duration was indicative of a better treatment outcome.

The fever curves were calculated by the Kaplan and Meier Product-limit method. In the univariate analysis, the statistical significance of the difference between the fever subsidence curves of a single variable were evaluated by the log-rank test. In the multivariate analysis, the prognostic significance of the use of PUAT on fever duration after adjustment of other confounders (such as age, gender, severity of CXR, and band form) was assessed using Cox regression model. A p value <0.05 was considered significant. The Statistical Package for the Social Sciences for Windows (Version 10.0; SPSS, Chicago, IL, USA) software package was used for statistical analysis.

Results

During the period of this study, 1167 patients admitted to VGHKS were diagnosed with pneumonia. Of these, the 252 cases that were CXR grade four and five were included in this study. Seven cases were subsequently excluded; six had been treated with macrolide (azithromycin) alone, while the remaining patient was discharged against medical advice, making the evaluation of fever impossible. As a result, 245 patients diagnosed with severe pneumonia were enrolled in this study. Of these, 172 (70.2%) were assessed using PUAT.

Table 3 displays the comparison of severity and the results of PUAT together with clinical outcomes between the group 1 and group 2 patients. In group 1, there were 130 patients (76.2%) with positive PUAT results and 31 patients (23.8%) with negative PUAT results. The mean duration of fever for PUAT-positive and -negative patients was 3.9 and 5.5 days, respectively. In group 2, 37 patients (88.1%) were PUAT-positive and five patients (11.9%) were PUAT-negative.

There were 133 patients aged five years or less whose clinical assessment included PUAT. Of these, 99 (74.4%) were PUAT-positive and 34 (25.6%) were PUAT-negative. Thirty nine patients whose assessment included PUAT were older than five years of age. Of

Table 3. Comparison of disease severity between pneumococcal urinary antigen test (PUAT)-positive and -negative patients in group 1 and group 2, and comparison of fever duration between PUAT-positive and -negative patients in group 1

Variable	Group 1 (no. [%])						Group 2 (no. [%])					
	Total	CXR (grade)		Band form of WBC		Fever (mean; days)	Total	CXR (grade)		Band form of WBC		Fever (mean; days)
		4	5	≤5%	>5%			4	5	≤5%	>5%	
PUAT-positive	99 (76.2)	30 (30.0)	69 (70.0)	84 (85.0)	15 (15.0)	3.9	37 (88.1)	10 (27.0)	27 (73.0)	13 (35.0)	24 (65.0)	6.7
PUAT-negative	31 (23.8)	7 (23.0)	24 (77.0)	21 (68.0)	10 (32.0)	5.5	5 (11.9)	2 (40.0)	3 (60.0)	3 (60.0)	2 (40.0)	5.1

Abbreviations: CXR = chest X-ray; WBC = white blood cells

these, 37 (94.9%) were PUAT-positive and two (5.1%) were PUAT-negative.

As summarized in Table 4, the duration of fever varied in the four groups, mean values being 4 days in group 1 (n = 130), 6 days in group 2 (n = 42), 6 days in group 3 (n = 31), and 8 days in group 4 (n = 42). Ninety one percent of the group 1 patients became afebrile within seven days after admission, while 95% of the patients experienced resolution of fever within 10 days. In the other groups, the mean respective percentages of fever subsiding within 7 and 10 days were 83% and 88% in group 2, 68% and 87% in group 3, and 67% and 79% in group 4 (p=0.047). The mean duration of hospitalization in these four groups was 8.4, 11.4, 10 and 18 days, respectively.

The statistical significance of association between the categorical variables and the resolution of fever was assessed using the log-rank test (univariate analysis) [Table 5]. Significant differences of the fever curves according to age group and band form were apparent, with p values of 0.0281 and 0.0234, respectively.

The pattern of fever among the four patient groups displayed significant differences (Fig. 1). The final results of multivariate analysis, which were evaluated by using Cox regression analysis (Table 6), showed that the patients in groups 1 and 2 were 1.673 and 1.663 times as likely to reach the afebrile stage, respectively, compared with patients in group 4. The likelihood of reaching this stage was comparable between groups 3 and 4. Patients who displayed a lower grade of pneumonia severity in the CXR classification and band form group were 1.389 and 2.017 times as likely, respectively, of reaching the afebrile stage as patients who displayed more severe pneumonia. Age and gender influences in reaching the afebrile stage were insignificant.

The positive blood culture rate was 4.0% (10/245), and the positive sputum culture rate was 12.2% (30/245). There were five fatalities during the study period; all had an underlying cardiac or neurological anomaly. One of these patients was from group 1, one was from group 2 and three were from group 4.

Discussion

Culture of sputum and blood are the traditional methods used to investigate pathogens in pneumonia. Despite this, very few pneumonia cases are bacteremic and blood cultures are frequently negative in septicemia cases, which usually involve antimicrobial therapy [8-10]. Moreover, collecting sputum or tracheal aspirates for culture is usually difficult in preschool-aged children [1]. Exemplifying the problems with the traditional methodologies, presently we observed positive blood and sputum culture rates of only 4.0% and 12.2%, respectively. This low level is impractical for clinical application.

Table 4. Comparison of the rates of fever resolution in groups 1 to 4

Group	Number of cases (%)	Mean time to fever resolution (days)	Median time to fever resolution (days)	Incidence of fever resolution within 7 days (%)	Incidence of fever resolution within 10 days (%)
1	130 (53.1)	4	3	91	95
2	42 (17.1)	6	2	83	88
3	31 (12.7)	6	3	68	87
4	42 (17.1)	8	3	67	79

Table 5. Rate of fever resolution according to clinical variables

Variable	No. (%)	Mean time to fever resolution (days)	Median time to fever resolution (days)	Incidence of fever resolution within 7 days (%)	Incidence of fever resolution within 10 days (%)	*p*
Gender						
Male	125 (51.0)	6	3	81	88	0.80
Female	120 (49.0)	5	3	84	92	
Age (years)						
≤5	192 (78.4)	6	3	82	89	<0.05
>5	53 (21.6)	4	2	83	91	
Band form of WBC						
≤5%	191 (78.0)	5	3	85	92	<0.05
6-20%	40 (16.3)	7	3	79	84	
>20%	14 (5.7)	9	7	50	71	
CXR grade						
4	86 (35.1)	4	3	83	93	0.14
5	159 (64.9)	6	3	57	82	

Abbreviations: WBC = white blood cells; CXR = chest X-ray

In this study, we assessed the practicality of PUAT in pneumonia diagnosis. In order to avoid selection bias, cases from January 1 to December, 2004 were enrolled. During this period, the cost of the PUAT had been incorporated into the coverage of the National Health Insurance in Taiwan. Thus, there was no financial incentive to avoid use of the test. In previous years, when universal PUAT coverage did not exist, the use of the test would likely have been biased towards cases of higher severity.

The enrolled patients were divided into four study groups (Table 1). Chi-squared test was used for percentage comparison, and one-way ANOVA for mean comparisons. The categories of gender, white blood cells and band form did not differ significantly among the four groups, whereas significant differences were found for the three baseline characteristics of age, C-reactive protein and severity of CXR among the four study groups. By using Sidak correction for comparison of multiple variables between groups, the age of group 2 was found to be significantly different from group 1 and group 4, while there were no significant differences between any other groups. Age had no significant effect on the outcome of treatment in multivariate analysis. Higher C-reactive protein levels and higher severity of CXR were found in groups 1 and 2, in which patients received PUAT. However, these groups achieved superior treatment outcome compared with the other groups, suggesting that the use of PUAT in the treatment of children is effective in shortening the duration of fever.

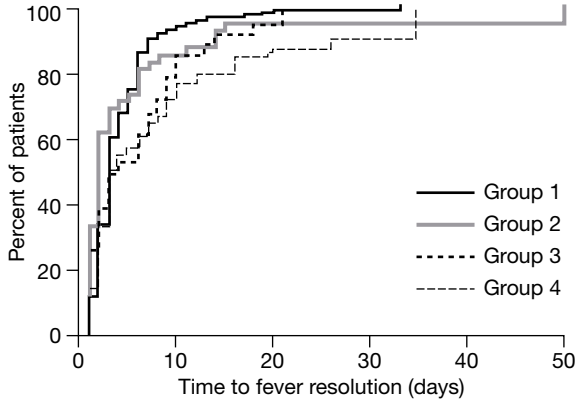

Fig. 1. Patients of the four groups reaching afebrile status during hospitalization.

The observed high percentage of PUAT-positive patients highlights the importance of the test. PUAT-positive patients (group 1) receiving penicillin G treatment (mean duration of fever, 3.9 days) had a reduced duration of fever compared with PUAT-negative patients treated with ampicillin-sulbactam (5.5 days), although the difference was statistically significant.

Among the 133 patients aged five or younger whose clinical evaluation included the use of PUAT, 74.4% were PUAT-positive, demonstrating the importance of the test for patients in this age group. Since pneumococcus is not a beta-lactamase-producing pathogen, PUAT-positive patients could be treated using penicillin G, allowing cost savings to be achieved compared with the use of beta-lactamase inhibitor combinations such as ampicillin-sulbactam or ampicillin-clavulanate as per the IDST guideline. Although the high rate of pneumococcus colonization in children could lead to

Table 6. Cox regression analysis of the effect of group assignment and use of the pneumococcal urinary antigen test and other variables in the treatment of pneumonia

Comparison	Adjusted relative risk	*p*	95% CI	
			Lower limit	Upper limit
Group 1 vs group 4	1.673	<0.05	1.15	2.43
Group 2 vs group 4	1.663	<0.05	1.05	2.64
Group 3 vs group 4	1.234	0.40	0.76	2.00
Age >5 vs ≤5 years	1.247	0.17	0.91	1.71
Female vs male gender	1.094	0.51	0.84	1.42
CXR grade 4 vs 5	1.389	<0.05	1.05	1.84
Band form of WBC ≤5% vs >5%	2.017	<0.05	1.15	3.54

Abbreviations: CI = confidence interval; CXR = chest X-ray; WBC = white blood cells

false-positive results in PUAT, its clinical advantage in children with severe pneumonia is shown by the results of the multivariate statistical analysis.

Analysis of the pattern of fever in the patient groups (Table 4) reveals that the duration of fever was shorter in group 1 patients than in group 3 or 4 patients. Group 1, which had a higher severity of CXR compared to groups 3 and 4, achieved a superior treatment efficacy among the four groups, indicating that the use of PUAT results to guide treatment is a prudent strategy. Despite not receiving treatment according to the IDST protocol, patients in group 2 had superior outcome compared with group 3 patients, who were treated according to the recommendations in the guidelines of IDST. As shown in Table 6, the final results of multivariate analysis, which were evaluated using Cox regression analysis, showed that patients in groups 1 and 2 were 1.673 and 1.663 times as likely to reach the afebrile stage, respectively, compared with patients in group 4. Compared with groups 1 and 2, group 3 had a less pronounced (non-significant) benefit in terms of fever duration over group 4.

Patients with higher CRX grades (i.e., more severe lung infections) and a higher band form in their blood profile displayed a longer duration of fever. It is reasonable to suppose that antimicrobial therapy requires more time in patients whose pneumonia is more severe. PUAT appeared to provide a useful guide to the appropriate initiation of antimicrobial therapy, regardless of age or gender, thus shortening the hospitalization course and leading to a saving of medical costs. CXR and the band form of white blood cells were the two variables that significantly affected treatment outcome (p=0.021 and p=0.014, respectively).

Six cases treated with azithromycin alone for pneumonia were excluded because of the high likelihood of mycoplasma or other atypical infection, whereas pneumococcal or other bacterial infections were not likely in these cases due to the high incidence of resistance to macrolides in *S. pneumoniae* in Taiwan. This phenomenon is due to the overuse and ready availability of macrolides in Taiwan [11].

Some cases in this study might have been co-infected with bacterial and non-bacterial pathogens, although this could not be confirmed by laboratory evidence. The incidence of non-bacterial involvement was limited by CXR screening, with only cases of grade four and five (more compatible with severe pneumonia) being enrolled in the study.

The uneven distribution of the age of patients, the extent of confounding factors and the number of cases in each group were limitations in the design of this study. The differences in the baseline characteristics such as age, gender, the index of severity of CXR and band form among the four groups were adjusted by multiple regression (Cox regression).

In conclusion, it is possible that PUAT is a suitable and non-invasive method that is effective in guiding the selection of antimicrobials as the initial therapy of severe pneumonia in pediatric patients, in whom sputum samples are often tedious to collect. Although the exact etiology cannot be determined in those cases with non-pneumococcal infection, PUAT is valuable in rapidly determining the strategy of antimicrobial selection, and might shorten both the course of infection and hospitalization.

Acknowledgments

We express our sincere appreciation to Dr. Calvin M. Kunin for his expert advice on this paper. This work was supported by a grant (VGHKS 95-077) from the Veterans General Hosptial, Kaohsiung, Taiwan.

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