診療局 原 著

Relationship between urinary pneumococcal antigens and primary antimicrobial agents

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Keywords : Community-acquired pneumonia, pneumococcus urinary antigen test, Gram staining

Abstract

Community-acquired pneumonia is one of the most frequently occurring life-threatening diseases. The most common causative organism is *Streptococcus pneumoniae*, and a pneumococcal urinary antigen test is often used to identify the causative organism. The sensitivity and specificity of the pneumococcal urinary antigen test are 86% and 94%, respectively, and a positive result indicates the involvement of pneumococci. In Japan, > 99% of pneumococcal pneumonia cases are responsive to penicillin G. However, accurate selection of appropriate antimicrobial agents is rarely done in pneumonia cases where the urinary antigen test is positive; a wide range of antimicrobial agents are selected in the treatment of most cases. There is no established method of using a pneumococcal urinary antigen test, which is problematic as this test is now routinely used to diagnose community-acquired pneumonia. In this study, we retrospectively analyzed 1188 cases of patients with community acquired pneumonia aged ≥18 years who were examined with the pneumococcal urinary antigen test between January 1, 2018 and December 31, 2018 at Asahi General Hospital, tertiary care facilities in Chiba Prefecture, Japan, and analyzed the selection of the first antimicrobial agent based on a positive or negative test result. The initially prescribed antimicrobial agents were classified into three groups: (1) the narrow-spectrum group with penicillin G and aminopenicillin, (2) the broad-spectrum group with other antimicrobial agents, and (3) the non-antimicrobial group. The results showed that 9.8% (116/1188 cases) of the analyzed cases had positive pneumococcal urinary antigen test results. In urine antigen-positive cases, first-line antimicrobial therapy was selected for the following patients: group 1, 4 patients (3.4%); group 2, 106 patients (91.4%); and group 3, 6 patients (5.2%), whereas in negative cases for the following patients: group 1, 1 patient (0.1%); group 2, 930 patients (86.8%); and group 3, 141 patients (13.2%). Ceftriaxone was the most commonly prescribed agent in group 2. The most prescribed antimicrobial agents were broad-spectrum antimicrobials such as third-generation cephems, regardless of a positive or negative pneumococcal urinary antigen test result; the urinary antigen test was not contributory to the initial selection of antimicrobial agents. It is therefore important to accurately interpret pneumococcal urinary antigen test results for appropriate antibiotic selection.

Introduction

In Japan, pneumonia is one of the most commonly encountered causes of death. *Streptococcus pneumoniae* is the most frequent causative agent of all community-acquired pneumonia, causing severe illnesses [1]. Although it is relatively easy to diagnose pneumonia in clinical practice, it is not so easy to identify the caus-

ative organism and provide appropriate intervention. Sputum Gram stain, sputum culture, pleural fluid culture, blood cultures, and urinary antigen tests are used to identify the causative organism; however, the sensitivity and specificity of each test, difficulty in submitting an appropriate specimen, and the empiric administration of antimicrobial drugs before the patient arrives at the hospital often pose challenges to causative organism identification.

The AP BinaxNOW® *Streptococcus pneumoniae* urinary antigen test has been adopted by many institutions for the diagnosis of pneumonia and the identification of the causative organism because test results can be determined in 15 minutes and the specimen can be submitted easily. Luis et al. reported that 71% of pneumococcal pneumonia cases are diagnosed by urinary antigen tests, and only 29% are diagnosed by standard microbiological tests such as Gram staining and microbial culture [2)]. The sensitivity and specificity of pneumococcal urinary antigen tests are reported to be 86% and 94%, respectively [3)]. However, the sensitivity and specificity of pneumococcal urinary antigens are confirmed by cases in which pneumococcal bacteria are detected in the sputum, pleural fluid, or blood cultures. Yet, since a positive pneumococcal urinary antigen test results has been shown to correlate with infection severity, the Infectious Diseases Society of America/American Thoracic Society recommends conducting urinary antigen tests only for patients with severe community-acquired pneumonia [4)]. Nevertheless, whether or not antimicrobial agents should be selected to treat severe pneumonia based on the confirmation of pneumococci as the pathogenic bacteria, even in patients with positive urinary antigen test results, remains debatable. In addition, according to the Japanese antibiogram, the preferred antimicrobial agents for pneumococcal pneumonia is penicillin G or ampicillin intravenously or amoxicillin orally, but it is still uncertain whether these agents are selected based on urinary antigen positivity. The purpose of this retrospective study on pneumococcal urinary antigen testing was to gain a better understanding of the current patterns of use surrounding urinary antigen testing and discuss the appropriate use of the tests in a clinical setting.

Methods

The first prescribed antimicrobial agents were analyzed retrospectively from the medical records of patients who underwent pneumococcal urinary antigen tests at the time of initial examination at Asahi General Hospital between January 1, 2018, and December 31, 2018. The initially prescribed antimicrobial agents were classified into three groups: (1) the narrow-spectrum group comprising patients who received penicillin G and aminopenicillin, (2) the broad-spectrum group comprising patients who received other antimicrobial agents, and (3) the group comprising patients who did not receive antimicrobial agents. We also analyzed the sputum and blood culture results when available.

Results

Urinary antigen tests were submitted in 1188 cases, of which 116 (9.8%) were positive. The mean age of the patients was 75.6 years, and 501 (42.2%) were females. Of the 1188 cases in which urinary antigen tests were submitted, antimicrobial agents were administered in 1041 (87.3%). In urine antigen-positive cases, first-line antimicrobial therapy was selected for the following patients: group 1, 4 patients (3.4%); group 2, 106 patients (91.4%); and group 3, 6 patients (5.2%), whereas in negative cases for

the following patients: group 1, 1 patient (0.1%); group 2, 930 patients (86.8%); and group 3, 141 patients (13.2%) (**Figure 1**). Of the patients treated with antimicrobial agents, the chosen agent was administered intravenously in 1036 (99.5%) patients and orally in 5 (0.5%) patients. Ceftriaxone was the most commonly administered intravenous antimicrobial agent (536 patients), and amoxicillin-clavulanic acid was the oral antimicrobial agent of choice in all patients.

Concurrently, sputum, blood, and pleural fluid cultures were evaluated in 875, 1060, and 23 cases, representing 73.7%, 89.2%, and 1.9% urinary antigen test submissions, respectively. Of these, pneumococci were detected in 72 (8.2% positivity rate) of sputum culture cases and 9 (0.8% positivity rate) blood culture cases. Pneumococci were not detected in any of the pleural fluid cultures.

	group 1	group 2	group 3	total
positive	4 (3.4%)	106 (91.4%)	6 (5.2%)	116
negative	1 (0.1%)	930 (86.8%)	141 (13.2%)	1072
	5 (0.04%)	1036 (87.2%)	147 (12.4%)	1188 (100%)

Figure 1 First-line antimicrobial therapy

Discussion

In the present study, we retrospectively examined the selection of the first prescribed antimicrobial agent in cases where pneumococcal urinary antigen tests were submitted for evaluation. The positivity rate was 9.8%, and very few of the patients with pneumococcal pneumonia were administered a narrow-spectrum antimicrobial agent such as penicillin G, ampicillin, or amoxicillin. There are several reasons why narrow-spectrum antimicrobial agents are not selected despite positive pneumococcal urinary antigen test results. One of such reasons is the high rate of false positive urinary antigen test results for *Streptococcus pneumoniae*. Urinary antigen tests remain positive for several months after a previous episode has been cured [5]. In addition, the vaccination history should also be checked because the results are positive for about a week after vaccination. Furthermore, it is essential to note that *Streptococcus mitis* and *Streptococcus pneumoniae* have similar antigens, and *Streptococcus pneumoniae* as an endemic bacterium is detected in children. In the present study, some of the patients who tested positive had a history of pneumonia a few months before they underwent the test, which may have influenced the interpretation of the urinary antigen test results.

Secondly, mixed infection is a possibility. Mixed infections account for 13% of the cases of community-acquired pneumonia requiring hospitalization, and the most commonly encountered mixed infection is the combination of pneumococcus and *Haemophilus influenzae* [6]. In the present study, of the 95 urinary antigen-positive cases in which sputum cultures were submitted, 5 were suggested to be mixed pneumococci infection, consisting of three cases of *Haemophilus influenzae* coinfection and one case each of *Moraxella catarrhalis* and *Pseudomonas aeruginosa* coinfections. Since urinary antigens can only be detected through the involvement of pneumococci, Gram staining may be useful for the rapid identification of the actual causative agent. In a report from Japan, the high specificity of Gram staining for identification of the causative agent of pneumonia was shown, and the sensitivity and specificity of Gram staining for confirming a case of pneumococcal pneumonia were 57.0% and 97.3%, respectively, indicating that gram-

positive diplococci, implicated in pneumococcal pneumonia can be identified by Gram staining as the causative agent of pneumococcal pneumonia [7) 8)] . The identification of pneumococci by Gram staining is considered very useful, but it requires high-quality specimens, proper staining, and evaluation skills.

The third reason is the problem with *Streptococcus pneumoniae* culture result interpretations. Penicillin-susceptible *Streptococcus pneumoniae* (PSSP) represents a large portion of all the pneumococci in Japan except for meningococcal specimens, and more than 99% of pneumococci, up to penicillin intermediate *Streptococcus pneumoniae* (PISP) , are included. This indicates that pneumococcal pneumonia can be treated with penicillin G and that there is no need to select broad-spectrum antimicrobial agents such as ceftriaxone except in cases of meningitis [9)] . In our hospital's 2017 data, the susceptibility of PSSP and PISP to pneumococcal antibiotics other than meningitis was 94.7% and 5.3%, respectively, and penicillin-resistant *Streptococcus pneumoniae* (PRSP) was not found. However, many clinicians do not know the correct way to interpret the susceptibility results of sputum and blood culture tests and think that PRSP is present even in the case of pneumonia, judging only by the notation of PSSP, PISP, and PRSP. In addition, the positivity rate of *Streptococcus pneumoniae* sputum culture tests is low due to the effect of the autolytic enzyme, autolysin, which is difficult to detect in the culture. The blood culture positivity rate is also approximately 20%, even in patients with pneumococcal pneumonia requiring hospitalization [10)] . Therefore, if no pneumococcal bacteria are detected in the sputum or blood culture, the urinary antigen test result may be considered as a false positive.

It is advisable to conduct the test if the results may lead to a change in the treatment course. If the pneumococcal urinary antigen test can identify the causative agent of bacterial pneumonia, it should be conducted if the patient is willing to accept penicillin G or ampicillin as a intravenous antimicrobial agent and amoxicillin as an oral antimicrobial agent in response to a positive result. Although overseas guidelines recommend conducting the test in severe cases, this may be due to the higher sensitivity and specificity of urinary antigen tests in severe cases than sputum, pleural fluid, and blood cultures [4)] . Since Gram staining is more widespread in Japan than in other countries, it is recommended that Gram staining be used, rather than a urinary antigen, test to identify the causative organism when possible. It should be noted that the urinary antigen tests do not evaluate the susceptibility of the organism.

When should the urinary antigen be conducted? In principle, Gram staining is preferred, but adequate training and experience are required for evaluation because it is difficult to submit an appropriate specimen compared to a urinary antigen test; it is necessary to obtain good quality sputum of Group 5 by Geckler's classification for proper evaluation by Gram staining because it is necessary to analyze the specimen accurately. In addition, the sensitivity of Gram staining is markedly reduced by the pre-administration of antimicrobial drugs [11)] . In consideration of the above, urinary antigen tests may be considered for the identification of the causative organism in cases where pneumonia is suggested from the medical history and physical examination, where there is no false-positive factor for the urinary antigen test, the causative organism cannot be identified by Gram staining alone, good quality phlegm cannot be collected

or prompt Gram staining cannot be done, or the causative organism cannot be identified by Gram staining owing to the pre-administration of antimicrobial drugs.

This study has several limitations. First, it is a retrospective, single-center study; thus, the findings cannot be generalized. Secondly, the factors that influence the initial choice of antimicrobial agents are not known. Finally, there is a relationship between urinary antigen test results and the first antimicrobial agent selection which may influence the choice of subsequent antimicrobials and dose de-escalation.

Conclusion

The results of pneumococcal urinary antigen tests do not appear to contribute to the selection of the initial antimicrobial therapy. Further studies are needed to determine when urinary antigen tests should be conducted.

Conflict of Interest

The authors declare no conflict of interest associated with this manuscript.

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