REVIEW
PNEUMOCOCCAL PNEUMONIA

Urinary antigen testing for pneumococcal pneumonia: is there evidence to make its use uncommon in clinical practice?

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ABSTRACT Microbiological confirmation of pneumonia caused by *Streptococcus pneumoniae* remains challenging as culture from blood or pleural fluid is positive in only 15–30% cases. It was hoped that a commercially available urine antigen test would improve diagnosis and consequently patient care, with improved antimicrobial stewardship. Urine antigen testing for pneumococcal pneumonia is recommended in current British Thoracic Society guidelines, whilst the National Institute for Health and Care Excellence and The American Thoracic Society and the Infectious Diseases Society of America guidelines consider its usage. Urine antigen testing is therefore widely used in hospital medicine. The assay is noninvasive, simple and culture-independent, producing a result within 15 min. Whilst initial evidence suggested urine antigen testing had a high sensitivity, recently data have suggested the actual sensitivity is lower than expected, at approximately 60–65%. Evidence has also emerged indicating that clinicians infrequently rationalise antibiotics following positive urine antigen testing, with multiple publications evaluating the role of urine antigen testing in clinical care. Furthermore, urine antigen testing does not appear to lead to any cost saving or reduction in length of hospital stay. We therefore conclude that the pneumococcal urinary antigen test does not alter patient management and leads to no cost saving, and has a lower than expected accuracy. Therefore, it may be time to make its use uncommon in clinical practice.

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This article reviews the pneumococcal urine antigen test (Pn UAT), recommended in BTS, NICE and ATS/IDSA guidelines. Pn UAT is less accurate than expected, and has not been shown to improve patient care or antimicrobial stewardship or lead to cost saving. http://bit.ly/2MJpjWL

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Introduction

Streptococcus pneumoniae remains the most common cause of bacterial community-acquired pneumonia (CAP) in both children and adults, despite the introduction of a conjugate vaccine as part of a vaccination programme [1]. Diagnosis relies upon microbiological confirmation of *S. pneumoniae* as the causative pathogen in patients with clinical and radiological features of pneumonia, although this can be challenging. Sputum samples can be insufficient and culture has a low specificity due to contamination from asymptomatic upper airway carriage [2]. The gold-standard method of confirmation is the culture of *S. pneumoniae* from blood or pleural fluid, but this only occurs in 15–30% of cases [3] and rates are lower in children [4]. Furthermore, treatment with antibiotics before sampling reduces culture sensitivity [5, 6], and this occurs in many patients before hospital admission.

Detection of *S. pneumoniae* antigens in clinical samples was performed as early as 1917 [7]. An immunochromatographic urinary antigen test (UAT) was first licenced by the United States Food and Drug Administration in 2003 and it was hoped that this test would enhance microbiological diagnosis of pneumococcal pneumonia. The British Thoracic Society CAP guidelines recommend that all patients with a CURB-65 score greater than 2 undergo urine antigen testing [8]. These guidelines were superseded by the National Institute for Health and Care Excellence 2014 guideline, that only suggests considering the use of pneumococcal UAT [9]. The Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) consensus guideline on the management of CAP was recently updated, and revised the recommendation of pneumococcal UAT. The earlier guideline recommended investigating for specific pathogens when this would significantly alter standard management decisions, if there is a strong suspicion of a responsible pathogen, or when certain patient characteristics are present [10]. However, the 2019 IDSA/ATS guideline makes a weak recommendation for using pneumococcal UAT only in severely ill patients, as part of a battery of tests, with the rationale of enabling antibiotic stewardship [11].

Accuracy

The Alere BinaxNOW® *Streptococcus pneumoniae* immunochromatographic membrane test detects soluble bacterial C-polysaccharide and is validated for human urine and cerebrospinal fluid [12]. The assay is rapid, producing a result within 15 min, noninvasive, simple and culture-independent. The manufacturer's website states that BinaxNOW® has a sensitivity of 86% and a specificity of 94% when testing urine samples, based on retrospective data [12]. The assay is known to have a specificity lower than 70% in a paediatric population, as children have high rates of nasopharyngeal colonisation with pneumococcus [13]. C-polysaccharide is present in the pneumococcal cell wall, and is common to all *S. pneumoniae* strains [14]. BinaxNOW® is therefore able to diagnose pneumococcal infection regardless of serotype, but since it does not discriminate between capsular polysaccharide, this assay does not provide any information about which serotype is causing disease [15]. This assay is currently widely used in clinical practice, in contrast with a serotype-specific pneumococcal urinary antigen test, is currently used in research settings and can detect 13 serotypes with a greater sensitivity in patients with pneumonia attributable to these *S. pneumoniae* serotypes [16].

A meta-analysis, published in 2013, of 27 studies comparing the BinaxNOW® assay with cultures in patients with CAP showed an overall assay sensitivity of 74.0% (CI 66.6–82.3%) and specificity 97.2% (CI 92.7–99.8%) [17]. This study concluded that the BinaxNOW® assay had a higher sensitivity than culture in the diagnosis of CAP, as well as a high specificity, making it a useful diagnostic tool in clinical practice. Several studies published after the meta-analysis have found the sensitivity of the BinaxNOW® UAT to be between 60% and 65% [18, 19], significantly lower than that found by Sinclair *et al.* [17]. There is evidence suggesting that UAT is less sensitive following the introduction of the 13-valent polysaccharide conjugate vaccine (PCV-13), with the sensitivity of UAT varying from 33.1% to 100% depending on the serotype [20]. The sensitivity of BinaxNOW® to *S. pneumoniae* serotypes not included in PCV-13 was below 70% in this study [20].

Furthermore, there are significant limitations in the ability of the UAT to detect pneumococcal disease. The C-polysaccharide detected by UAT also occurs in other pathogens including *Streptococcus mitis* and *Streptococcus oralis* [15]. A positive test result may not represent a current pneumococcal infection. UAT can be falsely positive within 48 h of vaccination against *S. pneumoniae* [12] and can remain positive for some time after a pneumococcal infection; 35% of patients are positive 2 months following pneumococcal disease, with 17% of patients positive at 4 months, and 6% of patients positive more than 6 months later [21]. Therefore, UAT cannot discriminate between current and past infection in patients with a second pneumonia.

Clinical usage and impact

A recent large prospective study found that patients who met IDSA/ATS guidelines for pneumococcal UAT infrequently had a positive result on testing (a positive test prevalence of 4.2%) [22], demonstrating

that current testing indications have poor sensitivity and specificity in identifying patients with positive pneumococcal urinary antigen. Other authors have found similar rates of positive test prevalence: between 5.2% and 8.8% in ward-based patients and 15% of those requiring intensive care [18, 23, 24]. The low rate of positive UAT results in over 90% of tests yielding negative results [18, 22, 23] and these do not contribute to clinical management as the low sensitivity of UAT means a negative test result cannot exclude infection with *S. pneumoniae*.

Attempts to find further discriminating clinical characteristics to improve patient selection for testing have yielded mixed results. Bellew *et al.* [22] failed to find any clinical characteristic strongly associated with a positive *S. pneumoniae* urinary antigen result, and therefore could find no parameters which would improve accuracy in selecting patients for testing. However, a large prospective study in 2015 found multiple clinical factors predictive of a positive *S. pneumoniae* UAT; the positive test rate was only 12% if only one factor was present, but this increased to 52% if over six factors were present [19].

As *S. pneumoniae* is the commonest bacterial cause of CAP, empirical antibiotic regimens universally provide cover against this organism. Multiple studies have shown that only one-third of patients have antibiotic treatment narrowed to targeted therapy against *S. pneumoniae* following a positive UAT [25, 26]. A US study found 15% of cases were changed to targeted therapy, with no change to treatment in 28% of cases and de-escalation to ceftriaxone and azithromycin in 57% patients [18]. There is also some evidence from randomised controlled trials showing higher rates of relapse in patients who have targeted therapy against *S. pneumoniae* following a positive UAT [25, 27]. However, in one of these trials only a few patients deteriorated after targeted oral antibiotics were prescribed, and there was no microbiological data explaining the worsening in their clinical condition. Overall, there was no improvement in clinical outcome using the pneumococcal UAT in this trial [27].

Cost-effectiveness

Bellew *et al.* [22] concluded that UAT cost US$425 per positive result, with a number needed to test of 25. A 2014 cost analysis found that the most cost-effective microbiological testing strategy was performing blood and sputum culture in patients with moderate-severe and high-severity CAP [28]. If sputum was unavailable, blood culture alone was the most cost-effective strategy [28]. A recent prospective study of patients in an Emergency Department found UAT had a 5.2% positivity rate, with only 14.3% of positive tests resulting in appropriate antimicrobial modification and €8748 per year saved through not using UAT [24]. The overall cost of inpatient care appears to be the same for patients who received targeted therapy based on UAT, with the cost of testing exceeding any savings through the reduced cost of antimicrobials [27]. Additionally, there was no difference in the length of hospital admission for patients who received antimicrobials targeted against *S. pneumoniae* following a positive UAT in comparison with those who received empirical antibiotics against pneumonia [27].

Conclusions

There is a compelling argument against the use of pneumococcal UAT in routine clinical practice as there are a lack of clinical indicators for a positive test result, failure to rationalise antibiotics following a positive result and the existing coverage against *S. pneumoniae* in all CAP regimens. Furthermore, usage of UAT has neither been shown to improve clinical care nor lead to any cost saving nor reduction in length of hospital stay. As such, we therefore conclude that the pneumococcal UAT has limited impact on clinical outcomes and processes of care, and suggest that it may be time to make its use uncommon in clinical practice.

Conflict of interest: None declared.

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