Despite progress in diagnostic technology, the confirmation of etiology of community-acquired pneumonia (CAP) and community-acquired meningitis (CAM) is still far from optimal accuracy and turnaround time. Pneumonia has the highest hospitalization and mortality rate among all infections diagnosed in the adult population in the United States (US) [1]. Every year, 4,000 cases of bacterial meningitis are reported nationwide with 12% fatality rate and up to 34% of cases resulting in permanent disability among survivors [2, 3]. These serious complications prompt the initiation of antibiotic therapy in patients with presumptive bacterial CAP or CAM regardless of ability to identify the culprit pathogen.

The causative pathogen of CAP in hospitalized patients in the United States remains unknown in up to 62% and on a lower scale in CAM [4]. The main diagnostic tools used for evaluation of CAP and CAM are microbiologic cultures; which have a relatively low yield. Hospitalized patients with CAP have positive blood cultures in less than 14% [5, 6]. The sensitivity of sputum culture for pneumococcal pneumonia is 60% [7]. The CSF cultures performed for CAM are positive in 70-85% cases however it takes an average of 48 hours to obtain the result. Although cerebrospinal fluid (CSF) Gram stain can identify the pathogen in 60-90%, this is only true for CSF with high bacteria load. The sensitivity drops to 25% for CSF with colony forming unit (CFU) ≤10³ [8]. Furthermore, if microbiology material is collected after initiation of antibiotic therapy the CSF culture sensitivity rate even further decreases.

Introduction

Despite progress in diagnostic technology, the confirmation of etiology of community-acquired pneumonia (CAP) and community-acquired meningitis (CAM) is still far from optimal accuracy and turn-around time. Pneumonia has the highest hospitalization and mortality rate among all infections diagnosed in the adult population in the United States (US) [1]. Every year, 4,000 cases of bacterial meningitis are reported nationwide with 12% fatality rate and up to 34% of cases resulting in permanent disability among survivors [2, 3]. These serious complications prompt the initiation of antibiotic therapy in patients with presumptive bacterial CAP or CAM regardless of ability to identify the culprit pathogen.
medication side effects including the deadly epidemic of C. difficile colitis [9]. The median length of stay (LOS) for CAP is 3 days [5]. In 2011 the cost of all CAP hospitalizations exceeded $10 billion [10]. Studies have already shown that de-escalation of antibiotics in hospitalized CAP cases is associated with decreased LOS without adversely affecting outcomes including mortality rate [11, 12]. The most common bacterial pathogen identified in both CAP and CAM is S. pneumoniae [3, 4]. Rapid S. pneumoniae C-polysaccharide antigen test (SPCAT) BinaxNOW has been approved by the Food and Drug Administration (FDA) to detect the antigen in the urine samples for diagnosis of pneumococcal pneumonia and in cerebrospinal fluid (CSF) for pneumococcal meningitis.

Methods

We reviewed the literature on S. pneumoniae antigen to highlight opportunities to optimize its use as a point of care diagnostic test to maximize the quality of patient care, antimicrobial stewardship outcomes and cost savings. A PubMed search was performed using key words “S. pneumoniae antigen; rapid diagnostic tests for S. pneumoniae”. We selected articles in English and sorted them out in Randomized controlled trials (RCT), case control, and retrospectives studies.

Results

Molecular properties of S. pneumoniae antigen.

S. pneumoniae are lancet shaped Gram-positive bacteria that grow in pairs or short chains. Their pathogenicity is attributed to many structures, most of them located on the surface. Three major surface layers have been found: the capsule, the cell wall, and the plasma membrane [13, 14]. The capsule is made of a high molecular weight polymer units of repeating oligosaccharides. There may be additional components to this like acidic components or phosphorylcholine (PC) [15]. Based on differences in the capsular polysaccharide (PS), pneumococci are sorted out into 90 plus serotypes [16]. This has been recognized as a major virulence factor as it has been found that encapsulated strains have 105 times more virulence than non-encapsulated. Also, there is 50% difference in lethal dose between encapsulated and non-encapsulated strains [13] [17].

The cell wall is mainly composed of peptidoglycan which is glycans cross-linked through peptide side chains. A complex teichoic acid containing PC residue known as cell wall polysaccharide (CWPS) is attached to peptidoglycan via N-acetyl muramic acid [18]. CWPS has various proposed mechanisms of virulence like inducing inflammation via activation of the alternative complement pathway, enhancement of vascular permeability, mast cell degranulation, polymorphonuclear leukocytes (PMN) activation and IL-1 production increase [19-21]. Capsular polysaccharide antigens of S. pneumoniae were first detected in urine of patients with pneumonia in 1917 [22]. The latex agglutination test was initially developed to detect urinary capsular polysaccharide of S. pneumoniae but the test was of limited usefulness because it was not easy to perform and could not detect all the different capsule serotypes [23]. Schaffner et al. used enzyme-linked immunosorbent assay (ELISA) for detection of this capsular polysaccharide in urine and found that the levels of this antigen varied depending on the severity of infection as well as the serotype of the bacteria. Notably, there is more than 250 fold variation in serotype-specific clearance rates [24]. Later in 2003, the FDA approved BinaxNOW S. pneumoniae assay, a rapid immunochromatographic test (ICT) detecting CWPS antigen that has shown good utility for diagnosis of S. pneumoniae via urine with high sensitivity and specificity [25]. The high analytical sensitivity for CWPS antigen urine specimens make it the point of care test [26]. Some of the advantages that S. pneumoniae ICT antigen offers is that it is easy to perform in all settings with 15 minutes turnaround time, the test is not serotype dependent and prior antibiotic use has less influence on the diagnostic yield [25] [26]. In a study by Said et al, prior antibiotic use has shown reduction in the relative diagnostic yield for S. pneumoniae ICT antigen only by 26%, sputum cultures by 34%, blood cultures by 67% [27].

S. pneumoniae antigen as the FDA-approved and non-approved diagnostic test

Though S. pneumoniae is a common pathogen in hospitalized patients with CAP, its microbiological diagnosis remains challenging. Conventional tests that have been used to identify the etiology of pneumonia include Gram stain of sputum, sputum cultures, and blood cultures. Other tests like latex agglutination, counter-immunoelectrophoresis that detect pneumococcal capsular antigens, have poor sensitivity and specificity [28]. They are not considered as useful diagnostic techniques in clinical practice. The ICT BinaxNOW has been cleared by the FDA to detect the pneumococcal antigen in both the urine and the CSF samples. It detects the pneumococcal C-polysaccharide present in the cell wall that is common to all serotypes [29].

Testing is not recommended in individuals vaccinated against pneumococcus in the last 5 days. S. pneumoniae ICT antigen was approved as an adjunct to culture for presumptive diagnosis of pneumococcal pneumonia. The most widely used indirect detection method for S. pneumoniae is the detection of pneumococcal antigen in urine. Wellcogen bacterial antigen test is another simple rapid test. This test utilizes a solid phase coated with polyclonal antibody to detect antigen in the human urine sample. This is a latex agglutination test runs with antibody coated polystyrene beads that agglutinate in the presence of sufficient antigen. S. pneumoniae ICT antigen has also been detected in other body fluids like blood, pleural effusion or sputum samples. The FDA has not approved any of them yet as a standard of practice. Several studies showed the promising results of S. pneumoniae antigen ICT in blood (Table 1.) The test sensitivity and specificity in blood samples were 87.1-100% and 96.9-100% respectively revealing higher diagnostic yield than the urinary antigen. In pleural effusion, the S. pneumoniae ICT antigen resulted in a sensitivity of 79-88% and specificity of 71-93.6%; which should be considered as a valuable diagnostic tool in clinical practice.

Discussion

We strongly believe that physicians should consider the best utilization and the missing diagnostic opportunities of S. pneumoniae ICT antigen when serving patients with CAP and CAM. The determination of the etiologic agent for the pneumonia is essential to maximize the selection of an effective narrowed spectrum antibiotic treatment aiming to prevent the risks of adverse effects and antimicrobial resistance [30, 31].
Table 1. Diagnostic test performance of *S. pneumoniae* C-polysaccharide antigen

<table>
<thead>
<tr>
<th>Body fluid sample</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>URINE [42] [43] [32] [44]</td>
<td>52–82</td>
<td>85.7–90.7</td>
<td>54.3–99.3</td>
<td>95.1–96.9</td>
</tr>
<tr>
<td>CSF [45] [46]</td>
<td>95.4–100</td>
<td>99.3–100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOOD [47] [41]</td>
<td>87.1–100</td>
<td>96.9–100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPUTUM [48] [49]</td>
<td>53.7–90.9</td>
<td>61.1–94.8</td>
<td>74.1–82.9</td>
<td>81.3–84.6</td>
</tr>
<tr>
<td>PLEURAL EFFUSION [50] [51]</td>
<td>79–88</td>
<td>72–93.6</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

CSF = Cerebrospinal fluid.

The SPCAT in urine and CSF support the etiological diagnosis in patients with *S. pneumoniae* pneumonia and CAM. In adult patients, the SPCAT in urine was reported to have a sensitivity of 50-80% in cases without bacteremia and 75-85% in those with bacteremia; the specificity is approximately 95%; the use of concentrated urine by selective ultrafiltration slightly increases the sensitivity of the test [32].

The IDSA guidelines from 2007 recommend SPCAT combined with at least blood culture for all patients with CAP with suspected pneumococcal etiology and at least one of the following risk factors: failure of outpatient management, ICU admission, leukopenia, active alcohol abuse, chronic severe liver disease, asplenia or pleural effusion. A meta-analysis from papers published from 1996 to 2012 showed that higher pooled sensitivity and specificity of the *S. pneumoniae* ICT urinary antigen test compared to culture supporting its use as part of the workup for diagnosis of community-acquired pneumonia [33].

In multiple studies, the urine *S. pneumoniae* assay has shown higher sensitivity for bacteremic pneumococcal pneumonia (77-92%) than for non-bacteremic pneumococcal pneumonia (52-78%) [34, 35]. The indication of SPCAT in Healthcare Associated Pneumonias (HCAP) is controversial, and it is not recommended [36, 37]. With increasing concern regarding antibiotic stewardship, the ability to safely and quickly narrow antibiotic therapy becomes crucial. Physicians are encouraged to target antibiotic therapy towards *S. pneumoniae* even if the *S. pneumoniae* urinary antigen ICT is the only positive microbiologic test and there is no evidence of any other etiology. The underutilization of *S. pneumoniae* urinary antigen or CSF antigen ICT test may lead to a suboptimal outcome in terms of recovery. This leads to increased risk of antibiotic related complications like C. difficile diarrhea in those receiving broad spectrum antibiotics that could have been obviated by early diagnosis and treatment. According to a multi-hospital observational study from 2016, *S. pneumoniae* urinary antigen ICT is an inexpensive, noninvasive test that favorably influences antibiotic prescribing practices [38]. The costs were reduced significantly as the regimens of antibiotics were changed based on the *S. pneumoniae* urinary antigen ICT result [39]. In a survey in 2013 among Physician IDSA members, the result of *S. pneumoniae* urinary antigen ICT led to 84% narrowed antibiotic regimen, 28% shortened the course of antibiotics, and 67% ordered fewer diagnostic tests [40].

The growing emergence of antibiotic resistant organisms is a major public health and financial burden. The use of rapid, non-invasive *S. pneumoniae* ICT urinary antigen may favorably influence antibiotic prescribing practices. Thus, *S. pneumoniae* ICT urinary antigen can guide to safely de-escalate antibiotics once a positive result is obtained [30].

The BinaxNOW *S. pneumoniae* antigen test detected pneumococcal antigen in 100% of blood culture bottles that grew *S. pneumoniae*. False positive reactions were seen due to cross-reactivity of polysaccharide antigen with *S. mitis* group [41].

Marcos et al. found that SPCAT testing in concentrated urine was positive in 70% of the patients with pneumococcal CAP proven by both culture and SPCAT 1 month after the diagnosis of CAP despite good clinical, laboratory and radiographic evolution. Therefore, further studies are needed to ascertain how long positive SPCAT results may persist after an episode of pneumococcal CAP to properly interpret the ICT test in clinical practice which will be of clinical significance especially in individuals who have recurrent pneumonia. They also found that five patients (11.1%) with bacteremic pneumococcal CAP tested SPCAT positive, only after concentrating the urine, which supports the necessity to concentrate the urine for this test [30].

One of the limitations of our review is that this is not a meta-analysis compiling the statistical data results. However, as part of the strengths of our paper is the systematic review of papers published in PubMed in the order of RTC, case-control studies and retrospective study.

**Conclusion**

The *S. pneumoniae* ICT urinary antigen is likely the best test to support the etiologic diagnosis of CAP with the optimal sensitivity and up to 15 minutes turn around result allowing to streamline the antibiotic de-escalation. The *S. pneumoniae* CSF antigen test, this test has optimal sensitivity and turnaround time; which should be considered a standard test for the evaluation of patients with meningitis.

**References**

7. García-Vázquez E, Marcos MA, Mensa J, de Roux A, Puig...