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REVIEW

Urinary antigen testing in community-acquired pneumonia in adults: an update

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) continues to be a leading cause of hospitalization and mortality worldwide. *Streptococcus pneumoniae* and *Legionella pneumophila* remain the major etiological agents and are responsible for a significant proportion of CAP mortality. Among diagnostic tests for CAP, urine antigen detection of *S. pneumoniae* and *L. pneumophila* is widely accepted due to the simplicity of collection and the rapidity of the test results.

Areas covered: This comprehensive review outlines the urinary antigen tests available, discusses their sensitivity and specificity, and assesses the usefulness of their results as the basis for targeted therapy.

Expert commentary: There have been advances in urine antigen detection tests for patients with CAP. New methodologies show greater sensitivity, detect *S. pneumoniae* and *L. pneumophila* in a single test, and also detect pneumococcal serotypes. In addition, urine antigen detection tests have shown a high specificity, which means that a positive result practically indicates the causative pathogen of CAP. Therefore, a positive result can lead to a targeted therapy that is likely to improve patient outcomes and reduce the risk of resistance and adverse events. However, well-designed studies are needed to evaluate the usefulness of urine antigen detection tests with regard to clinical outcomes.

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Urinary antigen test; *Streptococcus pneumoniae*; *Legionella pneumophila*; community-acquired pneumonia; sensitivity; specificity

1. Introduction

Community-acquired pneumonia (CAP) continues to be a leading cause of hospitalization and mortality worldwide [1,2]. Incidence and hospital admissions due to CAP have increased in recent years in all age groups. The frequency of CAP ranges between 1.2 and 11.6 cases per 1,000 population per year, a figure that grows in certain risk groups such as patients with chronic obstructive pulmonary disease or the elderly. However, CAP incidence differs by region, season, and population characteristics [2–5]. Moreover, between 20 and 25% of CAP patients require inpatient treatment. Severe CAP, defined as CAP requiring admission to intensive care units, develops in 10% to 20% of hospitalized patients [1,2]. Importantly, patients with CAP have high morbidity and mortality and impaired quality of life. Overall mortality in hospitalized patients with CAP ranges from 8% to 30%; these rates are higher in patients requiring intensive care unit admission, in older patients, and in those who received inappropriate empiric antibiotic therapy [6].

Despite thorough clinical investigation [2,7], the causative pathogen of CAP remains unknown in 30% to 60% of cases. The most frequently isolated pathogens are *Streptococcus pneumoniae* (20% – 60% of cases), *Haemophilus influenzae* (3% – 10%), Legionella species (2% – 8%), aspiration (6% – 10%), *Mycoplasma pneumoniae* (1% – 6%), *Chlamydophila pneumoniae* (4%), Gram-negative bacilli (3% – 5%) and other identified causes (10% – 20%) [7–9].

In spite of the high diversity of pneumococcal serotypes (more than 93), 30 or fewer cause more than 90% of invasive pneumococcal disease (IPD) or pneumococcal CAP. In recent years, the use of the pneumococcal conjugate vaccines targeting 7 (PCV7), 10 (PCV10) or 13 (PCV13) serotypes for childhood vaccination has been associated with a decline in pneumococcal diseases. A decrease in IPD due to vaccine-serotypes has been observed in young children (target population) but also in older children and adults because of herd protection [10–12]. In this way, a reduction in the incidence of pneumonia in ≥18-year-old adults (from 9.03 to 6.0 episodes per 100.000 population) was observed in a multicentre study analysing adult IPD in Spain after PCV13 introduction [10]. In the other hand, adult vaccination with PCV13 has been recently recommended in some countries. The results of a clinical trial performed in the Netherlands showed the efficacy of PCV13 vaccination in adults in prevention of pneumococcal CAP being most notorious in at risk patients. Moreover, the rate of hospitalization of pneumococcal pneumonia per 100.000 persons (916 vs 1272) and also that due to vaccine types (418 vs 774) also was lower in the vaccinated group [13].

Besides the benefits of the overall decrease of IPD after PCV13 introduction for children, other non-PCV13 serotypes

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Article highlights

- *Streptococcus pneumoniae* and *Legionella pneumophila* remain the major etiological agents of CAP
- New urinary antigen detection tests offer greater sensitivity, are able to detect *S. pneumoniae* and *L. pneumophila* in a single test and can also detect pneumococcal serotypes.
- Urine antigen detection tests have shown a high specificity, which means that a positive result practically indicates the causative pathogen of CAP
- Urinary antigen detection tests still present important limitations such as the inability to identify all pneumococcus serotypes and other species of Legionella.
- Adequately designed studies are now needed to evaluate the tests usefulness with regard to clinical outcomes

have filled the gap left by previous PCV13 serotypes (replacement) [14]. In this way, an increase in IPD due to certain non-PCV13 serotypes has been detected in recent years (8, 11A, 12F, 22F, 24F, 35B) [10–12,15]. Especially alarming is the rise of the highly invasive serotype 8 as a cause of IPD in most European countries [10–12]. The increase in disease due to serotypes 11A and 24F that could be betalactam- and multidrug-resistant is another cause of concern [11,12,16]. In areas such as the US or Canada the presence of other non-PCV13 serotypes is increasing (35B); however, the current rates of IPD are below the rates recorded prior to the introduction of PCV7 [15].

Furthermore, the genus *Legionella* comprises 61 species (28 associated with human disease) and 70 serogroups [17]. The structural and antigen diversity of bacteria lipopolysaccharide (LPS) is the basis for the *Legionella* serogroup classification. Fifteen serogroups of *L. pneumophila* have been described to date, among which serogroup 1 is the most frequently associated with human disease [17,18]. More than 90% of cases of Legionnaire disease in patients with CAP are caused by *L. pneumophila*, and 50% to 90% of these are caused by *L. pneumophila* serogroup 1. Other Legionella species obtained from patients with CAP are *L. micdadei* and *L. longbeachae*, and *L. pneumophila* serotype 6 [19].

Clinicians should try to identify the causative pathogen of CAP [20]. The diagnostic tests available to determine the aetiology of CAP are blood cultures, Gram stain and culture of respiratory secretions, detection of bacterial antigens and polymerase chain reaction-based methods. The need for diagnostic testing to determine the aetiology of CAP can be justified from several perspectives. The results of these tests can change the antibiotic treatment for an individual patient: the spectrum of antibiotic can be broadened, narrowed, or completely altered on the basis of results of the diagnostic testing. Increased mortality and clinical failure are more frequent with inappropriate antibiotic therapy. Similarly, de-escalation or narrowing of antibiotic therapy may decrease cost, drug adverse effects, and antibiotic resistance pressure. In addition, some etiologic pathogens, such as influenza or Legionnaire's disease have significant epidemiologic implications. These infections may affect not only the individual but many other persons as well [21].

Among the diagnostic tests for CAP, urine antigen detection of *S. pneumoniae* and *L. pneumophila* serogroup 1 have a high acceptability due to their simplicity of collection and the rapidity of the test results. In this article, we present a narrative review of the current status of urinary antigen tests in adult patients with CAP, their sensitivity and specificity, and their usefulness for diagnosis and targeted therapy.

2. Urinary antigen test for diagnosis of pneumococcal CAP

The pneumococcal urinary antigen test (PUAT) detects the pneumococcal C-polysaccharide antigen, which is the teichoic acid in the cell wall in the patient's urine. The first assay appeared in the late 1990s in an immunochromatographic membrane assay format (Binax, Alere®) and improved the etiological diagnosis of CAP. In recent years several other immunochromatographic tests for detecting *S. pneumoniae* have been marketed. Among them, Immunoview® offers the advantage of simultaneous detection of pneumococcus and Legionella, with similar sensitivity and specificity [22]. Moreover, an immunofluorescent assay automatically read has recently been introduced which improves the sensitivity of the immunochromatographic assays [23,24]. Finally, new PUATs have been developed for the detection of *S. pneumoniae* serotypes. A Luminex-technology based multiplex urinary antigen detection was developed by Pfizer® and has been used in several studies such as the CAPiTA trial [25]. This test is based on individual serotype-specific monoclonal antibodies that are able to capture the 13 capsular polysaccharides included in the PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) in the patient's urine. However, this test is time-consuming, requiring more than 24h for the results to become available and it is not currently useful for diagnosis in clinical practice (Table 1). Besides, the knowledge of serotypes will provide very important epidemiological data for evaluating the effectiveness of pneumococcal vaccination, for surveillance, and for guiding health policies [26].

2.1. Sensitivity and specificity of PUAT

Some meta-analyses have evaluated the sensitivity and specificity of immunochromatographic Binax for the diagnosis of pneumococcal CAP. Boulware *et al.*'s meta-analysis [27] was based on 24 studies that included patients with CAP, pneumococcal bacteraemia and empyema, and estimated a pooled sensitivity of 74% (95% confidence interval (CI): 72% to 77%) and a pooled specificity of 94% (95% CI: 93% to 95%). The authors included only patients in whom the aetiology had been established (mainly blood or sputum cultures), children, non-pneumonia cases and studies that used concentrated urine or pleural fluid. Recently, Sinclair et al. [28] also performed a systematic review and meta-analysis to evaluate the sensitivity and specificity of Binax for diagnosing *S. pneumoniae* in comparison with culture methods in hospitalized patients with CAP. A meta-analysis of 27 studies (only 16 studies of them included in previous meta-analyses) gave a sensitivity of 74.0% (95% CI: 66.6%–82.3%) and a specificity of 97.2% (95% CI: 92.7%–99.8%). The analysis found significant heterogeneity across studies, which

Table 1. Urine antigen test for Legionella and pneumococcus.

Methodology	Principle of assay	Time to process	Result interpretation	Commercial UAT
Enzyme immunoassay (EIA)	'Antigen sandwich' EIA (microwells pre-coated with purified rabbit antibodies to Lp1)	90′	Automated plate reader	Binax ®EIA (Alere, USA); Bartels ELISA (Trinity Biotech,USA)
Immunochromatographic membrane assay (ICT)	Colorimetric immunochromatographic test (rabbit anti-Lp1/anti- *S. pneumoniae* cell wall polysaccharide adsorbed onto nitrocellulose membrane conjugated to visualizing particles dried onto an inert fibrous support)	15′	Visual (visually detectable coloured lines)	Legionella: Binax NOW® (Alere,USA)[a] bioNexia® (bioMérieux, France) SAS™ (SA Scientific,Texas) Uni-Gold™ (Trinity Biotech, USA) Oxoid Xpect™ (Oxoid,UK) ImmuView® (SSD, Denmark)[b] Pneumococcus: Binax NOW® (Alere,USA)[a] Uni-Gold™ (Trinity Biotech, USA) ImmuView® (SSD, Denmark)[b]
Fluorescence immunoassay (FIA)	Lateral-flow immunofluorescence test (rabbit polyclonal anti-*Legionella*/anti- *S. pneumoniae* cell wall polysaccharide absorbed onto test strip conjugated to fluorescence particles)	15′	Sofia™ STANDARD F Analyzers	Sofia® (Quidel,San Diego) STANDARD F FIA (SD Biosensor, Korea)
Luminex xMAP bead technology	Multiplex Luminex bead coated with PCV13 capsular antibodies (serotype specific).	>24h	Luminex ®	Pfizer (Not commercially available)

[a]Results are interpreted by the analyzer Alere™Reader; [b]Detection of *S. pneumoniae and L. pneumophila* in a single test
[c]For proven pneumococcal pneumonia caused by PCV13 serotypes

did not decrease with adjustment for covariates. Importantly, authors included studies that evaluated adult patients with clinical suspicion of CAP, including those with an unknown organism. Conversely, they excluded studies with a case-control design that used patients without CAP as controls, studies that included children, patients with nosocomial pneumonia, and outpatients. Horita et al. [29] also carried out a meta-analysis to assess the sensitivity and specificity of the Binax PUAT for unconcentrated urine from adult patients with CAP. Their analysis of 10 studies yielded a pooled sensitivity of 75% (95% CI: 71%–79%) without heterogeneity or publication bias. The analysis of six studies yielded a pooled specificity (using only patients with pneumonia of identified other aetiologies) of 95% (95% CI, 92%–98%) also without any heterogeneity or publication bias.

Furthermore, an immunofluorescent assay automatically read has recently been introduced. The immunofluorescent assay has higher sensitivity (78.6% vs 50%) for proven pneumococcal CAP and (74.2% vs 58%) for proven plus probable pneumococcal CAP than the immunochromatographic assay, and a similar specificity (83.3% and 85.5% respectively) [23]. Another study also reported improved detection with the immunofluorescent assay compared with Binax. Among 133 urine samples from adult patients requiring hospital admission and respiratory symptoms, these tests yielded 20 and 11 positive results for *S. pneumoniae* respectively [24]. Finally, Vicente et al. [30] performed a study in patients older than 14 years with an episode of CAP requiring hospitalization. Immunofluorescent assay showed a moderately good sensitivity (77.4%) for urinary antigen detection in unconcentrated urine of patients with confirmed pneumococcal CAP, and a specificity of 86.7%.

Luminex-technology-based multiplex urinary antigen tests have recently been developed which achieve a sensitivity of 97–98% and a specificity of 100% for proven pneumococcal CAP caused by PCV13 serotypes [31]. Also, the addition of the urinary antigen detection test to conventional diagnostic methods increased the prevalence of *S. pneumoniae* CAP by 39%. In another study in adult patients hospitalized with CAP [32], the introduction of this Luminex-based test increased the identification of the pneumococcal CAP from 5.4% to 9.7%. However, since this test detected only 13 pneumococcal serotypes, the sensitivity for proven pneumococcal CAP was low (44%). This limits its use in clinical practice to establish the diagnosis, but on the other hand it provides support for epidemiological surveillance due to the serotypes identification. Similarly, Elberse et al. [33] evaluated three approaches for the detection and serotyping of pneumococci using samples from patients with CAP. Using quantitative polymerase chain reaction (qPCR) and inhibition multiplex immunoassay (MIA) and multiplex immunoassay (IMIA) both based on Luminex technology, their detection rate of the pneumococcus in patient samples was 56% higher than that of conventional methods. Furthermore, serotypes to the infecting pneumococcus from samples were identified in 25% of all CAP patients.

Other studies have determined factors associated with a positive PUAT in CAP patients. Zhou et al. [34] found that disease severity, chronic obstructive pulmonary diseases, increased age, respiratory rate, neutrophil ratio, blood urea nitrogen, procalcitonin, and decreased oxygenation index were associated with positive results of Binax rapid immunochromatographic membrane test. Similarly, Molinos et al. [35] also described factors associated with urinary antigen positivity in CAP patients: female sex, heart rate > 124, systolic blood pressure <90 mmHg, oxygen saturation <90%, absence of antibiotic treatment, pleuritic chest pain, chills, pleural effusion and BUN >29 mg/dl were predictors of positivity. Another study found that the test was more sensitive for patients with high-risk pneumonia and for those without demonstrative results of a sputum Gram stain, and showed a tendency towards higher sensitivity for patients with bacteraemic pneumococcal pneumonia [36]. Some authors recommend a sequential approach for performing PUAT in patients with CAP; they advocate its use only if bacteriological tests are still negative after 48 hours [37], or in high-risk patients for whom demonstrative results of a sputum Gram stain are unavailable [36].

Few studies have analysed the variability of pneumococcal immunochromatographic tests depending on the serotype [38,39]. The immunochromatographic tests detect in the patient's urine the C-polysaccharide (teichoic acid), a component of the pneumococcal cell wall presents in all pneumococcal strains. However, differences in its composition have been associated with serotypes [40], which may explain the variations in the sensitivity of pneumococcal immunochromatographic tests depending on the serotype assessed (from 33.3% to 100%). These differences may also explain the changes in the sensitivity of the immunochromatographic tests linked to changes in the pneumococcal serotype distribution after the introduction of PCV13. In fact, a recent study in patients with pneumococcal pneumonia revealed a decrease in the sensitivity of pneumococcal immunochromatographic tests from 76.4% (95% CI,70.5%-82.4%) between 2001 and 2005 to 60.5% (95% CI, 55.4%-65.6%) between 2011 and 2015. This reduction was linked to the shift in the serotype distribution. The low sensitivity found for serotype 8 (55.2%) and the emerging frequency of this serotype in most European countries [12,38] are findings that merit attention. Although these studies evaluated the Binax immunochromatographic test, similar results might be expected with other tests using the same technology.

It is important to note that there is no a gold standard test for the diagnosis of *S. pneumoniae* in patients with CAP. Most studies compare urine antigen tests with results from sputum and blood cultures. However, these culture tests have important limitations such as not all patients have expectoration and cough, and the sensitivity of blood cultures in this context is low, which is a big problem in assessing the performance of pneumococcal disease assays in CAP patients. In addition, prior vaccination with polysaccharide vaccine or pneumococcal infection and colonization with pneumococcus may influence PUAT results [41–43].

2.2. Targeted therapy with PUAT

Some studies have assessed the association between PUAT and clinical outcomes in CAP. Zalacain et al. [44] documented that antigen-positive patients among bacteraemic pneumococcal CAP had a higher risk of intensive care unit admission, treatment failure, and adverse outcomes. In another study comparing patients with invasive pneumococcal pneumonia (positive blood culture or pleural fluid culture) and non-invasive pneumococcal pneumonia (defined as positive UAT with negative blood or pleural fluid culture), despite differences in clinical features and outcomes between study groups, there was an association with a higher risk of mortality [26].

Antibiotic de-escalation is a measure that reduces selection pressure, adverse drug effects, and costs. Antibiotic de-escalation seems to be safe and effective; in recent studies it did not adversely affect outcomes of patients with CAP, not even in those with bacteraemia and severe disease or in those who were clinically unstable [45–48]. However, some of these studies have evaluated antibiotic de-escalation in cohorts of patients in which the etiology has been extensively investigated with multiple tests or only with results of blood cultures. Moreover, studies evaluating the impact of only positive PUAT results on antibiotic treatment in patients with CAP in a clinical setting are scarce.

In a retrospective multicentre study including patients with CAP with a positive urinary antigen for *S. pneumoniae* or Legionella, Mothes et al. [49] reported that targeted antibiotic therapy was prescribed in 32% of cases. Four factors were found to be independently associated with a lower rate of targeted therapy: a PSI score ≥ 4, a particular hospital, hospitalization in the intensive care unit, and cardiac comorbidities. In another study, a positive PUAT result led physicians to narrow the spectrum of antibiotic treatment in 45.1% patients (10.1% of all patients with CAP) [50]. Similarly, Sorde et al. [51] found that positive results of the PUAT led physicians to change the spectrum of antibiotic therapy in 8.6% of CAP patients. Despite positive urinary antigen results, treatment was not modified in 69% of patients with positive PUAT. Other studies have reported similar findings, with low frequency of antibiotic modification in patients with positive PUAT [52–55]. Moreover, one study found that, in the context of severe CAP with positive PUAT, targeted therapy with amoxicillin was associated with a reduction in mortality [56]. Similarly, in a prospective study [51] the narrow antibiotic spectrum in patients with positive PUAT was not associated with poor prognosis.

Falguera et al. [57] assessed the clinical impact of antibiotic treatment modification due to PUAT results in a prospective randomized study of 177 CAP patients. They did not find any substantial benefit of urinary antigen for *L. pneumophila* and *S. pneumoniae*-based therapy, suggesting that microbiological information does not provide benefits in terms of patient outcome or cost-effectiveness. Conversely, the narrowing of therapy on the basis of antigen test results was related with a higher risk of clinical relapse. However, this study has some limitations that should be acknowledged. The sample size was small, and patients were only assigned to an empirical or targeted treatment regimen once clinical stability was reached after admission. Thus, patients received multiple doses of appropriate broad-spectrum antimicrobial therapy prior to modification guided by the positive result of the urinary antigen test [58].

3. Urinary antigen test for diagnosis of Legionella CAP

There has been a dramatic increase worldwide in the proportion of cases of Legionnaire disease diagnosed as a result of the use of the Legionella urine antigen test (LUAT) [19]. From 2000 to 2011, passive surveillance for Legionellosis in the United States demonstrated a 249% increase in crude incidence. An active bacterial core surveillance programme during this period identified a rise in the incidence from 0.39 to 1.36 cases per 100,000 population. Among all patients, 1,300 (91%) received a diagnosis of Legionellosis based on urine antigen testing [59]; in 1998, the proportion of patients who received a diagnosis of Legionellosis on the basis of urine antigen testing had been 69% [60]. LUAT also confirmed 81% of all European Legionella cases in the years 2009 to 2010 [61]. Similarly, since the test's introduction in Australia, the median delay until notification for Legionellosis has fallen by around five days compared with culture [62,63]. Engel et al. [64] also found that LUAT results

became available an average of 13 days earlier than culture and/or serology. Interestingly, some studies have shown a decrease in the use of other diagnostic tests for legionellosis in CAP. In a 15-year prospective study of 215 hospitalized patients with CAP due to *L. pneumophila*, the use of the urinary antigen test remained stable during the study period, but the use of serology and culture fell ($p = 0.42$, $p < 0.001$, and $p = 0.001$ respectively) [65].

Among the advantages of LUAT are the rapid identification of *Legionella* antigens in urine and the early detection, which allow prompt notification of public health services and may lead to identification/control of potential environmental sources and thus prevent further cases. Similarly, positive LUAT allows an early switch from empirical to targeted treatment in hospitalized CAP patients. Finally, sample collection is very simple. Its main disadvantage is that it is designed to detect only L. *pneumophila* serogroup 1, although varying cross-reactions with other species and serogroups may occur [61,66].

Molecular tests such as PCR and loop-mediated isothermal amplification (LAMP) can detect any *Legionella* subspecies as these methods are usually based on conserved and not specific regions of rRNA sequences for amplification. Avni et al. [67] performed a systematic review to assess the diagnostic accuracy of PCR in comparison with LUAT. The study shows a higher sensitivity of the PCR in respiratory samples compared to LUAT and may result in additional diagnosis of CAP due to *L. pneumophila* of all serogroups and other *Legionella* species. Limitations of PCR methods are the lack of standardization protocols, requires specific laboratory equipment, trained personnel and PCR commercial kits are expensive. However, PCR-based methods might improve CAP diagnosis when non-*pneumophila* Legionella species is possible.

In Australia and New Zealand, species like *L. longbeachae* and *L. micdadei* are frequent. LUAT is not sensitive for these species or for other serogroups such as *L. pneumophila* serogroup 6 [19]. The capture antibody used in these assays is specific for *L. pneumophila* serogroup 1, and so diagnoses based only on a urinary antigen test may miss 20–50% of cases caused by other serogroups and species [68,69]. In addition, due to the low incidence of CAP caused by *Legionella spp*., LUAT needs a high number of samples to test, and so for every case identified the cost is relatively high [64,70]. One study found that microbiological information does not provide benefits in terms of patient outcome or cost-effectiveness [64].

The first report of an enzyme-linked immune specific assay for the detection of *L. pneumophila* antigen in urine samples was published in 1979 [71,72]. Subsequently, different LUATs were developed based on enzyme immunoassay, immunochromatographic membrane assay, and more recently immunochromatographic assays using immunofluorescence technology (Table 1). The results of some of immunochromatographic assays and all the available immunofluorescence assays are interpreted with an automatic reader, which increases their sensitivity. The antigen detected in all these LUATs is a heat-stable component of the cell wall of *Legionella* that is excreted three days after the onset of symptoms and can persist for more than one year [73]. A recent study evaluating the limit of detection of three commercial LUATs reported that they were able to detect most *L. pneumophila* serogroups, with the exception of serogroup 15 [74]. Moreover, although LUAT is highly accurate for *L. pneumophila* serogroup 1 detection, other diagnostic tests should also be used in combination with the urinary antigen because other Legionella species and serogroups are pathogenic. There is still a need to develop antigen capture assays that can detect infections due to all species and serogroups of *Legionella*.

A combined test for pneumococcus and Legionella urinary antigen is currently available. Jorgensen et al. [75]'s comparative study in frozen urine samples of patients with confirmed infection for legionella and pneumococcus found that its sensitivity was significantly better than that of other commercial tests for Legionella (88.9% compared to 71.7% and 74.7%). Like other LUATs, this novel test was developed for the detection of the *L. pneumophila* serogroup 1 antigen.

3.1. Sensitivity and specificity of LUAT

Urinary antigen testing for *L. pneumophila* has a sensitivity of 75% to 80% and a specificity of nearly 100% [76–78]. In a meta-analysis, Shimada et al. [78] include 30 studies and found a sensitivity for LUAT of 74% (95% CI: 68%-81%) and a specificity of 99% (95% CI: 98.4%-99.7%) but concluded that the estimates may be overoptimistic due to the low study quality and publication bias. In a report of an outbreak in 295 patients diagnosed with Legionella pneumonia in Spain, Blazques et al. [79] found that the sensitivity of LUAT depended on disease severity: sensitivity was 38% in mild to moderate disease, and 86% in severe pneumonia. The tests' sensitivity and specificity vary according to the pre-treatment of the urine samples, as the concentration of urine samples by centrifugation using filter units increases their sensitivity, and urine boiling to suppress nonspecific reactions enhances their specificity in most cases [80,81]. Moreover, in a study performed by Harris et al. [82] in hospitalized patients with clinical and radiographically confirmed CAP, the urinary antigen detection rates were similar when comparing specimens with and without prehospital antibiotic exposure. The antibiotic administration did not appear to be associated with yield from urinary antigen detection assays for *S. pneumoniae* or *L. pneumophila* serogroup 1.

Roed et al. [61] found in hospitalized patients with suspected CAP that positive LUAT to be associated with high grade fever, hyponatremia, confusion, and CURB-65 score > 3. In contrast, absence of sepsis, C-reactive protein <200 mg/dL, normal heart rate, and pleural effusions were highly suggestive of LUAT negativity.

3.2. Targeted therapy with LUAT

The urinary antigen test is a rapid, effective test that has allowed targeted therapy for Legionnaire disease. The high specificity (>95%) allows clinicians to administer appropriate anti-Legionella therapy based on a single rapid test. However,

its relatively low sensitivity means that a notable number of cases of Legionnaire disease will go undiagnosed if other tests, especially culture, are not performed [19].

Several studies have assessed targeted antibiotic adjustment based on LUAT. Two single-centre retrospective cohort studies showed that a positive LUAT led to adequate treatment alterations in 22%-60% of cases [64,67]. Garbino et al. [66] evaluated 792 hospitalized CAP patients, of which 27 had positive LUAT; in two-thirds of the cases, the test had a direct impact on the clinical management of CAP. However, patient comorbidities and individual clinical judgment continue to be important for determining optimal treatment. In contrast, Dionne et al. [70] found that 62% of CAP patients, who were admitted from the emergency room or who had developed pneumonia in hospital, received empirical therapy for *L. pneumophila* but in 68% of these cases the treatment was not influenced by the negative LUAT. Furthermore, Lettinga et al. [83] analysed the effect of timely target treatment during an outbreak in the Netherlands. One hundred eighty-eight patients were identified with confirmed or probable Legionnaires' disease during the outbreak, 141 required hospitalization, 40 ICU admission had confirmed disease, and 16 death. They finding that positive LUAT and early adequate therapy reduced the risk of intensive care unit admission and death by 38%.

4. Conclusion

CAP is not only associated with high morbidity, but it is also the most common infectious cause of death worldwide. The identification of the causative microorganism of CAP is essential for the adequate use of antibiotics and targeted therapy. The urinary antigen tests have an important role in achieving this aim, due to their rapid results and their high sensitivity and specificity. The latest advances in the development of these tests have improved their sensitivity and specificity and their ability to detect serotypes, thus increasing their epidemiological usefulness. However, antigen detection tests still present important limitations such as the inability to identify other pneumococcus serotypes and other species of Legionella. Finally, adequately designed studies are now needed to evaluate the tests usefulness with regard to clinical outcomes, as well as other issues such as development of antimicrobial resistance or adverse events in CAP.

5. Expert opinion

CAP continues to be the leading cause of mortality due to infectious disease all over the world. Despite advances in diagnosis, antibiotic treatment and critical support, mortality remains high. *S. pneumoniae* and *L. pneumophila* continue to be among the main etiological agents and cause significant mortality. The aetiology of CAP has not changed significantly, in spite of the long list of causative pathogens. Therefore, current guidelines recommend that broad-spectrum empirical therapy should be administered to cover the most common causative pathogens of CAP.

In recent years antibiotic resistance has emerged as a major problem, in patients with CAP as in other settings. Measures proposed to deal with this situation include the development of new antibiotics and the improvement of the use of antimicrobial agents. Thus, antibiotic therapy should be carefully selected for patients with CAP, in order to reduce unnecessary adverse effects and costs, and so as not to contribute to the further development of resistance to antibiotics. Broad spectrum empirical approaches to the initiation of antibiotic therapy should no longer be applied in CAP patients [84]. To achieve this goal, physicians require accurate and rapid diagnostic tests to identify the pathogenic microorganism of CAP.

Among the diagnostic tests available for determining the aetiology in patients with CAP, urine antigen tests present several advantages over the alternatives. They are easy to perform, have a relatively low cost and their results are obtained quickly (usually in 15 minutes). In addition, urine antigen detection tests have shown a high specificity, which means that a positive result practically indicates the causative pathogen of CAP and is thus a reliable guide for targeted therapy. However, studies show that in more than half of the cases, physicians fail to initiate or narrow the spectrum of antibiotic therapy in response to the results of etiologic diagnosis tests in CAP. Recently, it has been found that antibiotic de-escalation is a safe measure that improves antimicrobial use and does not adversely affect patient outcomes. Therefore, medical education is necessary to reinforce antibiotic de-escalation or initiation of targeted antibiotic therapy in CAP.

Although some studies have suggested that a positive result of urinary antigen detection tests does not justify the modification of antibiotic therapy or the prognosis of patients with CAP, we consider that the usefulness of these tests in this context should not be evaluated alone. In addition, these studies have not assessed other effects related to the use of broad-spectrum antibiotics compared with a targeted therapy: for instance, adverse effects, the generation of resistance, or complications such as *Clostridium difficile* infection. The urine antigen test is part of a set of diagnostic tests that must be used in CAP patients to improve antibiotic use. In this regard, studies assessing antibiotic de-escalation or targeted therapy in CAP have considered the use of several etiological diagnostic tests and have documented a lower number of complications; some of them have also reported a beneficial effect on survival.

Recently significant progress has been made in the development of urine antigen detection tests for patients with CAP. New methodologies offer greater sensitivity, are able to detect *S. pneumoniae* and *L. pneumophila* in a single test, and can also detect pneumococcal serotypes. These advantages favour the rapid detection of the aetiology in CAP and improve the use of antibiotics. In addition, when applied to clinical practice, the knowledge of serotypes will provide very important epidemiological information for assessing the effectiveness of pneumococcal vaccination, for surveillance, and for guiding health policies [25].

The studies performed to date have not satisfactorily established whether the results of urine antigen tests alone or in combination with other etiologic diagnostic tests can be used to initiate or de-escalate antimicrobial treatment regimens. What is needed are studies that address this question but use

a design that will minimize confounding issues and maximize the potential benefits to be accrued from these rapid diagnostic tests [57]. Further research is necessary using appropriately designed clinical trials and standardized outcome variables, in order to determine the optimal strategies (for example, the use of urinary antigen tests as point-of-care tests in the emergency department) [84] in order to ensure appropriate antibiotic use and to contain or prevent antimicrobial resistance. Similarly, the effectiveness of these strategies should be examined in subpopulations of hospitalized patients with CAP, including elderly patients and severely immunocompromised patients [46].

Although there have been advances in urine antigen detection tests for patients with CAP, these tests are only accurate for detecting *L. pneumophila* serogroup 1 or certain *S. pneumoniae* serotypes. Therefore, other diagnostic tests should now also be used in combination with the urine antigen test, since other Legionella species and pneumococcal and Legionella serogroups are pathogenic. There is still a need to develop antigen capture assays able to detect infections due to all species and serogroups of Legionella and serotypes of *S. pneumoniae*.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. N Engl J Med. 2014;370(6):543–551.
2. Mandell LA. Community-acquired pneumonia: an overview. Postgrad Med. 2015;127(6):607–615.
3. Jain S, Self WH, Wunderink RG, et al. CDC EPIC study team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415–427.
4. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68(11):1057–1065.
5. Arnold FW, Wiemken TL, Peyrani P, et al. Mortality differences among hospitalized patients with community-acquired pneumonia in three world regions: results from the Community-Acquired Pneumonia Organization (CAPO) international cohort study. Respir Med. 2013;107(7):1101–1111.
6. Ewig S, Torres A. Community-acquired pneumonia as an emergency: time for an aggressive intervention to lower mortality. Eur Respir J. 2011;38:253–260.
7. Apisarnthanarak A, Mundy LM. Etiology of community-acquired pneumonia. Clin Chest Med. 2005;26(1):47–55.
8. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. JAMA. 1996;275:134–141.
9. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014;20(Suppl 5):45–51.
10. Càmara J, Marimón JM, Cercenado E, et al. Decrease of invasive pneumococcal disease (IPD) in adults after introduction of pneumococcal 13-valent conjugate vaccine in Spain. PLoS One. 2017;12:e0175224.
11. Hays C, Vermee Q, Agathine A, et al. Demonstration of the herd effect in adults after the implementation of pneumococcal vaccination with PCV13 in children. Eur J Clin Microbiol Infect Dis. 2016;36:831–838.
12. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018;18(4):441–451.
13. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands. Vaccine. 2018;pii:S0264-410X(18)30763–1. [Epub ahead of print].
14. Lindstrand A, Galanis I, Darenberg J, et al. Unaltered pneumococcal carriage prevalence due to expansion of non-vaccine types of low invasive potential 8 years after vaccine introduction in Stockholm, Sweden. Vaccine. 2016;34:4565–4571.
15. Olarte L, Kaplan SL, Barson WJ, et al. Emergence of multidrug-resistant pneumococcal serotype 35B among children in the United States. J Clin Microbiol. 2017;55:724–734.
16. Aguinagalde L, Corsini B, Domenech A, et al. Emergence of amoxicillin-resistant variants of Spain9V-ST156 pneumococci expressing serotype 11A correlates with their ability to evade the host immune response. PLoS One. 2015;10:e0137565.
17. European Centre for Disease Prevention and Control. European Legionnaires' Disease Surveillance Network (ELDSNet). Operating procedures for the surveillance of travel-associated Legionnaires'disease in the EU/EEA. Stockholm: ECDC; 2017.
18. Williams A, Lever MS. Characterisation of Legionella pneumophila antigen in urine of guinea pigs and humans with Legionnaires' disease. J Infect. 1995;30:13–16.
19. Yu VL, Stout JE. Rapid diagnostic testing for community-acquired pneumonia: can innovative technology for clinical microbiology be exploited? Chest. 2009;136:1618–1621.
20. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371(17):1619–1628.
21. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases society of America; American thoracic society. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–S72.
22. Athlin S, Iversen A, Özenci V. Comparison of the ImmuView and the BinaxNOW antigen tests in detection of *Streptococcus pneumoniae* and *Legionella pneumophila* in urine. Eur J Clin Microbiol Infect Dis. 2017;36:1933–1938.

•• **Important study about the usefulness of novel lateral flow ImmuView test which detects pneumococcal and *L. pneumophila* serogroup 1 antigens in a combined test in CAP patients.**

23. Burgos J, Garcia-Pérez JN, Di Lauro SG, et al. Usefulness of Sofia Pneumococcal FIA® test in comparison with BinaxNOW® Pneumococcal test in urine samples for the diagnosis of pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis. 2018;37:1289–1295.

•• **Important study about a recently introduced immunofluorescent assay automatically read aimed to detect *Streptococcus pneumoniae* antigen in urine in CAP patients.**

24. Loïez C, Duployez C, Wallet F. A promising new test to detect Streptococcus pneumoniae urinary antigen. Med Mal Infect. 2017;47(7):494–497.

25. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–1125.
26. Ceccato A, Torres A, Cilloniz C, et al. Invasive disease vs urinary antigen-confirmed pneumococcal community-acquired pneumonia. Chest. 2017;151(6):1311–1319.
27. Boulware DR, Daley CL, Merrifield C, et al. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. J Infect. 2007;55(4):300–309.
28. Sinclair A, Xie X, Teltscher M, et al. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by *Streptococcus pneumoniae*. J Clin Microbiol. 2013;51(7):2303–2310.
29. Horita N, Miyazawa N, Kojima R, et al. Sensitivity and specificity of the *Streptococcus pneumoniae* urinary antigen test for unconcentrated urine from adult patients with pneumonia: a meta-analysis. Respirology. 2013;18(8):1177–1183.
30. Vicente D, López-Olaizola M, de la Caba I, et al. Evaluation of Sofia Fluorescent immunoassay analyzer for pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia. J Microbiol Methods. 2017;141:25–27.
31. Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. Eur Respir J. 2013;42:1283–1290.
32. Wunderink RG, Self WH, Anderson EJ, et al. Pneumococcal community-acquired pneumonia detected by serotype-specific urinary antigen detection assays. Clin Infect Dis. 2018;66:1504–1510.
•• **Important study about the usefulness of new serotype-specific urinary antigen detection tests in CAP patients.**
33. Elberse K, van Mens S, Cremers AJ, et al. Detection and serotyping of pneumococci in community acquired pneumonia patients without culture using blood and urine samples. BMC Infect Dis. 2015;15:56.
34. Zhou F, Gu L, Qu JX, et al. For CAP-China network. Evaluating the utility of Binax NOW Streptococcus pneumoniae urinary antigen test in adults with community acquired pneumonia in China. Clin Respir J. 2018;12(2):425–432.
35. Molinos L, Zalacain R, Menéndez R, et al. Sensitivity, specificity, and positivity predictors of the pneumococcal urinary antigen test in community-acquired pneumonia. Ann Am Thorac Soc. 2015 Oct;12 (10):1482–1489.
36. Rosón B, Fernández-Sabé N, Carratalà J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis. 2004;38(2):222–226.
37. Camou F, Issa N, Bessede É, et al. Usefulness of pneumococcal antigen urinary testing in the intensive care unit? Med Mal Infect. 2015;45(8):318–323.
38. Shoji H, Domenech A, Simonetti AF, et al. The Alere BinaxNOW pneumococcal urinary antigen test: diagnostic sensitivity for adult pneumococcal pneumonia and relationship to specific serotypes. J Clin Microbiol. 2018;56:e00787–17.
• **Important study about sensitivity of the BinaxNOW pneumococcal urinary antigen test for adult pneumococcal pneumonia caused by different serotypes over a 15-year period.**
39. Choi MJ, Song JY, Cheong HJ, et al. Clinical usefulness of pneumococcal urinary antigen test, stratified by disease severity and serotypes. J Infect Chemother. 2015;21:672–679.
40. Vialle S, Sepulcri P, Dubayle J, et al. The teichoic acid (C-polysaccharide) synthesized by *Streptococcus pneumoniae* serotype 5 has a specific structure. Carbohydr Res. 2005;340:91–96.
41. Turner P, Turner C, Kaewcharernnet N, et al. A prospective study of urinary pneumococcal antigen detection in healthy Karen mothers with high rates of pneumococcal nasopharyngeal carriage. BMC Infect Dis. 2011;11:108.
42. Murdoch DR, Laing RT, Cook JM. The NOW S. pneumoniae urinary antigen test positivity rate 6 weeks after pneumonia onset and among patients with COPD. Clin Infect Dis. 2003;37(1):153–154.
43. LeBlanc JJ, ElSherif M, Ye L, et al. Serious Outcomes Surveillance (SOS) network of the Canadian Immunization Research Network (CIRN). Burden of vaccine-preventable pneumococcal disease in hospitalized adults: a Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) network study. Vaccine. 2017;35(29):3647–3654.
44. Zalacain R, Capelastegui A, Ruiz LA, et al. Streptococcus pneumoniae antigen in urine: diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients. Respirology. 2014;19(6):936–943.
45. Viasus D, Simonetti AF, Garcia-Vidal C, et al. Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia. J Antimicrob Chemother. 2017;72 (2):547–553.
46. Viasus D, Vecino-Moreno M, De La Hoz JM, et al. Antibiotic stewardship in community-acquired pneumonia. Expert Rev Anti Infect Ther. 2017;15(4):351–359.
• **Important review article about elements that can be applied to antibiotic stewardship strategies for CAP in order to maintain or improve patient outcomes.**
47. Yamana H, Matsui H, Tagami T, et al. De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia. J Infect. 2016;73(4):314–325.
48. Carugati M, Franzetti F, Wiemken T, et al. De-escalation therapy among bacteraemic patients with community-acquired pneumonia. Clin Microbiol Infect. 2015;21(10):936.e11-8.
49. Mothes A, Léotard S, Nicolle I, et al. Community-acquired pneumonia and positive urinary antigen tests: factors associated with targeted antibiotic therapy. Med Mal Infect. 2016;5:1–7.
50. Laijen W, Snijders D, Boersma WG. Pneumococcal urinary antigen test: diagnostic yield and impact on antibiotic treatment. Clin Respir J. 2017;11(6):999–1005.
51. Sordé R, Falcó V, Lowak M, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med. 2011;171(2):166–172.
52. Engel MF, van Velzen M, Hoepelman AIM, et al. Positive urinary antigen tests for Streptococcus pneumoniae in community-acquired pneumonia: a 7-year retrospective evaluation of health care cost and treatment consequences. Eur J Clin Microbiol Infect Dis. 2013;32:485–492.
53. Stralin K, Staum Kaltoft M, Bosson Konradsen H, et al. Comparison of two urinary antigen tests for establishment of pneumococcal etiology of adult community-acquired pneumonia. J Clin Microbiol. 2004;42:3620–3625.
54. Matta M, Kerneis S, Day N, et al. Do clinicians consider the results of the BinaxNOW Streptococcus pneumoniae urinary antigen test when adapting antibiotic regimens for pneumonia patients? Clin Microbiol Infect. 2010;16:1389–1393.
55. Piso RJ, Iven-Koller D, Koller MT, et al. The routine use of urinary pneumococcal antigen test in hospitalised patients with community acquired pneumonia has limited impact for adjustment of antibiotic treatment. Swiss Med Wkly. 2012;142:w13679.
56. Blanc V, Mothes A, Smetz A, et al. Severe community-acquired pneumonia and positive urinary antigen test for S. pneumoniae: amoxicillin is associated with a favourable outcome. Eur J Clin Microbiol Infect Dis. 2015;34(12):2455–2461.
57. Falguera M, Ruiz-González A, Schoenenberger JA, et al. Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. Thorax. 2010;65:101–106.
58. Mandell L. Prospective randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. Thorax. 2010;65(2):93–94.
59. Dooling KL, Toews K, Hicks LA. Active bacterial core surveillance for legionellosis — United States, 2011–2013. Morb Mortal Wkly Rep. 2015;64(42):1190–1193.
60. Benin AL, Benson RF, Besser RE. Trends in legionnaires disease, 1980–1998: declining mortality and new patterns of diagnosis. Clin Infect Dis. 2002 Nov;35(9):1039–1046.
61. Roed T, Schonheyder HC, Nielsen H. Predictors of positive or negative legionella urinary antigen test in community-acquired pneumonia. Infect Dis (Auckl). 2015;47:484–490.

62. NNDSS Annual Report Working group. Australia's notifiable disease status, 2014: Annual report of the National Notifiable Diseases Surveillance System. Commun Dis Intell Q Rep. 2016;40(1):E48-145.
63. Formica N, Yates M, Beers M, et al. The impact of diagnosis by legionella urinary antigen test on the epidemiology and outcomes of Legionnaires' disease. Epidemiol Infect. 2001;127:275–280.
64. Engel MF, Van Manen L, Hoepelman AIM, et al. Diagnostic, therapeutic and economic consequences of a positive urinary antigen test for Legionella spp. in patients admitted with community-acquired pneumonia: a 7-year retrospective evaluation. J Clin Pathol. 2013;66:797–802.
65. Viasus D, Di Yacovo S, Garcia-Vidal C, et al. Community-acquired *Legionella pneumophila* pneumonia. Medicine (Baltimore). 2013;92 (1):51–60.
66. Garbino J, Bornand J, Uçkay I, et al. Impact of positive legionella urinary antigen test on patient management and improvement of antibiotic use. J Clin Pathol. 2004;57:1302–1305.
67. Avni T, Bieber A, Green H, et al. Diagnostic accuracy of PCR alone and compared to urinary antigen testing for detection of Legionella spp.: a systematic review. J Clin Microbiol. 2016;54 (2):401–411.
68. Fields BS, Benson RF, Besser RE. Legionella and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev. 2002;15(3):506–526.
69. Pierre DM, Baron J, Yu VL, et al. Diagnostic testing for Legionnaires'disease. Ann Clin Microbiol Antimicrob. 2017;16(1):59.
70. Dionne M, Hatchette T, Forward K. Clinical utility of a Legionella pneumophila urinary antigen test in a large university teaching hospital. Can J Infect Dis. 2003;14(2):85–88.
71. Berdal BP, Farshy CE, Feeley JC. Detection of Legionella pneumonophila antigen in urine by enzyme-linked immunospecific assay. J Clin Microbiol. 1979;9(5):575–578.
72. Tilton RC. Legionnaires' disease antigen detected by enzyme-linked immunosorbent assay. Ann Intern Med. 1979;90(4):697–698.
73. Kohler RB, Winn WC Jr, Wheat LJ. Onset and duration of urinary antigen excretion in Legionnaires disease. J Clin Microbiol. 1984;20 (4):605–607.
74. Ranc AG, Carpentier M, Beraud L, et al. Legionella pneumophila LPS to evaluate urinary antigen tests. Diagn Microbiol Infect Dis. 2017;89 (2):89–91.
75. Jørgensen CS, Uldum SA, Sørensen JF, et al. Evaluation of a new lateral flow test for detection of *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigen. J Microbiol Methods. 2015;116:33–36.
76. Chalmers JD. The modern diagnostic approach to community-acquired pneumonia in adults. Semin Respir Crit Care Med. 2016;37(6):876–885.
77. Ruf B, Schürmann D, Horbach I, et al. Prevalence and diagnosis of Legionella pneumonia: a 3-year prospective study with emphasis on application of urinary antigen detection. Source J Infect Dis. 1990;162 (6):1341–1348.
78. Shimada T, Noguchi Y, Jackson JL, et al. Systematic review and metaanalysis urinary antigen test for legionellosis. Chest. 2009;136 (6):1576–1585.
79. Blázquez RM, Espinosa FJ, Martínez-Toldos CM, et al. Sensitivity of urinary antigen test in relation to clinical severity in a large outbreak of Legionella pneumonia in Spain. Eur J Clin Microbiol Infect Dis. 2005;24(7):488–491.
80. Domínguez JA, Manterola JM, Blavia R, et al. Detection of *Legionella pneumophila* serogroup 1 antigen in nonconcentrated urine and urine concentrated by selective ultrafiltration. J Clin Microbiol. 1996;34(9):2334–2336.
81. Pontoizeau C, Dangers L, Jarlier V, et al. Ruling out false-positive urinary *Legionella pneumophila* serogroup 1 and Streptococcus pneumoniae antigen test results by heating urine. J Clin Microbiol. 2014 Dec;52(12):4347–4349.
82. Harris AM, Bramley AM, Jain S, et al. Influence of antibiotics on the detection of bacteria by culture-based and culture-independent diagnostic tests in patients hospitalized with community-acquired pneumonia. Open Forum Infect Dis. 2017;4(1):ofx014.
83. Lettinga KD, Verbon A, Weverling G-J, et al. Legionnaires' disease at a Dutch flower show: prognostic factors and impact of therapy. Emerg Infect Dis. 2002;8(12):1448–1454.
84. Yu VL. A clinical solution to antimicrobial resistance in community-acquired pneumonia: narrowing the spectrum of antimicrobial therapy: comment on "Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy". Arch Intern Med. 2011;171(2):172–173.