Hindawi Publishing Corporation
ISRN Infectious Diseases
Volume 2013, Article ID 518205, 5 pages
http://dx.doi.org/10.5402/2013/518205

Clinical Study

Prevalence and Utility of Positive Pneumococcal Urinary Antigen Tests in Australian Patients with Community-Acquired Pneumonia

Lauren K. Troy,[1,2] Keith K. H. Wong,[1,2,3] and David J. Barnes[1,2]

[1] *Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Missenden Road Camperdown, Sydney, NSW 2043, Australia*
[2] *Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia*
[3] *Woolcock Institute of Medical Research, Glebe, NSW 2037, Australia*

Correspondence should be addressed to Lauren K. Troy; ltroy@med.usyd.edu.au

Received 10 July 2012; Accepted 9 August 2012

Academic Editors: F. Su, N. Uchide, and P. Viale

Background and Objectives. The pneumococcal urinary antigen test (UAT) has superior sensitivity to other investigations in determining the aetiology of community-acquired pneumonia (CAP), but data specific to Australian populations is limited. This study aimed to establish the prevalence and clinical utility of positive UAT in patients admitted to hospital with CAP, as well as associations with positive testing. *Methods*. A prospective, cross-sectional, single-centre study was performed. Urine antigen tests were performed on all adult patients admitted to hospital with the diagnosis of CAP. Sputum and blood culture results, CURB-65 score of severity, current and prior antibiotics, comorbidities, mortality, and length of hospital stay were recorded. *Results*. There was a positive test prevalence of 13/170 [7.6% (95% confidence intervals 4.3–13%)]. The overall prevalence of pneumococcal pneumonia was 19/170 (11%), including 8 patients confirmed on positive UAT alone. Patients with a positive UAT result had a higher mean CURB-65 score compared with those with a negative result ($P = 0.01$), and a greater likelihood of requiring intensive care support ($P = 0.006$). *Conclusions*. The prevalence of positive UAT was low. Positive results were more often recorded in those with greater severity pneumonia. The clinical utility of the test in this cohort of patients was low.

1. Introduction

Community-acquired pneumonia (CAP) is an important and common disease entity, accounting for more than 100 000 hospital admissions in Australia per year [1]. In-hospital mortality can be as high as 20% in certain subgroups of patients admitted with CAP [2]. Increased attributable mortality is also observed beyond the acute episode, particularly in the elderly [3, 4]. Not surprisingly, the economic and disability costs to the community are significant.

Even where extensive and invasive investigations are undertaken in CAP studies, diagnostic yield is often low, with no causative organism identified in up to 50% of cases. In clinical practice, this yield is even lower. As a result, data on CAP aetiology is imprecise [5]. A lack of diagnostic tests with sufficient sensitivity and specificity has led to the development of new methods.

The *S. pneumoniae* Urinary Antigen Test (Binax NOW), an immunochromatographic membrane assay that detects the C-polysaccharide antigen in the cell wall of *S. pneumoniae*, has been in widespread clinical use since 2001 [6]. The test is rapid, simple to perform, and less likely to be influenced by prior antibiotic use than sputum and blood cultures. Sensitivity is reportedly 58–100%, and specificity is 82–100% [6–13]. Prevalence of positivity appears to vary widely between populations, with figures of 10–40% cited [6–16].

The pneumococcal urine antigen test (UAT) has been investigated in both immunocompetent and HIV adult patients hospitalized with CAP, with comparable high-standard performance in both populations [6–13]. Despite its

validation as a superior investigation in terms of sensitivity and specificity compared with more conventional microbiological tests, the role of the pneumococcal UAT in evaluating CAP patients remains uncertain, with no clear consensus on when the test should be performed [5, 17, 18].

The evidence for a positive result impacting on management is also limited. Guidelines on antibiotics in CAP incorporate therapy to cover *S. pneumonia* [5, 17, 18], and increasing data suggest a survival benefit in empiric strategies that include a macrolide, particularly in those with severe illness [19, 20]. The primary aims of this study were to establish the prevalence of positive pneumococcal UAT in patients requiring hospital admission for CAP, and to determine the utility of the test both in terms of diagnostic yield, and influence on management. A secondary aim was to define particular patient characteristics associated with test positivity.

2. Methods

2.1. Design and Patient Population. We performed a prospective study of all patients (age ≥18 yrs) admitted consecutively to a single centre with community-acquired pneumonia between May 2010 and January 2011. The study was conducted at a 985-bed tertiary teaching hospital in Sydney, Australia, with a local catchment population of 350,000. Human Research Ethics Committee approval was obtained.

A total of one hundred and seventy patients with new diagnosis of CAP were included in the study. Exclusion criteria included aspiration or hospital acquired pneumonia, cystic fibrosis, or a subsequent alternative diagnosis to account for the clinical presentation (e.g., *Mycobacterium* infection, extrinsic allergic alveolitis, or malignancy).

2.2. Measurements. Urine specimens were collected from all patients within the first 48 hours of admission. Samples were tested for pneumococcal antigen using the Binax NOW *S. pneumoniae* urinary antigen test (Binax, Scarborough, ME, USA), in accordance with manufacturer's instructions. Test swabs were dipped into nonconcentrated urine within 2 hours of specimen reception, with results read at 15 minutes. Further microbiological investigations were performed at the discretion of the treating clinician. These included blood cultures, pleural fluid, sputum, and bronchial alveolar lavage (BAL) samples for Gram stain and culture, urinary antigen testing for *Legionella*, and paired sera for *Chlamydophilia pneumoniae*, *Mycoplasma pneumonia,* and *Legionella pneumophila*; each performed by conventional methods.

Data on other clinical parameters were also collated, including age, gender, chest radiograph changes, antibiotic use within the 2 weeks prior to admission, length of hospital stay, in-hospital mortality, antibiotic therapy during admission, requirement for intensive care support, CURB-65 scores of pneumonia severity (scoring by confusion, uraemia, respiratory rate, low blood pressure, and age ≥65 years) [21], tobacco and ethanol use, and comorbid illness. Results of all variables were entered into a computer database.

2.3. Definitions. CAP was defined by new infiltrates on chest radiograph along with 2 or more consistent clinical features (cough, purulent sputum, fever, pleuritic chest pain, leukocytosis (white blood cell count >10,000/L), or dyspnoea). The diagnosis of pneumococcal pneumonia was considered definite or probable if the pathogen was cultured from blood, pleural fluid, or good quality sputum, or if urinary antigen testing was positive. Excessive ethanol consumption was defined as >6 standard drinks per day for men and >4 per day for women. Patients were defined as immunosuppressed if they were receiving prednisone therapy ≥10 mg/day or equivalent for >3 months, had concurrent malignancy, were treated with systemic chemotherapy, had received solid organ, bone marrow or stem cell transplantation, or had human immunodeficiency virus (HIV) infection.

2.4. Statistical Analysis. Statistical calculations were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Differences in proportions of binary variables were compared using the chi-square test or Fisher's exact test. Student's t test was used to compare continuous variables. Logistic regression was applied to variables that were significantly associated with a positive test result. A P value <0.05 was considered to be statistically significant. The 95% confidence interval was calculated to indicate the reliability of the observed estimates.

3. Results

3.1. Urine Antigen Test Results and Aetiology. All 170 patients admitted to hospital with CAP underwent pneumococcal urine antigen testing (UAT). UAT was positive in 13 patients, giving a positive test prevalence of 7.6% (95% CI 4.3–13%). Overall, a definite or probable diagnosis of pneumococcal pneumonia was established in 19 of 170 patients (11%). Characteristics of study participants are described in Table 1.

3.2. Utility of Test. Of the patients diagnosed with pneumococcal pneumonia, 8 patients had positive UAT alone. There were 6 patients with positive blood and/or sputum cultures for *S. pneumoniae* in whom the UAT was negative, as outlined in Table 2. A positive urine antigen test resulted in modification of initial antibiotic therapy in 5 out of 13 patients (38%). In these cases, patients were changed to either ampicillin or benzylpenicillin monotherapy. The other 8 patients were continued on initial empirical therapy, which included a combination of a penicillin or third-generation cephalosporin with a macrolide. There was one in-hospital fatality in each group ($P = 1.0$). There was no significant difference in length of hospital stay between those treated empirically and those with pathogen-directed therapy (15.2 versus 8.0 days, $P = 0.2$).

3.3. Patient Characteristics associated with Positive Pneumococcal UAT. Characteristics of patients with positive test results were compared with those with negative results and are summarized in Table 3. There were no significant differences between the two groups with respect to age, gender and mortality. Specific comorbidities, including the

Table 1: Characteristics of patients admitted to hospital with community-acquired pneumonia.

Characteristic	
Males, *n* (%)	112 (66)
Age, yrs ± SD[†]	64 ± 18
Length of hospital stay, days ± SD[†]	9 ± 8.5
In hospital mortality, %	5.9
CURB-65 score[‡], *n* (%)	
0-1 (mild)	83 (49%)
2 (moderate)	39 (23%)
3–5 (severe)	48 (28%)
Prior antibiotic use, *n* (%)	65 (38%)
Microbiologic testing obtained, *n* (%)	
Pneumococcal urine antigen test	170 (100%)
Blood culture	110 (65%)
Sputum Gram stain and culture	94 (55%)
Comorbidities, *n* (%)	
Current smoking	45 (26%)
Excessive ethanol	13 (7.6%)
COPD	59 (35%)
Asthma	20 (11.8%)
Immunosuppressed	28 (16.5%)
Diabetes mellitus	34 (20%)

Abbreviations—[†]SD: standard deviation; [‡]CURB-65 score: pneumonia severity according to confusion, uraemia, elevated respiratory rate, low blood pressure, and age greater than or equal to 65 years.

Table 2: Diagnostic tests leading to the confirmation of definite or probable pneumococcal pneumonia.

Diagnostic test positive	Number of patients
Blood culture only	1
Sputum culture only	4
Blood culture + Sputum	1
UAT[†] only	8
Blood culture + UAT[†]	3
Blood culture + Sputum + UAT[†]	2
Total	19

Abbreviation—[†]UAT: pneumococcal urine antigen test.

presence of asthma, COPD, diabetes, immunosuppression, and hazardous ethanol intake did not differ in proportions in either group. Prior antibiotic use was not significantly different (15.4% in positive UAT versus 36.5% in negative UAT, $P = 0.14$).

Patients who tested positive were more likely to have higher CURB-65 severity scores (mean of 2.7, compared with 1.6 in patients with negative results, $P = 0.01$). Figure 1 demonstrates the spread of CURB-65 scores with respect to UAT result. There was a greater requirement for intensive care support in patients with positive results ($P = 0.006$). There were also a greater proportion of current smokers in the positive group ($P = 0.049$).

Table 3: Differences between patients with positive and negative UAT.

	UAT positive	UAT negative	*P* value
Male gender (%)	69	59	NS
Mean age (years)	63.7	62.2	NS
Mean CURB-65[†] score	2.7	1.6	0.01
Death (%)	15.4	5	NS
ICU[‡] (%)	46	13.3	0.006
COPD (%)	46	33.8	NS
Asthma (%)	23	10.8	NS
Immunosuppressed (%)	30.8	15.3	NS
Current smoking (%)	53.8	25.7	0.049
Current heavy ethanol (%)	23	6.4	NS[x]
Prior antibiotics (%)	15.3	36.3	NS[x]

Abbreviations—[†]CURB-65 score: pneumonia severity according to confusion, uraemia, elevated respiratory rate, low blood pressure and age greater than or equal to 65 years; [‡]ICU: intensive care unit admission; [x]NS: not significant.

Table 4: Univariate and multivariate analysis of factors associated with positive UAT.

	Univariate OR (95% CI)	Multivariate OR (95% CI)
ICU[†]	5.6 (1.6–18.3)	—
Current smoker	3.4 (1.1–11.1)	6.7 (1.8–28.9)
CURB-65[‡]		
(i) mild	1.0	1.0
(ii) moderate	1.1 (0.1–11.1)	1.3 (0.1–14.4)
(iii) severe	10.7 (2.6–71.6)	18.7 (4.0–142)

Abbreviations—[†]ICU: intensive care unit admission [‡]CURB-65 score: pneumonia severity according to confusion, uraemia, elevated respiratory rate, low blood pressure, and age greater than or equal to 65 years.

Logistic regression was performed to analyse the specific factors significantly associated with a positive UAT. The requirement for ICU was not an independent predictor of positivity on multivariate analysis, but severe disease (CURB-65 score >2) and current smoking status demonstrated increased odds ratios of 18.7 (95% CI 4–142) and 6.7 (95% CI 1.8–28.9), respectively. These results are included in Table 4.

4. Discussion

Our study demonstrated a low prevalence of positive pneumococcal urinary antigen tests in Australian patients hospitalised with community-acquired pneumonia. This finding is contrary to many previously published studies with relatively high rates of positivity. Although numbers were small, there appeared to be a strong correlation between positive results and severe illness, requiring intensive care support, as well as a possible association with current smoking. Even when tests were positive, management was not altered in the majority of cases, with no apparent differences in outcomes.

The reason for disparity between this and previously published studies may partly be related to methodology.

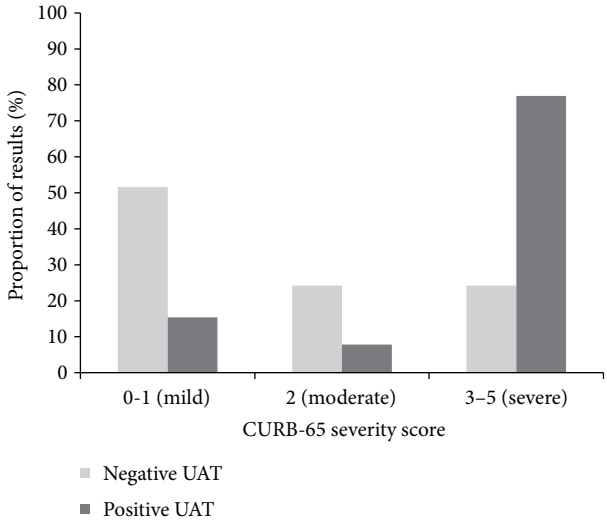

Figure 1: Spread of CURB-65 severity scores with respect to UAT result.

Extrapolating previous study results to every-day clinical use is limited by differences between trial methods and routine practice. A number of studies have evaluated *concentrated* urine specimens with corresponding high yield [6, 7, 10, 12, 14, 22]. Although sensitivity improves with such an approach, the cost is a greater likelihood of false-positive results. Current clinical practice, following manufacturer's instructions, is to analyse *nonconcentrated* urine to establish the presence of antigen.

Variations in local epidemiology are also likely to influence the findings. Studies of UAT in hospitalized CAP patients from Europe, Asia, and New Zealand have demonstrated positivity rates of 28–39% [6–13]. The large prospective Australian epidemiologic study of CAP aetiology, published by Charles et al. in 2008 had a significantly lower rate of only 11.2% of positive UAT. There was also a low overall prevalence of pneumococcal pneumonia, with only 14% of cases attributed to this organism [16]. A Spanish retrospective analysis including over four hundred thousand hospitalized CAP patients over 5 years showed pneumococcus to be the causative agent in 17% [23]. The difference between these recent studies and previously reported rates of 30–50% is striking and cannot fully be explained by the previous employment of invasive investigations no longer in use [24, 25]. The declining incidence of pneumococcal pneumonia may be a phenomenon related to increasing rates of vaccination against *S. pneumoniae* as well as patterns of antibiotic use in the community, but the explanation remains unclear at this stage.

Our study, demonstrating a prevalence of positive pneumococcal UAT in only 7.6%, is possibly reflective of both real-life practice and local pneumonia aetiology. Although this study did not incorporate extensive diagnostic evaluation in all participants beyond the UAT, it is interesting to note our comparable rates of pneumococcal pneumonia with the more definitive aetiologic study by Charles et al. (11 versus 14%) [16]. We cannot, however, draw specific conclusions about the rate of pneumococcal infection from our data, given that this was not a study of CAP aetiology.

Our research revealed a number of patient characteristics associated with a greater likelihood of testing positive for pneumococcal antigen. Increasing disease severity, as measured by CURB-65 score, was a predictor for positive UAT. The relationship between severe illness and positive testing may be explained by a higher antigen burden, as suggested by previous studies in bacteraemic patients [6, 10, 12, 14]. Current smoking was another significant predictor for positive UAT. This is consistent with the previous observation that tobacco use is strongly associated with pneumococcal infection, and in particular, with invasive disease [26, 27]. Other established risk factors for pneumococcal disease, including alcoholism, immunosuppression, diabetes mellitus, underlying lung disease, and advancing age [28] were not predictors for UAT positivity in this study.

There are a number of limitations in this study. With a low prevalence of positivity, the associations with particular patient characteristics had wide confidence intervals. These inferences might have been strengthened by recruitment of increased patient numbers across a number of testing centres over a longer trial period. Although this study included all patients admitted under the respiratory service with CAP, there were subgroups of patients that were potentially missed. Very elderly patients with multiple comorbidities presenting with CAP would often be cared for by the geriatric service, and as such, may have been underrepresented in this cohort.

In conclusion, the present study demonstrates a low diagnostic utility of pneumococcal urine antigen testing when applied in general CAP populations in Australia. The test appears to be most useful in the setting of severe pneumonia, as determined by a high CURB-65 score or the need for admission to the intensive care unit. The test might also have higher yield in patients who are current smokers. Its influence on clinical management appears to be diminished by the current widespread evidence-based practice of treating community acquired pneumonia with empirical therapy to cover pneumococcus, along with macrolide antibiotics. This study would suggest a limited role for pneumococcal UAT in diagnostic algorithms for the management of CAP.

Conflict of Interests

The authors declare they have no conflict of interests.

Acknowledgments

The authors wish to acknowledge the support of the Department of Microbiology and Infectious Diseases, Royal Prince Alfred Hospital, with respect to the funding of assays. They also acknowledge the hard work of the clinical teams in both the Departments of Emergency and Respiratory Medicine.

References

[1] *The Victorian Admitted Episodes Dataset: An Overview April 2000*, Acute Health Division, Victorian Government Department of Human Services, Melbourne, Victoria, 2000.

[2] Respiratory Infectious Diseases Consultative Group, *Respiratory Infectious Diseases Burden in Australia Case Statement*, The Australian Lung Foundation, 1st edition, 2007.

[3] G. W. Waterer, L. A. Kessler, and R. G. Wunderink, "Medium-term survival after hospitalization with community-acquired pneumonia," *American Journal of Respiratory and Critical Care Medicine*, vol. 169, no. 8, pp. 910–914, 2004.

[4] S. Yende, D. C. Angus, I. S. Ali et al., "Influence of comorbid conditions on long-term mortality after pneumonia in older people," *Journal of the American Geriatrics Society*, vol. 55, no. 4, pp. 518–525, 2007.

[5] Antibiotic Expert Group, *Therapeutic Guidelines: Antibiotic*, Version 14, Therapeutic Guidelines Limited, Melbourne, Victoria, 2010.

[6] J. Domínguez, N. Galí, S. Blanco et al., "Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples," *Chest*, vol. 119, no. 1, pp. 243–249, 2001.

[7] D. R. Murdoch, R. T. R. Laing, G. D. Mills et al., "Evaluation of a rapid immunochromatographic test for detection of *Streptococcus pneumoniae* antigen in urine samples from adults with community-acquired pneumonia," *Journal of Clinical Microbiology*, vol. 39, no. 10, pp. 3495–3498, 2001.

[8] Y. Kobashi, K. Yoshida, N. Miyashita, Y. Niki, and T. Matsushima, "Evaluating the use of a *Streptococcus pneumoniae* urinary antigen detection kit for the management of community-acquired pneumonia in Japan," *Respiration*, vol. 74, no. 4, pp. 387–393, 2007.

[9] T. Ishida, T. Hashimoto, M. Arita, Y. Tojo, H. Tachibana, and M. Jinnai, "A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology," *Journal of Infection and Chemotherapy*, vol. 10, no. 6, pp. 359–363, 2004.

[10] M. A. Marcos, J. de Anta, J. P. de la Bellacasa et al., "Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults," *European Respiratory Journal*, vol. 21, no. 2, pp. 209–214, 2003.

[11] R. Sordé, V. Falcó, M. Lowak et al., "Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy," *Archives of Internal Medicine*, vol. 171, no. 2, pp. 166–172, 2011.

[12] M. L. Briones, J. Blanquer, D. Ferrando, M. L. Blasco, C. Gimeno, and J. Marín, "Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults," *Clinical and Vaccine Immunology*, vol. 13, no. 10, pp. 1092–1097, 2006.

[13] D. R. Boulware, C. L. Daley, C. Merrifield, P. C. Hopewell, and E. N. Janoff, "Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection," *Journal of Infection*, vol. 55, no. 4, pp. 300–309, 2007.

[14] S. Lasocki, A. Scanvic, F. le Turdu et al., "Evaluation of the Binax NOW *Streptococcus pneumoniae* urinary antigen assay in intensive care patients hospitalized for pneumonia," *Intensive Care Medicine*, vol. 32, no. 11, pp. 1766–1772, 2006.

[15] J. P. Watt, J. C. Moïsi, R. L. A. Donaldson et al., "Use of serology and urine antigen detection to estimate the proportion of adult community-acquired pneumonia attributable to *Streptococcus pneumoniae*," *Epidemiology and Infection*, vol. 138, no. 12, pp. 1796–1803, 2010.

[16] P. G. P. Charles, M. Whitby, A. J. Fuller et al., "The etiology of community-acquired pneumonia in Australia: Why penicillin plus doxycycline or a macrolide is the most appropriate therapy," *Clinical Infectious Diseases*, vol. 46, no. 10, pp. 1513–1521, 2008.

[17] W. S. Lim, S. V. Baudouin, R. C. George et al., "British thoracic society guidelines for the management of community acquired pneumonia in adults: update 2009," *Thorax*, vol. 64, no. 3, pp. iii1–iii55, 2009.

[18] L. A. Mandell, R. G. Wunderink, A. Anzueto et al., "Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults," *Clinical Infectious Diseases*, vol. 44, no. 2, pp. S27–S72, 2007.

[19] M. I. Restrepo, E. M. Mortensen, G. W. Waterer, R. G. Wunderink, J. J. Coalson, and A. Anzueto, "Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia," *European Respiratory Journal*, vol. 33, no. 1, pp. 153–159, 2009.

[20] M. M. van der Eerden, F. Vlaspolder, C. S. de Graaff et al., "Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study," *Thorax*, vol. 60, no. 8, pp. 672–678, 2005.

[21] W. S. Lim, M. M. van der Eerden, R. Laing et al., "Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study," *Thorax*, vol. 58, no. 5, pp. 377–382, 2003.

[22] F. Andreo, J. Domínguez, J. Ruiz et al., "Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults," *Respiratory Medicine*, vol. 100, no. 5, pp. 884–891, 2006.

[23] R. Gil-Prieto, L. Garcia-Garcia, A. Alvaro-Meca, C. Méndez, A. García, and A. Gil de Miguel, "The burden of hospitalisations for community-acquired pneumonia (CAP) and pneumococcal pneumonia in adults in Spain (2003–2007)," *Vaccine*, vol. 29, no. 3, pp. 412–416, 2011.

[24] I. Lim, D. R. Shaw, D. P. Stanley, R. Lumb, and G. McLennan, "A prospective hospital study of the aetiology of community-acquired pneumonia," *Medical Journal of Australia*, vol. 151, no. 2, pp. 87–91, 1989.

[25] M. M. van der Eerden, F. Vlaspolder, C. S. de Graaff, T. Groot, H. M. Jansen, and W. G. Boersma, "Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 24, no. 4, pp. 241–249, 2005.

[26] J. P. Nuorti, J. C. Butler, M. M. Farley et al., "Cigarette smoking and invasive pneumococcal disease," *New England Journal of Medicine*, vol. 342, no. 10, pp. 681–689, 2000.

[27] C. Feldman and R. Anderson, "New insights into pneumococcal disease," *Respirology*, vol. 14, no. 2, pp. 167–179, 2009.

[28] T. van der Poll and S. M. Opal, "Pathogenesis, treatment, and prevention of pneumococcal pneumonia," *The Lancet*, vol. 374, no. 9700, pp. 1543–1556, 2009.