ORIGINAL ARTICLE
PNEUMONIA

Pneumococcal urinary antigen test use in diagnosis and treatment of pneumonia in seven Utah hospitals

Devin M. West[1], Lindsay M. McCauley[2,3], Jeffrey S. Sorensen[2], Al R. Jephson[2] and Nathan C. Dean[2,3]

Affiliations: [1]Dept of Medicine, Intermountain Medical Centre, Salt Lake City, UT, USA. [2]Division of Pulmonary and Critical Care Medicine, Intermountain Medical Centre, Salt Lake City, UT, USA. [3]Division of Respiratory, Critical Care, and Occupational Medicine, Dept of Internal Medicine, University of Utah, Salt Lake City, UT, USA.

Correspondence: Nathan Dean, 6th floor, Heart and Lung Building, Intermountain Medical Center, 5121 South Cottonwood Murray, 84107, UT, USA. E-mail: Nathan.Dean@imail.org

ABSTRACT The pneumococcocal urine antigen test increases specific microbiological diagnosis over conventional culture methods in pneumonia patients. Data are limited regarding its yield and effect on antibiotic prescribing among patients with community-onset pneumonia in clinical practice.

We performed a secondary analysis of 2837 emergency department patients admitted to seven Utah hospitals over 2 years with international diagnostic codes version 9 codes and radiographic evidence of pneumonia.

Mean age was 64.2 years, 47.2% were male and all-cause 30-day mortality was 9.6%. Urinary antigen testing was performed in 1110 (39%) patients yielding 134 (12%) positives. Intensive care unit patients were more likely to undergo testing, and have a positive result (15% *versus* 8.8% for ward patients; p<0.01). Patients with risk factors for healthcare-associated pneumonia had fewer urinary antigen tests performed, but 8.4% were positive. Physicians changed to targeted antibiotic therapy in 20 (15%) patients, de-escalated antibiotic therapy in 76 patients (57%). In 38 (28%) patients, antibiotics were not changed. Only one patient changed to targeted therapy suffered clinical relapse. Length of stay and mortality were lower in patients receiving targeted therapy.

Pneumococcal urinary antigen testing is an inexpensive, noninvasive test that favourably influenced antibiotic prescribing in a "real world", multi-hospital observational study.

@ERSpublications
Pneumococcal urinary antigen test in pneumonia http://ow.ly/sm8R303lOe0

Received: Jan 29 2016 | Accepted after revision: Aug 12 2016

Support statement: This study was supported by the Intermountain Research and Medical Foundation, Salt Lake City, UT, USA. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: None declared.

Introduction

Streptococcus pneumoniae is the most commonly identified bacteria causing community-acquired pneumonia [1]. The pneumococcal urine antigen test (UAT) is an assay commonly used to identify pneumococcal antigens excreted into the urine to increase the rate of specific microbiological diagnosis over conventional culture methods [2, 3]. Positive tests have been associated with more severe disease including admission to the intensive care unit (ICU), in-hospital treatment failure and increased 30-day mortality [4]. The BinaxNOW (Alere, Waltham, MA, USA) is the most common pneumococcal UAT utilised in the USA and, in a recent meta-analysis, it had a pooled sensitivity and specificity of 74.0% (95% CI 66.6–82.3%) and 97.2% (95% CI 92.5–99.8%), respectively [5]. Data are limited regarding the test's use and effect on antibiotic prescribing in clinical practice settings.

The Infectious Diseases Society of America/American Thoracic Society 2007 community-acquired pneumonia guidelines state that more research is needed regarding whether or not the pneumococcal UAT allows for narrowing of empiric antibiotic therapy to a single, specific antibiotic [1]. Two randomised, controlled trials examined the impact of pneumococcal UAT testing on therapy choice with one of the studies showing increased rate of relapse among those treated with *Streptococcus pneumoniae*-targeted therapy after positive UAT [6, 7]. There were otherwise no differences in clinical outcomes between the study groups. VAN DER EERDEN *et al.* [8] demonstrated fewer side effects in a randomised controlled trial of pathogen directed therapy *versus* empirical, broad-spectrum antibiotics. There are little existing data regarding pneumococcal UAT-based antibiotic therapy alteration. The British Thoracic Society 2009 pneumonia guidelines recommend that the pneumococcal UAT only be performed on patients with moderate or high-severity pneumonia [9].

We hypothesised that the pneumococcal UAT is often misapplied in clinical practice, becoming a needless expense without much added clinical benefit. We also hypothesised that its results are often ignored, with clinicians giving more heed to blood or sputum cultures. We therefore investigated the yield and impact of the pneumococcal UAT among emergency department patients with community-onset pneumonia admitted to seven Utah hospitals.

Methods

We performed a secondary analysis of electronic medical data from 2837 patients aged 18 years and older admitted with international diagnostic codes version 9 (ICD-9) and radiographic evidence of pneumonia evaluated in the emergency departments of seven Intermountain Healthcare hospitals [10]. All patients were enrolled during two study periods: December 2009–November 2010 and December 2011–November 2012. The gap year stems from the original purpose of this database to study impact of an electronic clinical decision support tool; additional details have been previously published [10]. Cultures of blood and sputum, ordering of urinary antigens, and viral PCR panels were at the discretion of clinicians as part of usual care. Standing orders instructed respiratory therapists to obtain tracheal aspirate for culture in patients for respiratory failure; methods for reporting causative pathogens have also been previously described [11].

These seven adult hospitals serve approximately half of the 2 million people residing in Northern Utah's urban corridor. Intermountain Medical Center is the largest of these hospitals, with 86 400 emergency department visits during 2012, and is affiliated with University of Utah residency programmes including emergency medicine and internal medicine. Three of the hospitals are smaller community hospitals with fewer than 30 000 emergency department visits annually. Standardised admission order sets for pneumonia patients included an order for UAT, pre-selected for ICU patients but requiring a check box for ward-admitted patients.

Two study authors (D.M. West and L.M. McCauley) manually reviewed medical records of patients with a positive pneumococcal UAT (obtained at any time during the hospital admission) to determine the test's impact on antibiotic treatment. These authors collaborated extensively to promote standardisation and avoid duplication and misclassification of data and counselled with the senior author (N.C. Dean) as needed for guidance. We classified change in antibiotic therapy as targeted (single penicillin-class antibiotic such as penicillin, ampicillin, or amoxicillin), de-escalated (decreased number of antibiotics and/or spectrum of antimicrobial activity) or unchanged (includes patients where additional antibiotics were administered). We also analysed the database for clinical factors predicting UAT positivity.

The study was approved by the Intermountain Healthcare Institutional Review Board and the Intermountain Privacy Board, and authorised by the Utah Population Database. Individual patient consent was not required.

Statistics

Pearson's Chi-squared test was used to compare proportions and rates, and Wilcoxon rank sum test was used to compare continuous, non-Gaussian distributions. Multivariable logistic regression was used to measure the effect of predictors on binary outcomes, with the Hosmer–Lemeshow goodness-of-fit test for model calibration.

Results

Of 2837 emergency department patients admitted to the hospital with pneumonia, 1110 (39%) underwent pneumococcal UAT yielding 134 positives (12%) (figure 1). Patients with healthcare-associated pneumonia (HCAP) [12] (n=541) were less likely than those with community-acquired pneumonia (n=2296) to have UAT performed (33.1 *versus* 40.5%, respectively; p=0.002) and less likely to be positive (8.4 *versus* 12.8%, respectively; p=0.13). Of the 2837 patients, mean age was 64.2 years, 47.2% were male and 41.7% were admitted to the intensive care unit within 72 h of their emergency department visit. All-cause 30-day mortality was 9.6%. Figure 2 shows the percentage of different pathogens identified by a combination of blood, sputum, tracheal aspirates, viral PCR and UAT for pneumococcus and legionella. Of 2837 patients, 6% were identified with pneumococcal pneumonia.

In a multivariable logistic regression measuring the likelihood of obtaining a pneumococcal UAT, those younger in age, those with lower arterial oxygen saturation/inspiratory oxygen fraction ratios, and those admitted to the intensive care unit were more likely to undergo UAT (tables 1 and 2). Most (94%) UAT were performed within 24 h of hospital admission.

Patients admitted to the intensive care unit had a greater proportion of positive UAT compared with those admitted to the hospital ward (15 *versus* 8.8%, respectively; p<0.01). On multivariable logistic regression, only those admitted to the intensive care unit were more likely to test positive (OR 1.84, 95% CI 1.24–2.74; p=0.004) (table 3).

In response to positive pneumococcal UAT, physicians changed to targeted antibiotic therapy in 15% of cases (n=20) with only one case of clinical relapse (5%) (figure 3). Reviewing that one case, follow-up cultures were negative and the relapse was attributed by treating clinicians to fluid overload. Of the 20 patients receiving targeted therapy, 19 had blood cultures obtained with only two positive for *Streptococcus pneumoniae*. We noted de-escalation of therapy in 76 (57%) patients, the most common patterns being de-escalation from empiric therapy of vancomycin and pipercillin–tazobactam to ceftriaxone and azithromycin or simply discontinuing vancomycin. De-escalation occurred within 24 h of the UAT result in 60 (62.5%) patients, and was not associated with relapse. We noted no change in antibiotic therapy in 38 (28%) patients, 13 of whom were already on ceftriaxone and azithromycin.

Length of stay was significantly lower among patients with targeted antibiotic therapy (median 1.9, CI 1.5–5.7; p=0.016) compared with de-escalated antibiotics (4.5, CI 2.8–7). Inpatient mortality was significantly lower for patients with de-escalated antibiotic therapy (0%, n=0) compared with unchanged antibiotics (21%, n=8; p<0.001).

The BinaxNOW Streptococcus UAT costs $16.32 per the 2015 Medicare pricing from Centre for Medicare and Medicaid Services.

Discussion

Pneumococcal UAT had a meagre positive yield overall of 12% (134 out of 1110) in emergency department pneumonia patients admitted to the hospital, but significantly higher yield in intensive care unit patients. In the 20 patients that received targeted anti-pneumococcal therapy, there were only two

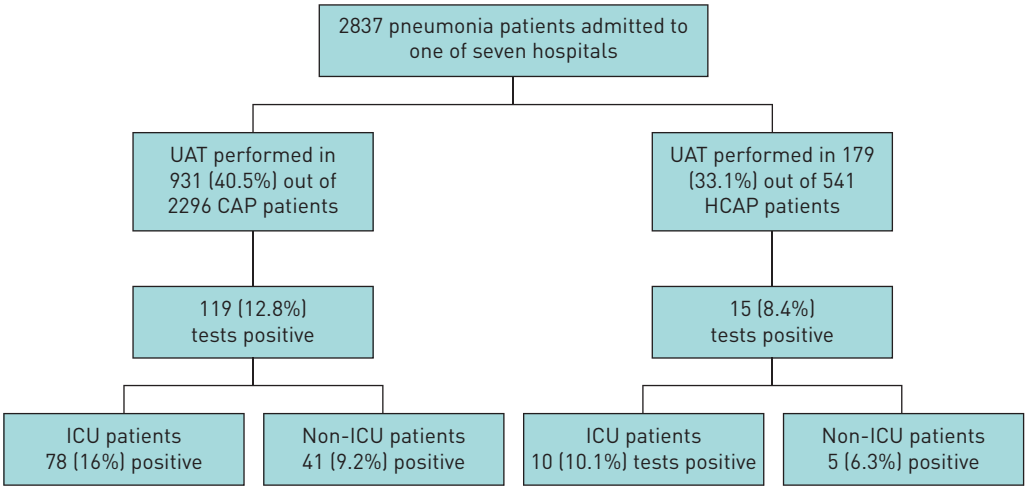

FIGURE 1 Study population: seven emergency departments. UAT: urine antigen test; CAP: community-acquired pneumonia; HCAP: healthcare-associated pneumonia; ICU: intensive care unit.

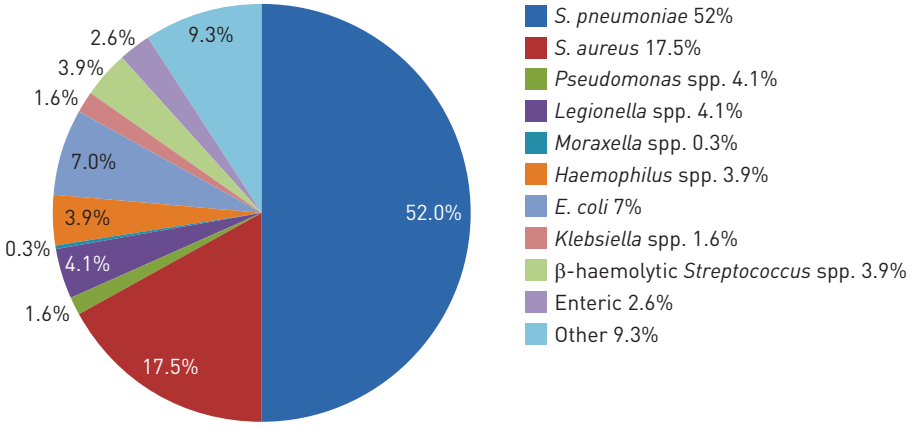

FIGURE 2 Percentage of positive results by pathogen among study patients with identified pathogens. "Other" includes respiratory viruses, *Stenotrophomonas, Prevotella, Peptostreptococcus* and other Streptococcal species.

positive blood cultures, making the positive UAT the only microbiological test in 18 patients to identify a causative organism. Physicians changed antibiotic management in the setting of a positive UAT in 72% of patients (combining targeted and de-escalated therapy together). Many of those without change in antibiotic were already receiving relatively narrow-spectrum ceftriaxone and azithromycin. The UAT is inexpensive; however, savings from de-escalating to targeted antibiotic therapy agents and experiencing fewer side effects from unnecessarily prolonged courses of broad-spectrum antibiotics may be substantial. While the yield is higher in intensive care unit patients, the low cost of UAT and the willingness of physicians who ordered the test to deescalate antibiotics based on its result suggest that it also has utility in patients admitted to ward settings. Our pessimistic hypothesis was therefore not confirmed by the findings of this study.

With the help of UAT, the pneumococcus was again the most commonly identified pathogen in patients admitted to the hospital with community-acquired pneumonia. The pneumococcus was identified in 52% of patients with an identified pathogen, 6% of the overall cohort of 2837. By comparison, recent studies of hospitalised patients with pneumonia have reported 21%, 17%, 15.9%, and 5% caused by the pneumococcus [15–18].

TABLE 1 Clinical parameters for community-acquired pneumonia patients stratified by whether a urine antigen test was obtained.

Variable	Urinary antigen test		p-value
	Obtained (n=931)	Not obtained (n=1365)	
Age years	63 (50–76)	68 (51–81)	<0.001
Male	458 (49.1)	622 (45.5)	0.10
Intensive care unit	486 (52.2)	430 (31.5)	<0.001
P_{aO_2}/F_{iO_2}	260.5 (202.4–319.1)	269.5 (226.2–319.1)	<0.001
Pleural effusion	134 (14.4)	229 (16.8)	0.14
eCURB	0.03 (0.014–0.08)	0.028 (0.014–0.072)	0.13
sCAP minor	2 (1–3)	2 (1–2)	0.001
CURB-65 score			0.28
0	260 (27.9)	352 (25.7)	
1	273 (29.3)	428 (31.3)	0.32
2	285 (30.6)	426 (31.2)	0.8
3	97 (10.4)	143 (10.5)	1
4	16 (1.7)	12 (0.9)	0.11
5	0	4 (0.3)	0.15

Data are presented as n (%) or median (interquartile range), unless otherwise stated. sCAP minor is the number of minor criteria for severe community-acquired pneumonia from the Infectious Diseases Society of America/American Thoracic Society 2007 community-acquired pneumonia guidelines 2007 and eCURB is the validated electronic version of CURB-65 (confusion, blood urea, respiratory rate, blood pressure, age 65 years) with weighted, continuous variables yielding a point estimate for 30-day mortality [13, 14]. P_{aO_2}: arterial oxygen tension; F_{iO_2}: fraction of inspired oxygen.

TABLE 2 Clinical parameters for healthcare-associated pneumonia patients, stratified by whether a urine antigen test was obtained

Variable	Urinary antigen test		p-value
	Obtained (n=179)	Not obtained (n=362)	
Age years	68 (55–80)	70 (57–81)	0.47
Male	76 (42.5)	184 (50.8)	0.08
Intensive care unit	99 (55.3)	168 (46.4)	0.06
P_{aO_2}/F_{iO_2}	248.2 (191.9–303.8)	252.2 (203.0–337.6)	0.20
Pleural effusion	50 (27.9)	108 (29.8)	0.72
eCURB	0.043 (0.019–0.134)	0.047 (0.019–0.116)	0.94
sCAP minor	2 (1–3)	2 (1–3)	0.64
CURB-65 score			
0	30 (16.8)	55 (15.2)	0.73
1	57 (31.8)	106 (29.3)	0.61
2	55 (30.7)	132 (36.5)	0.22
3	29 (16.2)	55 (15.2)	0.86
4	7 (3.9)	13 (3.6)	1
5	1 (0.6)	1 (0.3)	0.55

Data are presented as n (%) or median (interquartile range), unless otherwise stated. sCAP minor is the number of minor criteria for severe community-acquired pneumonia from the Infectious Diseases Society of America/American Thoracic Society 2007 community-acquired pneumonia guidelines 2007 and eCURB is the validated electronic version of CURB-65 (confusion, blood urea, respiratory rate, blood pressure, age 65 years) with weighted, continuous variables yielding a point estimate for 30-day mortality [13, 14]. P_{aO_2}: arterial oxygen tension; F_{iO_2}: fraction of inspired oxygen.

We found a low (one (5%) out of 20) relapse rate in those patients de-escalated to targeted therapy after positive UAT; even the one patient did not have relapse attributable to antibiotic de-escalation. Similarly, an observational study by Sorde *et al.* [6] showed that simplified therapy based on the urinary antigen test enabled directed therapy in 41 (8.6%) out of 474 of patients with community-acquired pneumonia without adverse effects. A prospective, randomised trial of 177 patients by Falguera *et al.* [7] showed that no difference in outcomes or adverse effects with targeted parenteral antibiotic therapy, although three (12%) out of 25 patients changed to oral amoxicillin did relapse *versus* three (2%) out of 150 other patients;

TABLE 3 Clinical parameters for patients with a positive UAT, stratified by antibiotic therapy

Variable	Antibiotic therapy		
	No change (n=38)	De-escalation (n=76)	Targeted (n=20)
Age years	58.5 (49.25–75)	63 (50.5–74.25)	57.5 (46.75–70.25)
Male	18 (47.4)	37 (48.7)	10 (50)
Intensive care unit	28 (73.7)	48 (63.2)	12 (60)
P_{aO_2}/F_{iO_2}	217.2 (178.4–274.8)	252.2 (204.9–303.8)	303.8 (214.5–360.5)
Pleural effusion	3 (7.9)	12 (15.8)	1 (5)
eCURB	0.053 (0.023–0.162)	0.04 (0.019–0.082)	0.028 (0.015–0.054)
sCAP minor	3 (2–3)	2 (1–3)	1 (0.75–2)
CURB-65 score			
0	6 (15.8)	12 (15.8)	7 (35)
1	10 (26.3)	25 (32.9)	8 (40)
2	16 (42.1)	30 (39.5)	5 (25)
3	6 (15.8)	7 (9.2)	0
4	0	2 (2.6)	0
5	0	0	0

Data are presented as n (%) or median (interquartile range), unless otherwise stated. sCAP minor is the number of minor criteria for severe community-acquired pneumonia from the Infectious Diseases Society of America/American Thoracic Society 2007 community-acquired pneumonia guidelines 2007 and eCURB is the validated electronic version of CURB-65 (confusion, blood urea, respiratory rate, blood pressure, age 65 years) with weighted, continuous variables yielding a point estimate for 30-day mortality [13, 14]. P_{aO_2}: arterial oxygen tension; F_{iO_2}: fraction of inspired oxygen.

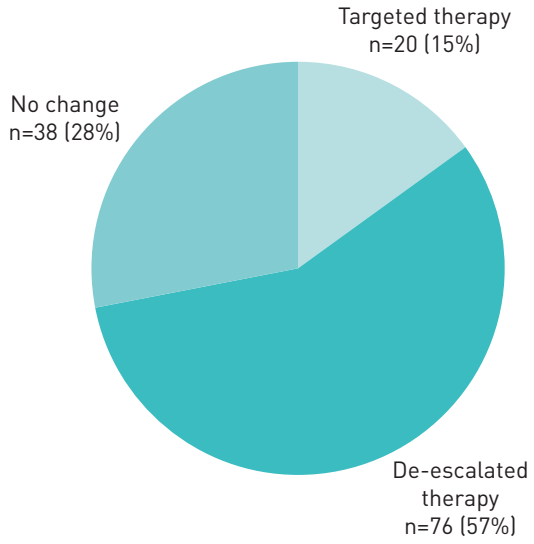

FIGURE 3 Changes in antibiotic therapy among patients with positive *Streptococcus* urinary antigen tests.

p=0.04). A recent multicentre Spanish study reported a 23% yield of the UAT among 3865 pneumonia patients where 30 day mortality (6%) and the rate of intensive care unit admission (7%) were lower than in our study [10]. The pneumococcus comprised 21% of the pathogens. Molinos *et al.* [15] derived predictors for a positive test, mostly factors associated with higher severity of illness. A similar analysis in our study resulted in the best prediction simply being intensive care unit admission.

Patients with risk factors for HCAP were less likely to be tested, and had a lower rate of positive UAT results. However, the positive yield of UAT again documents the presence of usual, non-resistant pathogens among HCAP patients. As HCAP does not accurately select patients with resistant pathogens, and broad-spectrum antibiotic therapy does not improve their outcome, we do not recommend considering HCAP factors in the decision to order pneumococcal UAT [19]. The HCAP concept was never adopted in Europe, and is "mostly dead" in North America.

Limitations

Our results may not be generalisable to other patient populations and hospitals since all seven hospitals are part of the same healthcare system located in a single geographic region. In addition, this is a secondary analysis of patients identified by ICD-9 coding and radiographic evidence of pneumonia. However, we previously reported that our case definition had a sensitivity of 0.68 and specificity of 0.99 compared with pneumonia diagnosis by physician case review [10]. Finally, this study is based on a "real world", observational database where the decision of a physician to order UAT testing and act on its results were not influenced by the study team.

This study supports the use of pneumococcal UAT testing as an inexpensive, noninvasive test that favourably influenced antibiotic prescribing. With increasing concern regarding antibiotic stewardship, the ability to safely and quickly narrow antibiotic therapy is increasingly important. Combined with clinical judgment demonstrated in this "real world" study, we encourage physicians to target antibiotic therapy towards *Streptococcus pneumonia* even if the UAT is the only positive microbiologic test.

Acknowledgement

This work was presented as an abstract at the American Thoracic Society International Conference 2015, Denver, CO, USA.

References

1 Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis* 2007; 44: S27–S72.
2 Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis* 2011; 52: Suppl. 4, S296–S304.
3 Blaschke AJ. Interpreting assays for the detection of *Streptococcus pneumoniae*. *Clin Infect Dis* 2011; 52: Suppl. 4, S331–S337.
4 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. *J Asian Pac Soc Respirology* 2014; 19: 936–943.
5 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* 51: 2303–2310.

6 Sorde R, Falco 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: 166–172.
7 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.
8 van der Eerden MM, Vlaspolder F, de Graaff CS, *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* 2005; 60: 672–678.
9 Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64: Suppl. III, iii1–iii55.
10 Dean NC, Jones BE, Jones JP, *et al.* Impact of an Electronic Clinical decision support tool for emergency department patients with pneumonia. *Ann Emerg Med* 2015; 66: 511–520.
11 McCauley LM, Webb BJ, Sorensen JS, *et al.* Use of tracheal aspirate culture in newly intubated patients with community-onset pneumonia. *Ann Am Thorac Soc* 2016; 13: 376–381.
12 American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
13 Jones J, Bewick T, Lim WS, *et al.* CURB-65 pneumonia severity assessment adapted for electronic decision support. *Chest* 2011; 140: 156–163.
14 Jones BE, Jones JP, Vines CG, *et al.* Validating hospital admission criteria for decision support in pneumonia. *BMC Pulm Med* 2014; 14: 149.
15 Molinos L, Zalacain R, Menendez R, *et al.* Sensitivity, specificity, and positivity predictors of the pneumococcal urinary antigen test in community-acquired pneumonia. *Ann Am Thorac Soc* 2015; 12: 1482–1489.
16 Musher DM, Roig IL, Cazares G, *et al.* Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect* 2013; 67: 11–18.
17 Postma DF, van Werkhoven CH, van Elden LJ, *et al.* Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med* 2015; 372: 1312–1323.
18 Jain S, Self WH, Wunderink RG, *et al.* Community-acquired pneumonia requiring hospitalization. *N Engl J Med* 2015; 373: 2382.
19 Webb BJ, Dascomb K, Stenehjem E, *et al.* Predicting risk of drug resistant organisms in pneumonia: moving beyond the HCAP model. *Respir Med* 2015; 109: 1–10.