

Utility of the Pneumococcal Urinary Antigen Test in the Management of Community-Acquired Pneumonia in Veterans Affairs Hospitals

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Abstract

Background: The pneumococcal urinary antigen test can help rapidly identify *Streptococcus pneumoniae* as the cause of community-acquired pneumonia (CAP). In this study, we assessed the utility of this test across an integrated healthcare system.

Methods: This retrospective cohort study included all acute-care admissions with CAP who were hospitalized during 2018-2023 and underwent pneumococcal urinary antigen testing at 85 Veterans Health Administration facilities. The primary outcome was days of antibiotic-spectrum coverage (DASC) score per length of antibiotic therapy (LOT). We used 1:5 propensity score matching to estimate the difference in the outcomes between patients who tested positive versus negative for the pneumococcal urinary antigen.

Results: The pneumococcal urinary antigen test was performed in 10,923 patient-admissions with CAP; 473 (4.3%) tested positive. There were 77 patient-admissions who grew *S. pneumoniae* in their blood, and 35 (45.5%) of these had a positive antigen test. After propensity-score matching with 454 patients across 66 medical centers who tested positive and 2,153 who tested negative, the median DASC per LOT was significantly smaller in patients with a positive versus negative test [positive: 8.0, negative 9.2; Wilcoxon $Z=6.68$; $p<0.0001$]. The median LOT was 8 days in both patients with a positive and negative test.

Conclusions: In this retrospective propensity-matched cohort study of patients with CAP, patients with a positive pneumococcal urinary antigen received more narrow-spectrum antibiotics than patients with negative results. However, the test had poor sensitivity. Because few patients tested positive, opportunities to practice antibiotic stewardship by leveraging the test's results were limited.

Summary

In this retrospective propensity-matched cohort of hospitalized patients with pneumonia, patients with a positive pneumococcal urinary antigen received more narrow-spectrum antibiotics than those with negative results. Because few patients tested positive, opportunities to act on the test's results were limited.

Introduction

Community acquired pneumonia (CAP) frequently results in hospitalization and the initiation of broad-spectrum antibiotics.¹ Establishing a microbiologic cause of pneumonia is often challenging, but if feasible, it can facilitate pathogen-directed antibiotic therapy.

The pneumococcal urinary antigen test is a noninvasive assay used to aid in the diagnosis of *Streptococcus pneumoniae*, the most common bacterial cause of CAP.² The test detects the C-polysaccharide antigen on the cell wall common to all types of *S. pneumoniae*. The most widely used assay, BinaxNow (Abbott, USA), was licensed by the US Food and Drug Administration in 1999. Other assays have since been developed.

The results of the pneumococcal urinary antigen test are available within 15 minutes, and the test's sensitivity is estimated at 66% with a specificity of 90%.³ Professional guidelines give different recommendations on when the pneumococcal urinary antigen should be used, ranging from recommendations to test in all cases of CAP to only those who have a severe infection.⁴⁻⁶

Prior studies on the clinical impact of the pneumococcal urinary antigen were done before or shortly after the widespread introduction of the 13-valent polysaccharide conjugate vaccine (PCV-13) in late 2011.^{7,8} In addition, prior studies only assessed inpatient antibiotic therapy.^{7,8} Because the average length of stay for community-acquired pneumonia is often ≤ 3 days,⁹ it is possible that the pneumococcal urinary antigen test would have a larger effect on antibiotics prescribed at hospital discharge.

To gain a more updated understanding of the effect of pneumococcal urinary antigen testing on patient outcomes, including both inpatient and post-discharge antibiotic therapy, we examined its use within the Veterans Healthy Administration (VHA) system, the largest integrated healthcare network in the United States.

METHODS

We performed a retrospective cohort study among all patients hospitalized with CAP within the VHA during 2018–2023.

Data Sources

We accessed national administrative data from all VA facilities through the VA Corporate Data Warehouse (CDW) via the VA Informatics and Computing Infrastructure.

Inclusion Criteria

We included patients discharged from a VHA hospital observation or inpatient bed between January 1, 2018 and December 31, 2023 who also had a principal discharge diagnosis, as defined by ICD-10 codes, of pneumonia or a principal discharge diagnosis of sepsis or acute respiratory failure with a secondary discharge diagnosis of pneumonia.¹⁰ Diagnoses of bacterial infection (e.g., pneumonia) were based on ICD-10 codes applied at hospital discharge, as defined by a publicly available Agency for Healthcare Research and Quality (AHRQ) resource.¹³

To be included, patient-admissions were also required to have had the pneumococcal urinary antigen test performed. Other inclusion criteria were: a) having a radiography or a computed tomography scan of their chest on admission, regardless of the result; b) received at least one dose of an intravenous antibiotic potentially used for pneumonia (i.e., ceftriaxone) within 24 hours of admission and have received greater than three days of continuous antibiotic therapy. We excluded patient-admissions who met any of the following criteria: a) died on or before day three of their hospital stay; b) discharge diagnoses for infections other than CAP (i.e., cellulitis,

urinary tract infection, etc.); b) rapid tests from respiratory samples that were positive for bacteria; c) urine *Legionella* antigen tests that were positive; d) transferred from or to an outside healthcare facility, as we could not accurately measure antibiotics; e) history of a lung transplant or cystic fibrosis; f) underwent a pleural drainage procedure during the 30 days prior to admission.

Variables

We collected demographics such as age at admission, sex, and race as patient-level data. For each patient-admission, we also collected data to calculate a modified Pneumonia Severity Index (PSI) score.¹¹ Variables we collected for the PSI score were as follows:

- Vital signs (temperature, heart rate, systolic blood pressure, and respiratory rate) from the period 24 hours before and 24 hours after the time of admission.
- Laboratory values (blood urea nitrogen, sodium, glucose, hematocrit) collected within 24 hours before and 48 hours after the time of admission. Missing values were assumed to be normal.
- Comorbidities (i.e., neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, renal disease), based on ICD-10 codes from outpatient and inpatient encounters over the 12 months prior to the index visit and from the index admission itself.¹²
- Patient's location of residence prior to admission (i.e., nursing home versus other location).
- Elements of the PSI score we could not collect were altered mental status, arterial pH, partial pressure of arterial oxygen, and pleural effusion on chest radiograph.

In addition to results for pneumococcal urinary antigen tests, we collected the results of testing for respiratory viruses, nasal swabs for methicillin-resistant *Staphylococcus aureus* (MRSA), and any sputum or blood cultures collected on the day before admission, on the day of admission, or during the subsequent 2 days (4-day window) were captured.

Antibiotics administered during the hospital stay were identified using the Barcode Medication Administration (BCMA) pharmacy data domain of the CDW. For each patient-admission, we collected data on all antibacterials (hereafter "antibiotics") included in the National Healthcare Safety Network (NHSN)'s Antimicrobial Use and Resistance Protocol. Antibiotics specific to treating pneumonia were also identified (Supplemental Table 1).¹⁴ Using outpatient medication files, we identified post-discharge antibiotics; these were oral antibiotics dispensed from the outpatient pharmacy during the discharge period.¹⁵ We assumed that all outpatient oral antibiotics dispensed during this time frame were initiated by the patient on the day following discharge.

Outcomes

The primary outcome was the days of antibiotic spectrum score (DASC) per length of antibiotic therapy (LOT), which was calculated by dividing total inpatient plus post-discharge DASC by total length of therapy (LOT), which included both inpatient and post-discharge antibiotics. Each day the patient received antibiotics, regardless of the number of different agents prescribed, was considered to be one LOT. Secondary outcomes included total LOT, or inpatient LOT plus post-discharge LOT. An additional secondary outcome was a composite measure of mortality and/or hospital readmission to a VHA hospital within 30 days of hospital discharge. Mortality and readmission can be competing risks, which is why we measured them as an either/or outcome. We obtained dates of death from the VHA Vital Status File, which combines mortality data from multiple VHA and non-VHA sources; this file strongly aligns with the National Death Index.¹²

Statistical analysis

Given the strong potential for selection bias, we used propensity score matching to estimate the difference in outcomes between patients who tested positive versus negative for the pneumococcal urinary antigen. To ensure matched patients would be exposed to similar clinical care (e.g., stewardship processes), patients were fixed matched on hospital site, in addition to being matched on propensity score. Propensity scores for the likelihood of having a positive pneumococcal urinary antigen test were computed for each patient using a logistic regression model with the following covariates: age, sex, admission to the intensive care unit on hospital days 1 and/or 2, an immunodeficiency (i.e., leukemia, lymphoma, human immunodeficiency virus infection, bone marrow transplantation or solid organ transplantation), certain comorbidities (i.e., malignancy, chronic lung disease, congestive heart failure, liver disease, cerebrovascular accident, and dialysis-dependent kidney disease), hospital stay in the prior 90 days, chemotherapy during the prior 30 days or the current hospital stay, MRSA nasal colonization, any positive results for respiratory viruses, PSI score, and calendar year at discharge.

Matched controls were required to score within a caliper of 0.2 (i.e., 0.2 times standard deviation of the logit of the propensity scores), relative to cases, and each case was matched with up to 5 controls. Standardized differences were calculated before and after matching to assess balance in baseline characteristics between groups. Discrete outcome measures were contrasted between patients with a positive versus negative pneumococcal urinary antigen test using a Wilcoxon rank sum test, and a chi-square test for dichotomous outcomes. Of 473 patient-admissions with a positive pneumococcal urinary antigen test, only 5 were repeat admissions of the same patient. Thus, the propensity score analysis used only the first observed admission for cases, and control patients with more than one admission could only be matched once, such that all patients in the analysis were unique. Cases that failed to match any controls were excluded from the propensity score analysis.

Results

After applying inclusion and exclusion criteria (Figure 1), there were 10,923 qualifying patient-admissions across 85 VHA medical centers in which the pneumococcal urinary antigen test was performed. The antigen test was positive in 473 (4.3%). Baseline characteristics of patient-admissions with a positive or negative test result are shown in Table 1.

In addition to the 473 patient-admissions with a positive pneumococcal urinary antigen, an additional 42 patients grew *Streptococcus pneumoniae* in their blood and 132 others grew only *Streptococcus pneumoniae* in their sputum. The total prevalence of *Streptococcus pneumoniae* community-acquired pneumonia was therefore 5.9%.

Empiric antibiotic therapy on hospital day 1 was comparable in patient-admissions regardless of the result of their pneumococcal urinary antigen test. Beta-lactam monotherapy was prescribed to 171 (36.2%) with a positive test versus 3,688 (35.3%) with a negative test. Fluoroquinolone monotherapy was prescribed to 11 (2.3%) with a positive test and 374 (3.6%) with a negative test. An anti-pneumococcal beta-lactam plus atypical coverage was given to 123 (26.0%) patient-admissions with a positive test compared to 2,445 (23.4%) with a negative test. Finally, broad-spectrum antibiotics were prescribed for 149 (31.5%) patient-admissions with a positive test compared to 3,615 (34.1%) with a negative test. Other antibiotic regimens were given to 19 (4.0%) with a positive test versus 328 (3.1%) with a negative test.

Sensitivity and specificity of the pneumococcal urinary antigen

There were 77 patient-admissions who grew *Streptococcus pneumoniae* in their blood, and 35 (45.5%) of these had a positive pneumococcal urinary antigen. There were 163 who grew *Streptococcus pneumoniae* in their sputum and did not have known *Streptococcus pneumoniae* bacteremia; 36 (22.1%) of these patients had a positive antigen. There were 5,435 patient-admissions who did not grow *Streptococcus pneumoniae* from a sputum culture +/- a blood culture; the pneumococcal urinary antigen test was negative in 5,251 (96.6%) of these patients. For 28 patient-admissions with a positive pneumococcal urinary antigen test and sputum cultures positive for non-pneumococcal organisms, the most common reported organisms were *Staphylococcus aureus* 10 (9 methicillin-susceptible *S. aureus*, 1 MRSA) and *Pseudomonas aeruginosa* 6.

Propensity score matching

Prior to matching, standardized differences greater than 0.10 between positive and negative patient-admissions were observed for several characteristics, including age 75-84 years (22.2% vs. 28.0%), congestive heart failure (22.8% vs. 31.3%), discharged in 2018 (25.2% vs. 19.4%) and discharged in 2019 (25.6% vs. 20.2%).

Using propensity scores, 454 unique patients across 66 medical centers were matched to 2,153 unique patients with a negative test (Table 1). There were 19 patient-admissions in the positive test result group who failed to satisfy matching criteria because they represented a patient who was already in the cohort (n=5) or because they failed to satisfy matching criteria with any control patient (n=14).

Findings from the analysis of the propensity-score matched cohort are shown in Table 2. In the propensity-score matched cohort, the median DASC per day of antibiotic therapy was significantly smaller in patients with a positive versus negative test [positive test: 8.0 (IQR 6.3-10.6), negative test: 9.2 (IQR 7.2-12.0); Wilcoxon $Z=6.68$, $p<0.001$]. The median length of antibiotic therapy was 8 days (IQR 6-11) in both patients with a positive and negative test (Wilcoxon $Z=1.25$, $p=0.211$). There were 55 (12.1%) patients with a positive test who died or were readmitted within 30 days compared to 385 (17.9%) in the patients with a negative test (Chi square = 8.89, $p=0.003$).

Discussion

In this national retrospective cohort study of hospitalized patients with CAP, the pneumococcal urinary antigen test was positive in approximately 1 of every 20 cases in which it was used. A positive test result was associated with using more narrow-spectrum antibiotics, which likely suggests clinicians were comfortable targeting *Streptococcus pneumoniae* with their antibiotic therapy. We also observed better clinical outcomes in those who tested positive, although the reasons for this association are unclear.

We found that 4.3% of patient-admissions with CAP who had the pneumococcal urinary antigen test performed were found to be positive. An additional 1.6% had *Streptococcus pneumoniae* detected on culture for an overall prevalence of 5.9%. This prevalence is largely in line with prior reports. In a 2010–2012 study of 3634 consecutive adults hospitalized with CAP at 5 US hospitals, *Streptococcus pneumoniae* was identified as the pathogen in 5%.² A retrospective 2010–2015 cohort study across 170 US hospitals found that 7.2% of patients with CAP or healthcare-associated pneumonia who were tested with the pneumococcal urinary antigen were found to be positive. Recent studies using a proprietary pneumococcal urinary antigen test, which assesses for 30 distinct pneumococcal serotypes, have shown that use of the test approximately doubles the rate at which *Streptococcus pneumoniae* is identified.^{13,14}

Our findings suggest that the pneumococcal urinary antigen test is less sensitive than previously reported.³ After introduction of the 13-valent polysaccharide conjugate vaccine (PCV13) in 2011, there is some evidence that the sensitivity of the BinaxNOW version of the test decreased as the prevalence of vaccine serotypes also decreased.¹⁵ For example, one study from Japan reported sensitivities of 48.7% in 2015 for the BinaxNOW assay.¹⁶ Non-vaccine serotypes may not be detected as well by the antigen test, leading to more false-negative results.¹⁵ In our study, only 45.5% of patient-admissions with *S. pneumoniae* bacteremia had a positive test even though prior studies have shown that the pneumococcal urinary antigen test is highly sensitive in these bacteremia cases.^{16,17} Such a low sensitivity in patients with a high-burden of *S. pneumoniae* infection calls into question the test's ongoing utility.¹⁸

Like prior reports, we found that a positive result on the pneumococcal urinary antigen test was associated with narrower-spectrum antibiotic use. In a study of 32 Swedish hospitals, a positive result was associated with less broad-spectrum beta-lactam monotherapy on hospital day 3 and

less use of atypical coverage.⁸ In a study from 170 US hospitals, patients initially treated with broad-spectrum antibiotics who had a positive test were more likely to have de-escalation performed while hospitalized than patients with a negative test or those not tested.⁷ A study from 3 hospitals in Denmark found that a positive test was associated with a lower risk of receiving broad-spectrum antibiotics at discharge.¹⁹ Our study adds to what is already known in that it shows that patients with a positive test had a more narrow antibiotic-spectrum prescribed, on average, over their inpatient plus post-discharge treatment course.

On average, patients in our cohort with a positive pneumococcal urinary antigen received an antibiotic with a 1-point lower antibiotic-spectrum score than patients with a negative antigen. This would equate to prescribing amoxicillin (ASC score = 5) instead of ceftriaxone (ASC score = 6) or amoxicillin-clavulanate (ASC score = 7) instead of cefepime (ASC score = 8). The benefits of using antibiotics with a slightly more narrow spectrum of activity are unclear. However, more narrow-spectrum antibiotics may be less likely to cause antibiotic resistance than broad-spectrum agents. In addition, prior studies show that de-escalating, or narrowing, antibiotics is one of the most common recommendations made by stewardship programs.^{20,21} Therefore, tracking antibiotic spectrum may be a way to assess the effectiveness of antibiotic stewardship activities.²²⁻²⁴

Our study also highlights continued opportunities to shorten antibiotic duration in patients with CAP. The median antibiotic duration was 8 days, which was longer than what professional guidelines would have recommended during the observation period.⁴ This finding is in line with several other studies that found excessively long antibiotic durations in patients with CAP.^{9,25,26} Professional guidelines now acknowledge that courses as short as 3 days are appropriate in carefully selected patients.²⁴

It is unclear why patients in our cohort who had a positive pneumococcal urinary antigen test had better outcomes than patients who tested negative. Further exploring reasons for this difference is beyond the scope of this analysis. A small randomized controlled trial of pathogen-directed therapy based on urine *Legionella* or pneumococcal antigen test results did not show substantial clinical or economic benefits.²⁷ In fact, patients treated according to their positive urine antigen test results had a incidence of clinical relapse than those who received empiric antibiotic therapy.²⁷ A stepped-wedge cluster-randomized non-inferiority trial across 12 Dutch hospitals showed that a multifaceted stewardship intervention, which included pneumococcal urinary antigen testing, reduced broad-spectrum antibiotic use without adversely affecting clinical outcomes.²⁸ This study did not compare outcomes specifically in patients who tested positive vs. negative by the antigen test.

Our study has some limitations that should be acknowledged. First, because the study is retrospective in design, we cannot prove that the positive result for the pneumococcal urinary antigen test caused clinicians to narrow antibiotics. It is possible that there were other factors that drove this decision. Second, we do not know which versions of the urinary antigen test were being used across all 85 hospitals. Different types of assays may have slightly different

diagnostic performance. Available assays include the Abbott Diagnostic BinaxNOW *S. pneumoniae* Urinary Antigen Enzyme Immunoassay, QuidelOrtho Sofia *S. pneumoniae* Fluorescent Immunoassay, and Trinity Biotech Uni-Gold. Third, we only captured hospital re-admissions that occurred within the VHA system, so the frequency of re-admissions may be falsely low. However, this bias should have been non-differential. Fourth, the PSI scores we calculated were missing certain required parameters (e.g., pH, altered mentation, pleural effusion), so the scores we calculated were likely falsely low for many patients. Fifth, because this study was done within the VHA system, it may not be generalizable to other settings.

In conclusion, this retrospective propensity matched cohort study from a national cohort of hospital admissions with CAP showed that patients with a positive pneumococcal urinary antigen received more narrow-spectrum antibiotics than patients with a negative result. However, less than 5% of tested patients were positive, and fewer than half of patients with *Streptococcus pneumoniae* bacteremia had a positive antigen result. Further monitoring of the test's utility is warranted as the epidemiology of *S. pneumoniae* changes.

Declarations

Ethics and consent to participate declaration: The Institutional Review Board (IRB) of the University of Iowa and the Iowa City Veterans Health Care System approved this study. Waiver for informed consent was granted by the IRB for this retrospective cohort.

Availability of data and materials: Data not publicly available.

Competing interests: All authors report no relevant conflicts of interest.

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Ethics and consent to participate declaration: not applicable

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Tables

Table 1. Baseline characteristics of patients with community-acquired pneumonia who tested positive and negative by the pneumococcal urinary antigen test at VHA medical centers, 2018-2021

	Overall cohort (85 hospitals)			Propensity-score matched analysis (66 hospitals)		
	Positive UAG (n=473)	Negative UAG (n=10,450)	Standard difference	Positive UAG (n=454)	Negative UAG (n=2153)	Standard difference
Age in years						
< 65	117 (24.7)	2047 (19.6)	0.124	110 (24.2)	512 (23.8)	0.010
65-74	195 (41.2)	4109 (39.3)	0.039	183 (40.3)	892 (41.4)	0.023
75-84	105 (22.2)	2922 (28.0)	0.133	105 (23.1)	486 (22.6)	0.013
≥ 85	56 (11.8)	1372 (13.1)	0.039	56 (12.3)	263 (12.2)	0.004
Female, n (%)	17 (3.6)	450 (4.3)	0.037	16 (3.5)	80 (3.7)	0.010
Prior hospital admission¹	82 (17.3)	2187 (20.9)	0.091	78 (17.2)	388 (18.0)	0.022
Chemotherapy during current admission or prior 30 days	11 (2.3)	321 (3.1)	0.046	10 (2.2)	61 (2.8)	0.040
Comorbidities						
Cerebrovascular accident	20 (4.2)	591 (5.7)	0.066	19 (4.2)	95 (4.4)	0.011
Congestive heart failure	108 (22.8)	3270 (31.3)	0.191	107 (23.6)	511 (23.7)	0.004
Chronic lung disease	282 (59.6)	5937 (56.8)	0.057	268 (59.0)	1226 (56.9)	0.042
Dialysis-dependent kidney disease	6 (1.3)	221 (2.1)	0.066	6 (1.3)	28 (1.3)	0.002
Immunodeficiency	37 (7.8)	727 (7.0)	0.033	32 (7.0)	166 (7.7)	0.025
Liver disease	39 (8.2)	659 (6.3)	0.075	35 (7.7)	154 (7.2)	0.021
Malignancy	111 (23.5)	2733 (26.2)	0.062	107 (23.6)	527 (24.5)	0.021
Pneumonia Severity Index						
I	8 (1.7)	281 (2.7)	0.068	8 (1.8)	47 (2.2)	0.030
II	61 (12.9)	1128 (10.8)	0.065	58 (12.8)	280 (13.0)	0.007
III			0.047			0.004

IV	122 (25.8)	2485 (23.8)	0.070	114 (25.1)	537 (24.9)	0.013
V	198 (41.9)	4738 (45.3)	0.010	195 (43.0)	911 (42.3)	0.004
	84 (17.8)	1818 (17.4)		79 (17.4)	378 (17.6)	
ICU on hospital day 1 and/or 2	53 (11.2)	964 (9.2)	0.065	49 (10.8)	250 (11.6)	0.026
MRSA nasal colonization upon admission, if checked	22 (4.7)	494 (4.7)	0.004	21 (4.6)	109 (5.1)	0.020
Positive test for a respiratory virus	30 (6.3)	449 (4.3)	0.091	27 (5.9)	114 (5.3)	0.028
Year of discharge						
2018	119 (25.2)	2024 (19.4)	0.140	109 (24.0)	522 (24.2)	0.006
2019	121 (25.6)	2107 (20.2)	0.129	117 (25.8)	551 (25.6)	0.004
2020	66 (14.0)	1604 (15.3)	0.109	65 (14.3)	327 (15.2)	0.016
2021	45 (9.5)	1352 (12.9)	0.088	44 (9.7)	219 (10.2)	0.027
2022	56 (11.8)	1548 (14.8)	0.094	55 (12.1)	242 (11.2)	0.015
2023	66 (14.0)	1815 (17.4)		64 (14.1)	292 (13.6)	

1. A hospital admission ≥ 2 days in length that occurred during the 90 days before admission.

Table 2. Primary and secondary outcomes for a propensity-matched cohort of patients hospitalized with community-acquired pneumonia who underwent pneumococcal urinary antigen testing, 2018-2023

	Positive UAG (n=454)	Negative UAG (n=2153)	Statistics Z or χ^2 ; p-value
Primary outcome			
DASC score per day of antibiotic therapy, median (IQR)	8 (6.3-10.6)	9.2 (7.2-12)	6.68; <0.001*
Secondary outcomes			
Total length of antibiotic therapy in days, median (IQR)	8 (6-11)	8 (6-11)	1.25; 0.211
Hospital readmission and/or death, n (%)	55 (12.1)	385 (17.9)	8.89; 0.003**

*The mean difference between positive UAG and negative UAG was 1.2 (95% CI, 0.8-1.5).

**The odds ratio was 0.63 (95% CI, 0.47-0.86).

Figures

Figure 1. Flow diagram for the study cohort

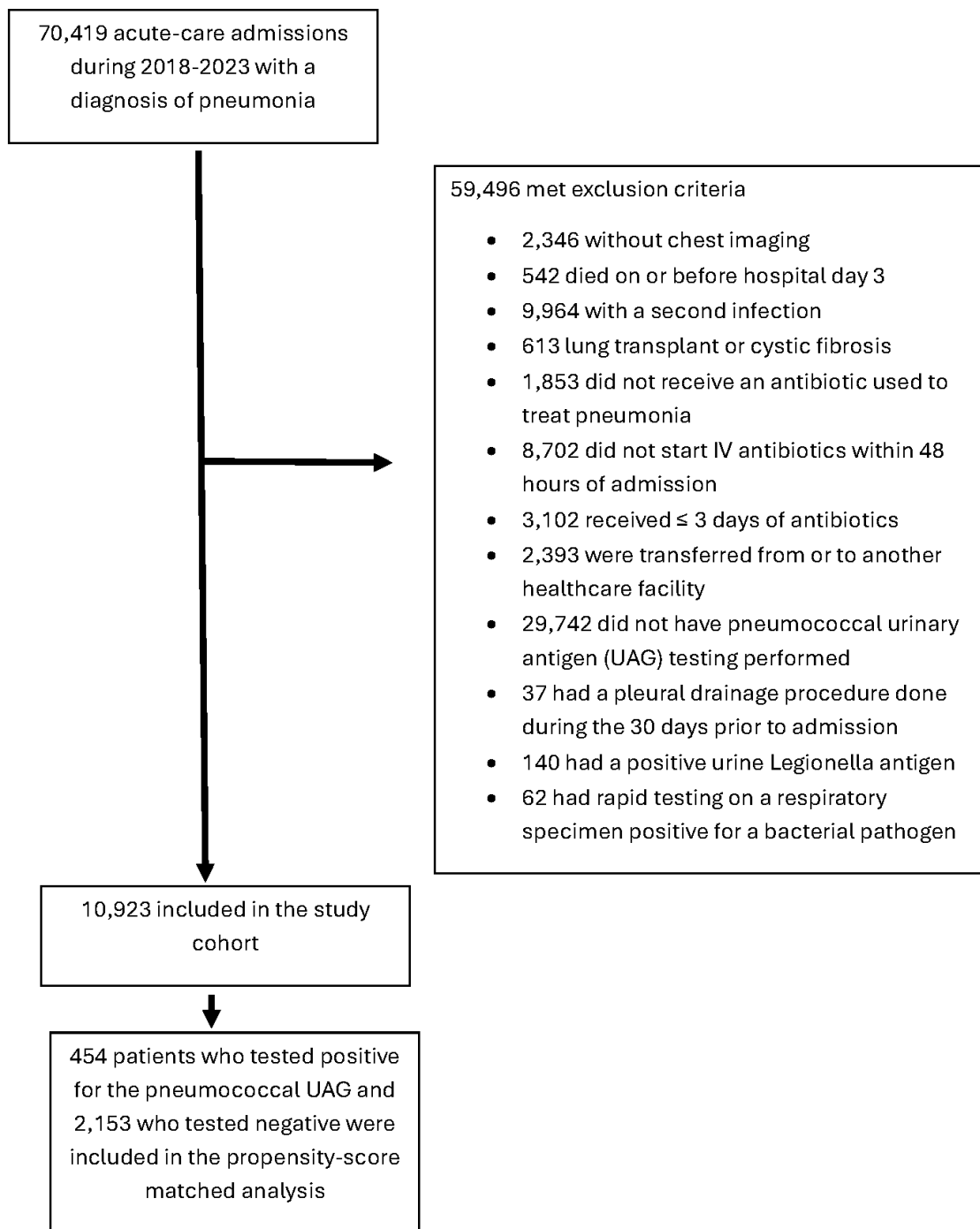


Figure 1

See image above for figure legend.