

Pneumococcal and *Legionella* Urinary Antigen Tests in Community-acquired Pneumonia: Prospective Evaluation of Indications for Testing

Shawna Bellew,¹ Carlos G. Grijalva,¹ Derek J. Williams,¹ Evan J. Anderson,² Richard G. Wunderink,³ Yuwei Zhu,¹ Grant W. Waterer,⁴ Anna M. Bramley,⁵ Seema Jain,⁵ Kathryn M. Edwards,¹ and Wesley H. Self¹

¹Vanderbilt University Medical Center, Nashville, Tennessee; ²Emory University School of Medicine, Atlanta, Georgia; ³Northwestern University Feinberg School of Medicine, Chicago, Illinois; ⁴University of Western Australia, Perth; and ⁵Centers for Disease Control and Prevention, Atlanta, Georgia

CID 2019;68(12):2026–33 (online 09/18)

Journal Club, 03.06.19

Background

Streptococcus pneumoniae Urinary Antigen Test (UAT)

- FDA 1999, Se 50-80%, Sp >90% (Mandell 2007)
- EIA, rapid test (15 min)
- C-polysaccharide (all serotypes)

Legionella pneumophila UAT

- LP Serogroup 1 soluble Ag (80-90% N.Amer)



Mandell LA 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(Suppl 2):S27-72.

IDSA/ATS consensus guidelines for CAP in adults (2007)

Routine testing of hospitalized adults with

- 1) severe/critical CAP
- 2) any of →

Expert opinion

No prospective evaluation

Dishomogeneity

Table 1. Indications for Urinary Antigen Test for *Streptococcus pneumoniae* and *Legionella pneumophila*

Indication	SP UAT	LP UAT
ICU admission	x	x
Failure of outpatient antibiotic therapy	x	x
Leukopenia	x	
Active alcohol abuse	x	x
Chronic liver disease	x	
Asplenia	x	
Recent travel		x
Pleural effusion	x	x

Objectives & Methods

Objectives:

- to evaluate the accuracy of the risk factor–based approach (IDSA/ATS 2007) for identifying which patients to test with UATs
- to evaluate the association of clinical characteristics not included in the current guidelines with SP and LP UAT results to identify additional risk factors that may improve future guidelines

Design: cross-sectional study

Data Source: Etiology of Pneumonia in the Community (EPIC) Study

- Multicenter, prospective study (active surveillance) → CDC
- Adults with CAP [01/01/10 – 30/06/12]
- 5 hospitals (3 in Chicago, IL, and 2 in Nashville, TN)

EPIC Study, eligibility criteria

Category / Variable	Definition
<i>Inclusion Criteria</i>	
Age ≥ 18 years old	Age at least 18 years old at the time of hospital admission.
Hospital admission	Hospital admission (in-patient or observation status) at a hospital participating in the study.
Clinical evidence of acute infection	At least one of the following at the time of hospital admission: body temperature $\geq 38.0^{\circ}\text{C}$; body temperature $< 35.5^{\circ}\text{C}$; white blood cell count ≥ 11.0 thousand cells/ mm^3 ; white blood cell count ≤ 3.0 thousand cells/ mm^3 ; altered mental status, or reported chills, fever, or feelings of feverishness prior to hospital arrival.
Clinical evidence of acute respiratory infection	At least one of the following at the time of hospital admission: shortness of breath, chest pain, respiratory failure, tachypnea, cough, or abnormal breath sounds.
Radiographic evidence of pneumonia	Interpretation of a chest xray or computed tomography scan by a study-dedicated thoracic radiologist blinded to clinical data as consistent with pneumonia.
<i>Exclusion Criteria</i>	
Recent hospitalization	Hospitalization within the past 28 days if immunocompetent or 90 days if immunosuppressed.
Functionally dependent nursing home resident	Resident of a nursing home who is dependent on others for activities of daily living
HIV with low CD4 count	Infection with the human immunodeficiency virus with a CD4 count < 200 cells/ mm^3 .
Recent transplant	Solid organ or stem cell transplant within the past 90 days.
Tracheostomy	Tracheostomy in place.
Gastrostomy tube	Gastrostomy tube in place.
Cancer with neutropenia	Diagnosis of cancer and neutrophil count < 500 cells/ mm^3
Cystic fibrosis	Patient with diagnosis of cystic fibrosis
Alternative diagnosis	Diagnosis other than pneumonia completely explains the patient's acute presentation, such as acute pulmonary embolism or acute heart failure

Indications according to IDSA/ATS 2007	Variables according to previous studies
ICU Admission	Age >65
Failure of outpatient AB therapy	Fever
Leukopenia	Nausea
Active alcohol abuse	Diarrhea
Chronic liver disease	Confusion
Asplenia	Headache
Recent travel	Hyponatremia (Na<130mmol/l)
Pleural effusion	Severe CAP
	Empiric use of broad spectrum AB

Definitions

severe CAP

- ≥ 3 IDSA/ATS minor criteria present at the time of hospital arrival
- Pneumonia Severity Index risk class IV or V

Broad spectrum AB

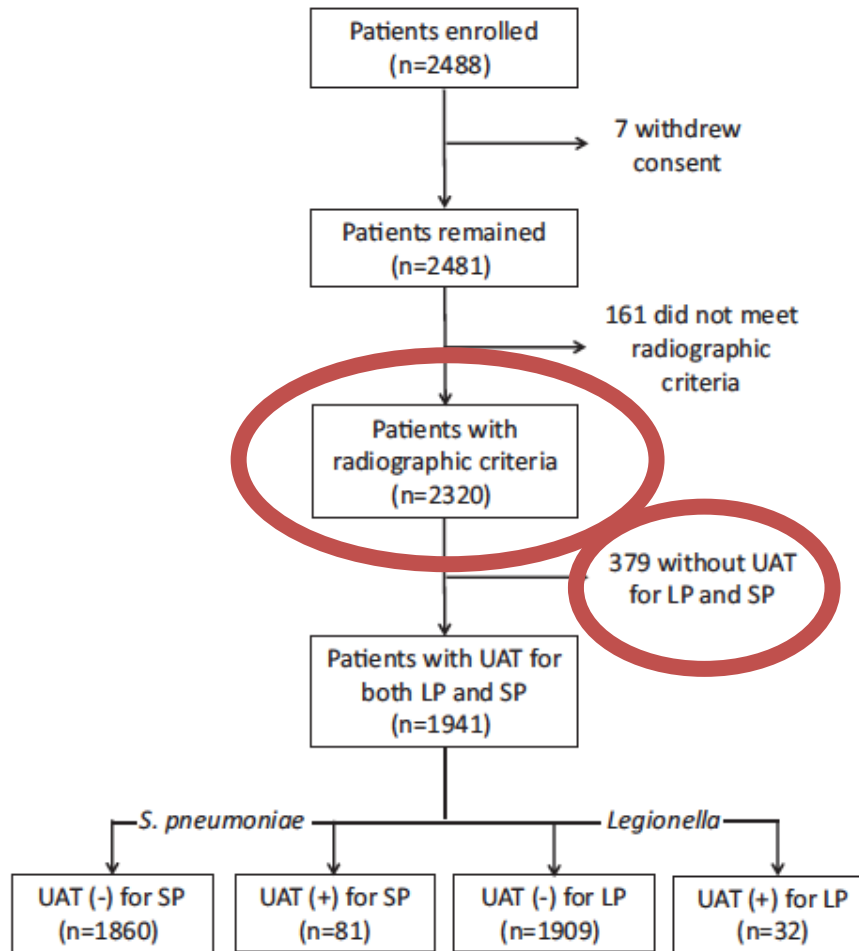
Antipseudomonal beta-lactam, aminoglycoside, carbapenem, vancomycin, linezolid, aztreonam, daptomycin

Predictor variables

SP	LP
Sex	Recent travel
Age ≥ 65 years	fever
Failure of outpatient antibiotics	diarrhea
fever	hyponatremia
hyponatremia	
ICU admission	
PSI risk class $\geq IV$	
Use of empiric broad-spectrum AB	

NB: predictor variables limited to the clinical data that are routinely available within the first few hours (no PCT / viral test)

Results



CKD / Dialysis

Characteristic	Overall Sample (n = 1941)	SP UAT Positive (n = 81)	SP UAT Negative (n = 1860)	LP UAT Positive (n = 32)	LP UAT Negative (n = 1909)
Median age, years (IQR)	57 (46–71)	60 (50–70)	57 (46–71)	58.5 (49–63)	57 (46–71)
Male sex	958 (49.4)	35 (43.2)	923 (49.6)	26 (81.3)	932 (48.8)
Race					
White	1055 (54.4)	46 (56.8)	1009 (54.3)	18 (56.3)	1037 (54.3)
Black	748 (38.5)	30 (37.0)	718 (38.6)	14 (43.8)	734 (38.5)
Asian	41 (2.1)	1 (1.2)	40 (2.2)	0	41 (2.2)
Other	97 (5.0)	4 (4.9)	93 (5.0)	0	97 (5.1)
Hispanic ethnicity	203 (10.5)	11 (13.6)	192 (10.3)	3 (9.4)	200 (10.5)
Current smoking	504 (26.0)	29 (35.8)	475 (25.5)	10 (31.3)	494 (25.9)
Heavy alcohol use	96 (5.0)	4 (4.9)	92 (5.0)	2 (6.3)	94 (4.9)
City of enrollment					
Chicago	1310 (67.5)	47 (58.0)	1263 (67.9)	19 (59.4)	1291 (67.6)
Nashville	631 (32.5)	34 (42.0)	597 (32.1)	13 (40.6)	618 (32.4)
Comorbidities					
Chronic kidney disease	268 (13.8)	17 (21.0)	251 (13.5)	5 (15.6)	263 (13.8)
Dialysis	23 (1.2)	1 (1.2)	22 (1.2)	0	23 (1.2)
Asthma	502 (25.9)	19 (23.5)	483 (26.0)	5 (15.6)	497 (26.0)
Chronic obstructive pulmonary disease	451 (23.2)	25 (30.9)	426 (22.9)	2 (6.3)	449 (23.5)
Heart failure	361 (18.6)	18 (22.2)	343 (18.4)	4 (12.5)	357 (18.7)
Liver disease	108 (5.6)	3 (3.7)	105 (5.7)	1 (3.1)	107 (5.6)
Sickle cell disease	29 (1.5)	0	29 (1.6)	0	29 (1.5)
Immunosuppressed	326 (16.8)	11 (13.6)	315 (16.9)	7 (21.9)	319 (16.7)
Human immunodeficiency virus infection	61 (3.1)	2 (2.5)	59 (3.2)	2 (6.3)	59 (3.1)
Cancer	398 (20.5)	13 (16.1)	385 (20.7)	2 (6.3)	396 (20.7)
Leukemia, lymphoma, or Hodgkin disease	62 (3.2)	1 (1.2)	61 (3.3)	0	62 (3.3)

25.9%

17.9%

Strep.pneumoniae UAT

- 1184 (61%) ≥ 1 IDSA/ATS indication
- 49 (4.1%) positive UAT
- P (pos*IDSA vs pos*no IDSA) = 0.92
- ≥ 1 IDSA/ATS indication: Se 61% (95% CI 49–71%), Sp 39% (95% CI 37–41)

Legionella pneumophila UAT

- 1258 (64.8%) ≥ 1 IDSA/ATS indication
- 32 (1.6%) positive UAT
- P (pos*IDSA vs pos*no IDSA) = 0.78
- ≥ 1 IDSA/ATS indication: Se 63% (95% CI 44–79%), Sp 35% (95% CI 33–37%)

Prevalence of IDSA/ATS indication by UAT result

univariate analysis

IDSA/ATS Indication	SP UAT Positive (n = 81)	SP UAT Negative (n = 1860)	SP OR (95% CI)	LP UAT Positive (n = 32)	LP UAT Negative (n = 1909)	LP OR (95% CI)
ICU admission	24 (29.6)	396 (21.3)	1.56 (0.95–2.54)	5 (15.6)	415 (21.7)	0.67 (0.26–1.74)
Failure of outpatient antibiotic therapy	12 (14.8)	386 (20.8)	0.66 (0.36–1.24)	4 (12.5)	394 (20.6)	0.55 (0.19–1.58)
Leukopenia	3 (3.7)	71 (3.8)	0.97 (0.30–3.15)	n/a	n/a	n/a
Active alcohol abuse	4 (4.9)	92 (5.0)	1.00 (0.36–2.79)	n/a	n/a	n/a
Chronic liver disease	3 (3.7)	105 (5.7)	0.64 (0.20–2.07)	1 (3.1)	107 (5.6)	0.54 (0.07–4.02)
Asplenia	0	28 (1.5)	n/c	n/a	n/a	n/a
Recent travel	n/a	n/a	n/a	10 (31.3)	330 (17.3)	2.17 (1.02–4.64)
Pleural effusion	25 (30.9)	564 (30.3)	1.03 (0.63–1.66)	9 (28.1)	580 (30.4)	0.90 (0.41–1.95)
≥1 IDSA/ATS indication	49 (60.5)	1135 (61.0)	0.98 (0.62–1.54)	20 (62.5)	1238 (64.9)	0.90 (0.44–1.86)

Prevalence of potential predictors (literature) by UAT result

univariate analysis

Characteristic	SP UAT Positive (n = 81)	SP UAT Negative (n = 1860)	SP OR (95% CI)	LP UAT Positive (n = 32)	LP UAT Negative (n = 1909)	LP OR (95% CI)
Age ≥65	33 (40.7)	647 (34.8)	1.29 (0.82–2.03)	5 (15.6)	675 (35.4)	0.34 (0.13–0.88)
Fever (>38°C)	28 (34.6)	476 (25.6)	1.54 (0.96–2.46)	18 (56.3)	486 (25.5)	3.76 (1.86–7.63)
Nausea	29 (35.8)	649 (34.9)	1.04 (0.65–1.66)	13 (40.6)	665 (34.8)	1.28 (0.63–2.61)
Diarrhea	18 (22.2)	382 (20.5)	1.11 (0.65–1.89)	14 (43.8)	386 (20.2)	3.07 (1.51–6.23)
Confusion	17 (21.0)	374 (20.1)	1.06 (0.61–1.82)	7 (21.9)	384 (20.1)	1.1 (0.47–2.59)
Headache	40 (49.4)	858 (46.1)	1.14 (0.73–1.78)	23 (71.9)	875 (45.8)	3.02 (1.39–6.56)
Hyponatremia Na ≤130 mE/L	13 (16.1)	152 (8.2)	2.15 (1.16–3.98)	13 (40.6)	152 (8.0)	7.91 (3.83–16.3)
Pneumonia Severity Index risk class ≥IV	37 (45.7)	636 (34.2)	1.62 (1.03–2.53)	6 (18.8)	667 (34.9)	0.43 (0.18–1.05)
≥3 ATS minor criteria	7 (8.6)	129 (6.9)	1.27 (0.57–2.81)	2 (6.3)	134 (7.0)	0.88 (0.21–3.74)
Empiric broad-spectrum antibiotics	31 (38.3)	583 (31.3)	1.36 (0.86–2.15)	9 (28.1)	605 (31.7)	0.84 (0.39–1.83)

Multivariable analysis

	Multivariable OR (95% CI)
<i>Streptococcus pneumoniae</i> (n = 81)	
Male sex	0.69 (0.43–1.09)
Age ≥65	1.04 (0.61–1.77)
Failure of outpatient antibiotics	0.67 (0.36–1.26)
Fever (>38°C)	1.50 (0.93–2.42)
Hyponatremia	1.81 (0.96–3.41)
ICU admission	1.29 (0.75–2.24)
Pneumonia Severity Index risk class ≥IV	1.46 (0.84–2.55)
Empiric broad spectrum antibiotics	1.16 (0.70–1.94)
<i>Legionella pneumophila</i> (n = 32)	
Recent travel	2.18 (0.99–4.76)
Fever (>38°C)	3.21 (1.56–6.60)
Hyponatremia	7.44 (3.5–15.67)
Diarrhea	2.88 (1.39–5.95)

Se 88% (95% CI 71–97%), Sp 47% (95% CI 45–49%)

Stratification by PCT level

Characteristic	SP UAT positive, n (%) [n=61]	SP UAT negative, n (%) [n=1443]	SP OR (95% CI)	LP UAT positive, n (%) [n=23]	LP UAT negative, n (%) [n=1481]	LP OR (95% CI)
Procalcitonin >0.25 ng/ml	44 (72.1)	539 (37.4)	4.34 (2.45–7.67)	18 (78.3)	565 (38.2)	5.84 (2.15– 5.81)
Procalcitonin >0.5 ng/ml	39 (63.9)	413 (28.6)	4.42 (2.59–7.55)	16 (69.6)	436 (29.4)	5.48 (2.24–13.41)

Discussion

- EPIC: positive SP and LP UAT results were infrequent
- Current IDSA/ATS recommendations: not associated with positive UAT
- SP UAT(+): no strong association with other variables
- **LP UAT(+): strong association with Hypo-Na, recent travel, fever, diarrhea**
- SP UAT: NNT if IDSA → 25 [1x 17\$ → 425\$ or 408\$ with any variable]
- LP UAT: NNT if IDSA → 50 [850\$], if any → 59 [1003\$]

If diarrhea, hypoNa, fever, recent travel → 37 [629\$]

Conclusion

- + based on prospective active surveillance data
- Systematic testing vs clinician's decision
- Low number of positive UAT (- precision)
- Exclusion of 379 EPIC patients (CKD / dialysis) → no urine
- False positive?
- EPIC exclusion criteria (severe immunosuppression, no informed consent)
- Geography
- No analysis of clinical impact / further considerations (outbreaks)

Waiting for the autumn

- Pneumonia: presentation betw. different etiologies overlaps
- Utility of SP UAT in the light of standard empirical coverage → deescalation
- Changing epidemiology? (SP vaccine)
- Adequate coverage for LP?

Abandon risk factor – based approach for testing indications

Patient types / clinical scenarios?