Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Huang DT, Yealy DM, Filbin MR, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med. DOI: 10.1056/NEJMoa1802670

Supplementary Materials for

The Procalcitonin Antibiotic Consensus Trial (ProACT)

The ProACT Investigators

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The ProACT Investigators

The members of the ProACT Trial are as follows**: Coordinating Center:** Derek C. Angus, Chung-Chou H. Chang, Yohei Doi, Tammy L. Eaton, Michael J. Fine, Elizabeth A. Gimbel, David T. Huang (Chair), Octavia M. Peck Palmer, Francis Pike, Ashley M. Ryman, Lisa A. Weissfeld, Kourtney A. Wofford, Tianyuan Xu, Jonathan G. Yabes, Donald M. Yealy **Recruiting Centers:** Beth Israel Deaconess Medical Center: Michael W. Donnino; Brigham and Women's Hospital: Imoigele P. Aisiku, Peter C. Hou, Raghu R. Seethala; Detroit Receiving Hospital: Robert L. Sherwin; Essentia Health St. Mary's Medical Center: John M. Holst; Hershey Medical Center: Michelle A. Fischer, Colleen M. Rafferty; Maricopa Medical Center: William D. Dachman, Frank LoVecchio; Massachusetts General Hospital: Michael R. Filbin, Michael K. Mansour; Norwalk Hospital: Jonathan M. Fine, Jean M. Hammel; Ohio State University Hospital: Matthew J. Exline, Lauren T. Southerland, Thomas E. Terndrup; University of Alabama Hospital: Michael C. Kurz, David L. McCullum, Henry E. Wang; University of California Irvine Medical Center: Alpesh N. Amin, Shahram Lotfipour; University of Maryland Medical Center: Feras H. Khan, R. Gentry Wilkerson; University of Pittsburgh Medical Center Mercy Hospital: Heather A. Prunty, Brian Suffoletto; University of Pittsburgh Medical Center Presbyterian Hospital: Aaron M. Brown, Franziska F. Jovin

The ProACT Coordinators

Beth Israel Deaconess Medical Center: Julia Balkema, Varun Konanki, Joceyln Portmann, Chris Sulmonte, Gabriel Verzino, Alexander Wulff; Brigham and Women's Hospital: Guruprasad Jambaulikar, Brian Sheehan, Gary Theroux, Wanlu Xu; Detroit Receiving Hospital: Katee Dawood,

Patrick Medado, Joshua Philip, Duane Robinson, Lauren Weber; Essentia Health St. Mary's Medical Center: Kristina Ankrum, Jennifer Gunderson, Kaitlyn Rikkola; Hershey Medical Center: Nancy Campbell, Alison Muller, Christina Rodriguez, Brittany Roughsedge,; Maricopa Medical Center: Norvie Albillar, Madeleine Goetz, Mary Mulrow; Massachusetts General Hospital: Rebecca Lee, Mohammad Matin-Nejad, Blair Alden Parry, Christopher A. Wisnik; Norwalk Hospital: Christine Belden; Ohio State University Hospital: Michael Hill, Diana Madarang; University of Alabama Hospital: Nivedita Patkar, Joel B. Rogers; University of California Irvine Medical Center: Rick Jones; University of Maryland Medical Center: Dana Beach; University of Pittsburgh Medical Center Mercy Hospital: Denise Scholl; University of Pittsburgh Medical Center Presbyterian Hospital: Denise Scholl.

The ProACT Coordinating Center also thanks from the University of Pittsburgh, Melinda Carter, Renee Anderko, Vanessa Jackson, Caroline Pidro, Valerie Davis, Edvin Music, Lucy (Yueru) Ma, and Barbara J. Early. Dedicated to May K. Huang.

Data Safety and Monitoring Board

Thomas J. Marrie, Dalhousie Medical School; Steven M. Opal (Chair), Alpert Medical School of Brown University; David A. Schoenfeld, Harvard Medical School; Stephen W. Trzeciak, Cooper Medical School of Rowan University

Supplementary Methods

Diagnosis definitions

All ProACT patients had an initial primary clinical diagnosis of lower respiratory tract infection (LRTI). Presence and absence of baseline characteristics were used to define final diagnoses as below, based on published criteria and precedents. Patients could have more than one diagnosis (e.g. community-acquired pneumonia and asthma).

i. Community acquired pneumonia - new radiologic pulmonary infiltrate, and one or more of the following criteria: cough, > 38.0 or < 36.0 C, sputum production, dyspnea, tachypnea, rhonchi, wheezing, chills, chest discomfort, white blood cell count > 10^{10} or < 4 x10^{9} cells/L[1-3]

ii. Acute exacerbation of chronic obstructive pulmonary disease - past medical history of or consistent with chronic obstructive pulmonary disease, and acute worsening dyspnea, cough, or sputum production[4]

iii. Asthma exacerbation – past medical history of or consistent with asthma, and acute worsening dyspnea, cough, wheezing, or chest discomfort[5-7]

iv. Acute bronchitis - acute onset of cough, lasting less than 3 weeks in the absence of underlying lung disease or new infiltrate on chest x-ray[2, 8, 9]

v. Other LRTI - ≥ 1 respiratory symptom (cough, sputum, dyspnea, tachypnea, chest discomfort), and ≥ 1 auscultation abnormality (wheezing, rhonchi) or ≥ 1 infection sign (> 38.0 C or < 36.0, chills, or white blood cell count > 10^{10} or < 4 x10^{9} cells/L), that does not meet (i)-(iv) criteria.[2, 3]

vi. not LRTI – those that do not meet (i) – (v) criteria.

Exclusion criteria

We excluded patients with conditions where: physicians were unlikely to withhold antibiotics (prior antibiotics, vasopressor use, mechanical ventilation via endotracheal tube, known severe immunosuppression, accompanying non-respiratory infection, known lung abscess/empyema), procalcitonin could be elevated without bacterial infection (chronic dialysis, metastatic cancer, surgery in the past seven days), or follow-up would be difficult (prisoners, homeless, enrolled in ProACT in the past 30 days).

Intervention implementation approach

Trials should test novel interventions on a background of "best care". We chose centers with >96% compliance with all Joint Commission pneumonia quality measures, and disseminated national LRTI guidelines to promote best practice. We incorporated LRTI guideline recommendations in all study lectures, posters, and promotion tools, and instructed sites to promote these guidelines with all hospital-based clinicians responsible for antibiotic decision-making. This approach balances the control arm extremes of "wild type" usual care, versus an "active control" arm with interventional enforcement, consistent with the NIH conference on Considering Usual Medical Care in Clinical Trial Design recommendations.[10]

We used several implementation strategies, with a primary message to clinicians to please look at the procalcitonin guideline recommendation, while emphasizing the final antibiotic decision was entirely theirs. Our intent was to mimic how a hospital might typically deploy quality improvement staff when introducing a new intervention. Sites conducted in-service training for all hospital clinicians involved in antibiotic prescription for LRTI. To promote easy reminders, we

embedded the procalcitonin information into sites' electronic health records where feasible (Table S1, Supplementary Appendix). Coordinators identified the clinician with primary responsibility for antibiotic decision-making and informed that clinician the procalcitonin information was available, but did not otherwise influence care. Upon emergency department or hospital discharge, patients received a packet with a letter to their primary care provider with a study synopsis, their last procalcitonin result, and the procalcitonin guideline.

We tracked adherence in the procalcitonin-guided antibiotic prescription arm across two domains: protocol adherence (fidelity in delivering the study intervention of measuring and reporting the procalcitonin results and guideline) and procalcitonin guideline adherence (clinician adherence to the procalcitonin guideline antibiotic recommendations). If antibiotics were administered when procalcitonin was low, coordinators queried the clinician and recorded the reasons for procalcitonin guideline nonadherence. Coordinators generally queried at the same time they contacted clinicians in-person to ensure receipt of the PCT result and guideline. Thus, coordinator queries were conducted real-time in the ED, and generally during or shortly after morning rounds in the hospital as serial PCT levels were coordinated with routine morning blood work so as to be available for morning rounds. Queries were performed without a script, while the enrolled participant was in ED or hospital, and variably in terms of timing relative to when the final antibiotic decision was made. Coordinators did not query clinicians if antibiotics were withheld despite high procalcitonin, nor if antibiotic decisions were non-adherent to national LRTI guidelines. We promoted both protocol and procalcitonin guideline adherence with regular feedback with each site principal investigator and coordinator.

To standardize study procedures, we provide standardized training and materials plus continuous coordinating center support. We conducted a group investigator and coordinator training meeting at study launch, and individual sessions for two centers that were added subsequently. Training materials are available on the study website. Regular center visits, newsletters, around-the-clock coordinating center access, center monitoring, protocol delivery and procalcitonin guideline adherence reports and feedback were used to further enhance standardization. To standardize procalcitonin measurement, bioMérieux provided the procalcitonin assay equipment and in-service training. We provided centers with a packet that outlined test result reporting procedures, troubleshooting procedures, frequently asked questions, and study contact information.

Supplementary Figures

Figure S1. – ProACT guidelines.

The ProACT Coordinating Center provided posters of this Figure to all sites. Other study education, in-service training, and promotion materials contained the same content.

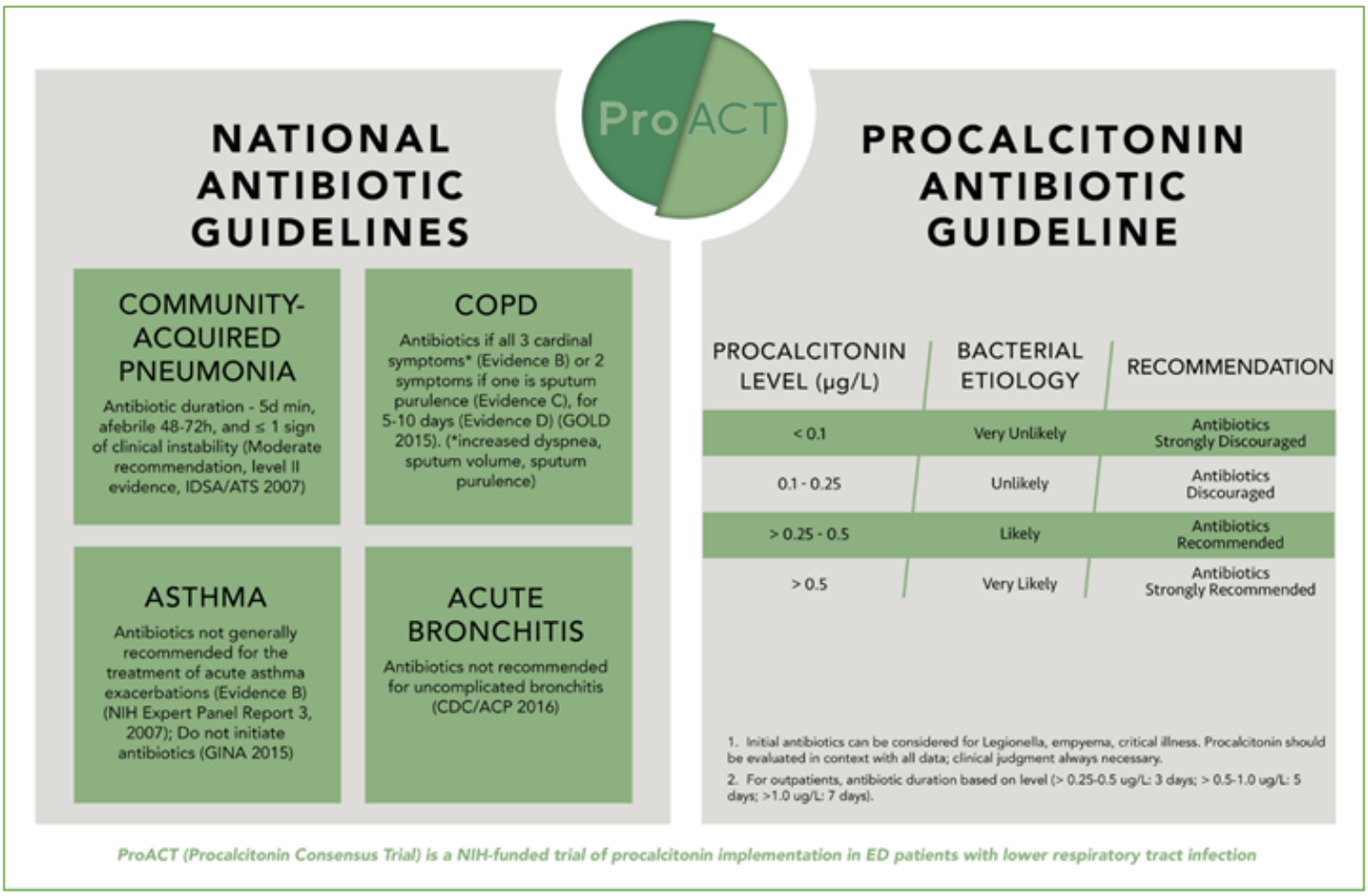


Figure S2. – Clinician adherence to procalcitonin-guided antibiotic prescription, by procalcitonin tier

The proportion of clinician decisions adherent to the provided procalcitonin guideline recommendation are shown, for each study timepoint, and stratified by procalcitonin tier. Across all timepoints, procalcitonin guideline adherence differed across procalcitonin tiers (<0.1 ug/L: 62.4% [588 of 943 timepoints], 0.1-0.25 ug/L: 62.0% [160 of 258 timepoints], >0.25-0.5 ug/L: 84.0% [42 of 50 timepoints], >0.5 ug/L: 95.6% [87 of 91 timepoints]; p<0.001).

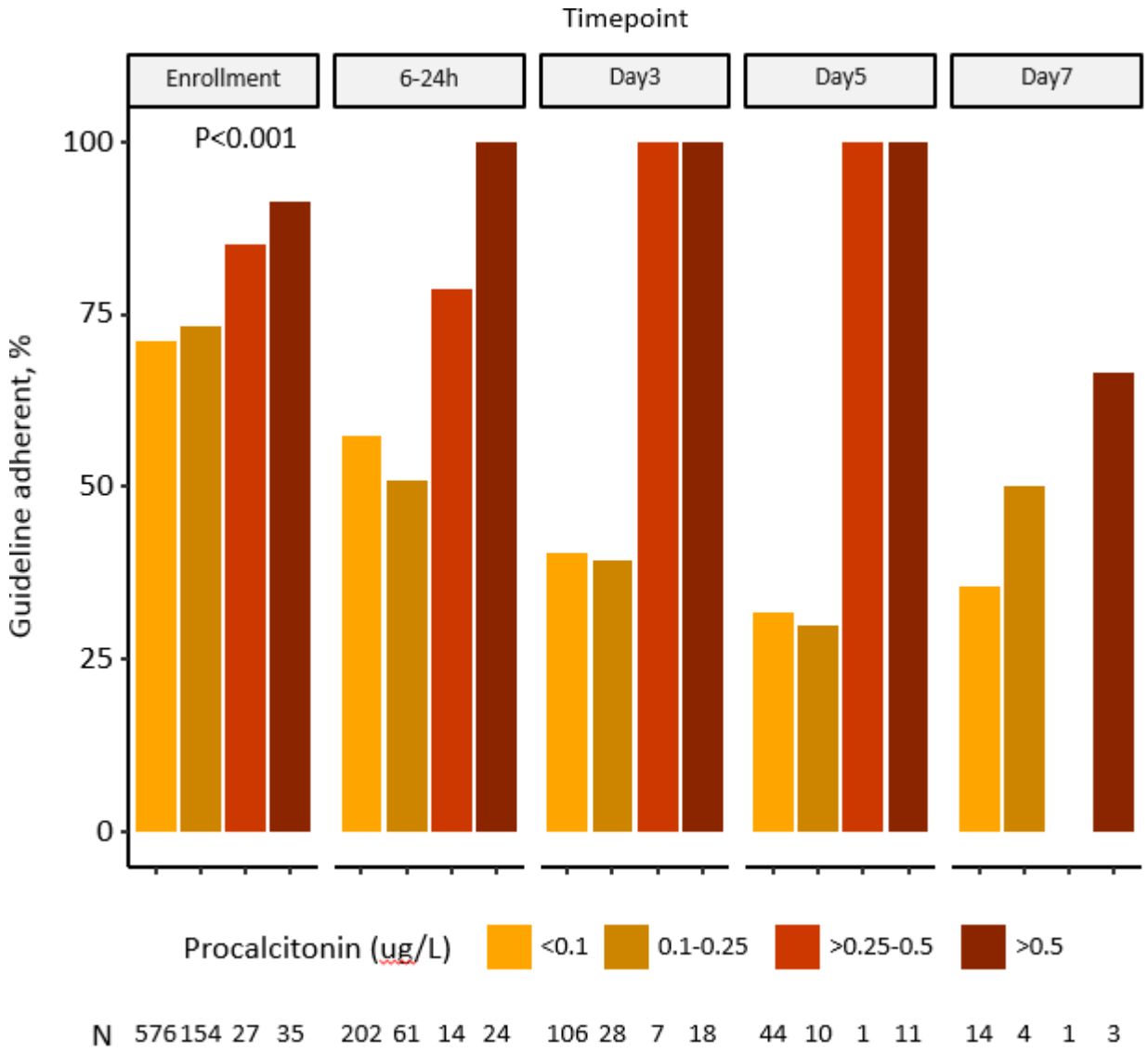
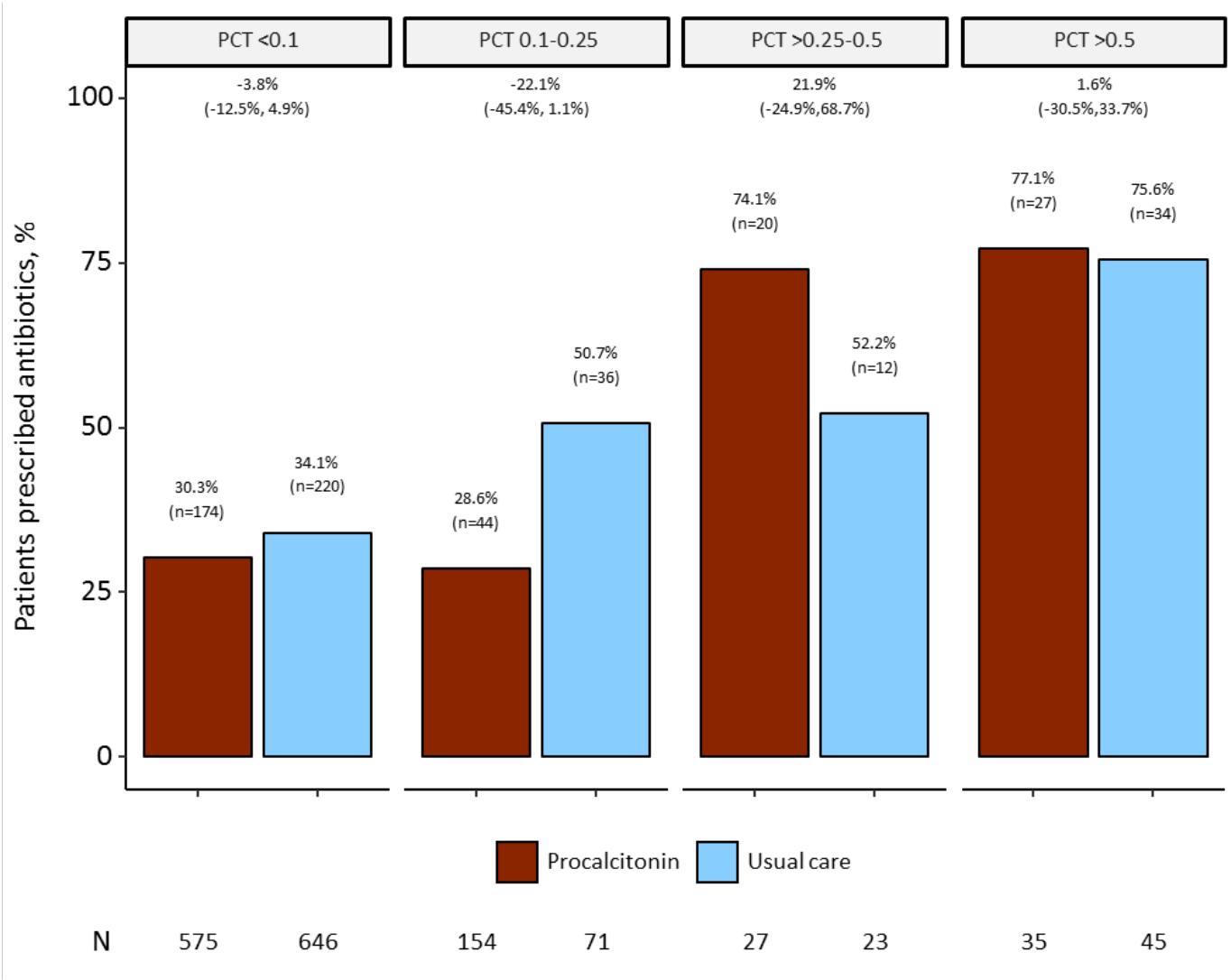


Figure S3. – Antibiotic prescription in emergency department, by procalcitonin tier.

In the usual care arm, procalcitonin was measured centrally in Pittsburgh, and unavailable to clinicians. Antibiotic prescription in emergency department includes post-randomization receipt of antibiotics in the emergency department and provision of an antibiotic prescription for patients discharged from the emergency department. For each procalcitonin tier, risk difference and 98.86% confidence intervals are shown to adjust for multiple comparisons. Excluded from the figure are 16 procalcitonin group patients whose procalcitonin measurement was not reported to the treating clinician, and four patients (1 procalcitonin, 3 usual care) with missing emergency department antibiotic prescription data.



Supplementary Tables

Table S1. Procalcitonin information delivery methods, by site

Center	PCT Delivery Method	EHR Type	Laboratory Information System
Beth Israel Deaconess Medical Center	Paper	N/A	N/A
Brigham and Women's Hospital	Paper	N/A	N/A
Detroit Receiving Hospital	Paper	N/A	N/A
Essentia Health St. Mary's Medical Center	Electronic Health Record	Epic	Soft Lab
Hershey Medical Center	Electronic Health Record	Cerner	Sunquest
Maricopa Medical Center	Electronic Health Record	Epic	Epic Beaker
Massachusetts General Hospital	Electronic Health Record	Epic	Sunquest
Norwalk Hospital	Electronic Health Record	Epic	Sunquest
Ohio State University Hospital	Electronic Health Record	Epic	Sunquest
University of Alabama Hospital	Electronic Health Record	IMPACT	IMPACT
University of California Irvine Medical Center	Paper	N/A	N/A
University of Maryland Medical Center	Paper	N/A	N/A
UPMC Mercy	Electronic Health Record	Cerner	Sunquest
UPMC Presbyterian	Electronic Health Record	Cerner	Sunquest

PCT – procalcitonin; EHR – electronic health record, N/A – not applicable

Table S2. – Baseline characteristics of patients with complete 30 day data versus those without.*

Characteristics	Complete 30-day data (n = 1303^)	Without complete 30-day data (n = 353^)	p-value
Age – yr	53.3 ± 18.2	52.1 ± 19.6	0.30
Male sex – no. (%)	543 (41.7%)	168 (47.6%)	0.053
Race – no. (%)			0.03
White	727 (55.8%)	198 (56.1%)	
Black	479 (36.8%)	114 (32.3%)	
Hispanic¶ – no. (%)	141 (11.0%)	71 (20.9%)	<0.001
Comorbidities§			
Charlson comorbidity score[11]	1.4 ± 1.5	1.3 ± 1.5	0.19
Current smoker – no. (%)	400 (31.1%)	119 (35.8%)	0.12
COPD	431 (33.1%)	98 (28.6%)	0.13
Asthma	507 (38.9%)	142 (41.4%)	0.44
Home medications – no. (%)‡			
Home oxygen	145 (11.1%)	31 (9.1%)	0.31
Oral corticosteroids	169 (13.0%)	46 (13.5%)	0.89
Inhaled corticosteroids	358 (27.5%)	78 (22.8%)	0.09
Inhaled long-acting bronchodilators	375 (28.8%)	93 (27.2%)	0.59
Leukotriene receptor antagonists	83 (6.4%)	19 (5.6%)	0.66
Symptoms§			
Duration - days	5.6 ± 5.1	5.0 ± 4.9	0.045
Cough – no. (%)	1153 (88.5%)	295 (86.3%)	0.30
Dyspnea – no. (%)	1111 (85.3%)	287 (83.9%)	0.59
Sputum production – no. (%)	752 (57.7%)	186 (54.4%)	0.30
Chest discomfort – no. (%)	694 (53.3%)	183 (53.5%)	0.98
Chills – no. (%)	436 (33.5%)	99 (28.9%)	0.13
Clinical findings§			
Temperature (degrees Celsius)	36.8 ± 0.6	36.9 ± 0.6	0.61

Heart rate	91.0 ± 18.1	91.3 ± 18.5	0.77
Respiratory rate	20.0 ± 5.8	19.8 ± 4.3	0.44
Mean arterial pressure (mmHg)	96.2 ± 14.9	96.4 ± 15.7	0.82
Oxygen saturation (%)	96.3 ± 4.2	96.7 ± 2.7	0.04
Rhonchi - no. (%)	182 (14.0%)	46 (13.5%)	0.87
Wheezing - no. (%)	718 (55.1%)	178 (52.0%)	0.34
White blood cell count, cells/uL, median (IQR)†	8.9 (6.8 - 11.8)	8.8 (7.0 - 11.3)	0.79
Procalcitonin, ug/L, median (IQR)§§	0.05 (0.05 - 0.10)	0.05 (0.05 - 0.08)	0.27
<0.1	968 (77.1%)	256 (78.8%)	
0.1 – 0.25	178 (14.2%)	48 (14.8%)	
>0.25 – 0.5	41 (3.3%)	9 (2.8%)	
>0.5	68 (5.4%)	12 (3.7%)	
Final diagnoses - no. (%)††			
Asthma	505 (38.8%)	141 (41.2%)	0.44
COPD	428 (32.8%)	96 (28.1%)	0.11
Acute bronchitis	314 (24.1%)	84 (24.6%)	0.92
CAP	261 (20.0%)	67 (19.6%)	0.92
PSI I	65 (24.9%)	17 (25.4%)	
PSI II	83 (31.8%)	21 (31.3%)	
PSI III	54 (20.7%)	9 (13.4%)	
PSI IV	49 (18.8%)	18 (26.9%)	
PSI V	9 (3.5%)	1 (1.5%)	
Other LRTI	68 (5.2%)	16 (4.7%)	0.79
Non-LRTI	32 (2.5%)	9 (2.6%)	1.00
Hospitalized – no. (%)**	615 (47.2%)	167 (47.3%)	1.00

* Plus-minus values are means + SD. COPD - chronic obstructive pulmonary disease; CAP - community-acquired pneumonia; PSI - pneumonia severity index, IQR – interquartile range, LRTI – lower respiratory tract infection.
^ Twenty-seven patients who completed 30-day follow-up could not recall their antibiotic use at day 30, and 15 patients who completed 15-day and 30-day follow-up could not recall their antibiotic use at day 15; these 42 patients are included in the without complete 30-day data group for this Table.
¶ Information on ethnicity was missing on 29 patients.
§ Information was missing on Charlson score for 16 patients, smoker status for 39 patients, COPD and asthma history for 11 patients.
‡ Home medications defined as medications taken by patient in last 7 days; information was missing on 13 patients, except for inhaled corticosteroids (14 patients) and inhaled long-acting bronchodilators (14 patients).
§ Information on symptoms and clinical findings was missing on 11 patients, except for symptom duration (no missingness), temperature (34 patients), respiratory rate (13 patients), and oxygen saturation (12 patients).
† White blood cell count data were available for 72.5% of the overall cohort (1200 of 1656 pts).
§§ Procalcitonin level data were available for 96.4% of the overall cohort (1596 of 1656 pts).
†† 215 patients had asthma and COPD, 109 patients had CAP and COPD, and 89 had CAP and asthma. Information on final diagnoses was missing on 11 patients.
** Includes eight patients with an emergency department length of stay >2 days.

Table S3. Initial presentation and outcomes, by procalcitonin tier

		Procalcitonin tier (ug/L)			
		I (< 0.1)	II (0.1 - 0.25)	III (≥ 0.25 - 0.5)	IV (> 0.5)
	p-value^	n = 1236	n = 230	n = 50	n = 80
Initial presentation					
SIRS criteria, n (%)					
SIRS by white blood cell	<0.001	180 (20.8%)	63 (35.8%)	19 (41.3%)	42 (56.8%)
SIRS by temperature	<0.001	87 (7.1%)	25 (11.2%)	11 (22.0%)	19 (24.1%)
SIRS by respiratory	0.13	299 (24.2%)	67 (29.1%)	18 (36.0%)	21 (26.2%)
SIRS by heart rate	<0.001	573 (46.4%)	119 (52.0%)	30 (60.0%)	55 (68.8%)
Total # of SIRS criteria met, mean (SD)	<0.001	0.9 (0.9)	1.2 (0.9)	1.6 (0.9)	1.7 (1.1)
Clinician % estimate of bacterial etiology, mean (SD)	<0.001	27.6 (25.4)	31.7 (24.2)	45.9 (30.2)	59.6 (29.5)
Outcomes					
Hospitalization, n (%)	<0.001	540 (43.7%)	124 (53.9%)	34 (68.0%)	57 (71.2%)
Hospital LOS*, mean (SD)	0.001	4.7 (3.9)	4.8 (3.3)	4.9 (3.4)	7.0 (6.1)
ICU admission, n (%)	0.001	45 (3.6%)	14 (6.1%)	4 (8.0%)	11 (13.8%)
Death within 30 days, n (%)	0.22	14 (1.1%)	4 (1.7%)	2 (4.0%)	1 (1.3%)

SIRS – systemic inflammatory response syndrome, SD – standard deviation, ED – emergency department, CAP – community acquired pneumonia, ICU – intensive care unit, LOS – length of stay.
^ Chi-square test of overall difference between procalcitonin tiers
* of hospitalized patients

Table S4. Additional prespecified subgroup analyses for primary outcome

	Antibiotic-days by day 30 (mean ± SD)		
	Procalcitonin (n = 826)	**Usual Care (n = 830)**	**Difference (99.86% CI)**
<65 years of age	**n = 608**	**n = 603**	
	4.0 ± 5.8	4.0 ± 5.5	0.03 (-1.0 to 1.1)
≥65 years of age	**n = 218**	**n = 227**	
	4.9 ± 5.9	5.1 ± 5.8	-0.2 (-2.1 to 1.6)
Male	**n = 357**	**n = 354**	
	4.3 ± 5.9	4.8 ± 6.1	-0.5 (-2.0 to 1.0)
Female	**n = 469**	**n = 476**	
	4.2 ± 5.7	3.9 ± 5.2	0.3 (-0.9 to 1.5)
Hispanic	**n = 108**	**n = 104**	
	2.9 ± 4.5	2.5 ± 4.8	0.4 (-1.7 to 2.5)
African-American	**n = 296**	**n = 297**	
	4.1 ± 5.9	3.7 ± 4.6	0.4 (-1.0 to 1.9)
White	**n = 455**	**n = 470**	
	4.4 ± 5.7	4.9 ± 6.2	-0.5 (-1.8 to 0.8)

We display 99.86% CIs to adjust for multiple comparisons of antibiotic exposure outcomes between groups.

Table S5. – Adverse outcomes by day 30*

	Procalcitonin (n = 826)	Usual Care (n = 830)	% Risk Difference (95% CI)
All patients (intention-to-treat)	**n = 826**	**n = 830**	
Overall adverse outcome	96 (11.7%)	109 (13.1%)	-1.5% (-4.6% to 1.7%)
Death	16 (1.9%)	10 (1.2%)	0.7% (-0.5% to 2.0%)
Endotracheal intubation	13 (1.6%)	20 (2.4%)	-0.8% (-2.2% to 0.6%)
Vasopressors	11 (1.3%)	21 (2.6%)	-1.3% (-2.7% to 0.1%)
Renal failure	3 (0.4%)	4 (0.5%)	-0.1% (-0.8% to 0.6%)
Lung abscess / empyema	4 (0.5%)	5 (0.6%)	-0.1% (-0.9 to 0.7%)
Pneumonia development in non-CAP patient	8 (1.0%)	9 (1.0%)	-0.1% (-1.1% to 1.0%)
Hospital readmission	62 (7.6%)	70 (8.5%)	-0.9% (-3.6% to 1.8%)
Per-protocol population	**n = 696**	**n = 830**	
Overall adverse outcome	79 (11.4%)	109 (13.1%)	-1.7% (-5.5% to 2.1%)
Per-guideline population	**n = 513**	**n = 830**	
Overall adverse outcome	55 (10.8%)	109 (13.1%)	-2.4% (-7.5% to 2.8%)
Complete case	**n = 821**	**n = 820**	
Overall adverse outcome	92 (11.2%)	100 (12.2%)	-1.0% (-4.1% to 2.1%)
Missing not at random analysis	**n = 826**	**n = 830**	
Overall adverse outcome	97 (11.7%)	110 (13.2%)	-1.5% (-4.7 to 1.7%)
Asthma	**n = 310**	**n = 336**	
Overall adverse outcome	27 (8.6%)	41 (12.1%)	-3.5% (-8.2% to 1.2%)
Death	2 (0.7%)	0 (0.0%)	0.7% (-0.3% to 1.7%)
Endotracheal intubation	2 (0.7%)	7 (2.2%)	-1.5% (-3.3% to 0.4%)
Vasopressors	1 (0.4%)	6 (1.8%)	-1.5% (-3.1% to 0.1%)
Renal failure	0 (0.0%)	0 (0.0%)	0.0% (-0.4% to 0.4%)
Lung abscess / empyema	0 (0.0%)	1 (0.3%)	-0.3% (-1.0% to 0.4%)
Pneumonia development in non-CAP patient	0 (0.1%)	3 (0.9%)	-0.9% (-2.0% to 0.2%)
Hospital readmission	21 (6.9%)	30 (9.0%)	-2.1% (-6.3%, 2.0%)
COPD	**n = 265**	**n = 259**	
Overall adverse outcome	57 (21.4%)	53 (20.4%)	1.0% (-6.0% to 8.0%)
Death	7 (2.7%)	3 (1.3%)	1.5% (-1.0% to 3.9%)
Endotracheal intubation	7 (2.7%)	9 (3.5%)	-0.8% (-3.8% to 2.2%)
Vasopressors	4 (1.6%)	8 (3.2%)	-1.6% (-4.3% to 1.0%)
Renal failure	2 (0.8%)	0 (0.0%)	0.8% (-0.4% to 1.9%)
Lung abscess / empyema	1 (0.4%)	0 (0.0%)	0.4% (-0.5% to 1.3%)
Pneumonia development in non-CAP patient	5 (1.9%)	3 (1.2%)	0.8% (-1.4% to 2.9%)
Hospital readmission	38 (14.4%)	37 (14.5%)	-0.0% (-6.1% to 6.0%)

Acute bronchitis	**n = 208**	**n = 190**	
Overall adverse outcome	13 (6.3%)	12 (6.3%)	-0.1% (-4.8% to 4.7%)
Death	2 (1.0%)	1 (0.5%)	0.4% (-1.2% to 2.1%)
Endotracheal intubation	0 (0.0%)	1 (0.5%)	-0.5% (-1.6% to 0.5%)
Vasopressors	1 (0.5%)	1 (0.5%)	-0.1% (-1.4% to 1.4%)
Renal failure	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Lung abscess / empyema	1 (0.5%)	1 (0.5%)	-0.1% (-1.4% to 1.4%)
Pneumonia development in non-CAP patient)	2 (1.0%)	2 (1.1%)	-0.1% (-2.1% to 1.9%)
Hospital readmission	9 (4.3%)	8 (4.2%)	0.1% (-3.9% to 4.1%)
Community-acquired pneumonia	**n = 167**	**n = 161**	
Overall adverse outcome	28 (16.8%)	29 (17.9%)	-1.2% (-9.4% to 7.0%)
Death	6 (3.6%)	5 (3.3%)	0.3% (-3.6% to 4.3%)
Endotracheal intubation	7 (4.2%)	6 (3.8%)	0.4% (-3.8% to 4.7%)
Vasopressors	5 (3.0%)	8 (5.1%)	-2.1% (-6.4% to 2.2%)
Renal failure	0 (0.0%)	2 (1.3%)	-1.3% (-3.1% to 0.5%)
Lung abscess / empyema	2 (1.2%)	2 (1.3%)	-0.1% (-2.5% to 2.3%)
Pneumonia development in non-CAP patient	n/a	n/a	n/a
Hospital readmission	14 (8.4%)	16 (10.2%)	-1.9% (-8.2% to 4.5%)
Other LRTI	**n = 42**	**n = 42**	
Overall adverse outcome	4 (9.5%)	5 (11.6%)	-2.0% (-15.3% to 11.2%)
Death	1 (2.4%)	0 (0.4%)	2.0% (-3.4% to 7.3%)
Endotracheal intubation	1 (2.4%)	2 (5.6%)	-3.3% (-11.9% to 5.4%)
Vasopressors	1 (2.4%)	2 (5.4%)	-3.1% (-11.6% to 5.5%)
Renal failure	0 (0.0%)	0 (0.3%)	-0.3% (-2.6% to 2.0%)
Lung abscess / empyema	0 (0.0%)	0 (0.2%)	-0.2% (-2.3% to 1.8%)
Pneumonia development in non-CAP patient	0 (0.0%)	1 (2.6%)	-2.6% (-7.5% to 2.4%)
Hospital readmission	3 (7.1%)	1 (3.2%)	3.9% (-5.8% to 13.6%)
Non-LRTI	**n = 20**	**n = 21**	
Overall adverse outcome	0 (0.0%)	1 (4.8%)	-4.8% (-13.9% to 4.4%)
Death	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Endotracheal intubation	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Vasopressors	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Renal failure	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Lung abscess / empyema	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Pneumonia development in non-CAP patient	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Hospital readmission	0 (0.0%)	1 (4.8%)	-4.8% (-13.9% to 4.4%)

<65 years of age	**n = 608**	**n = 603**	
Overall adverse outcome	50 (8.2%)	67 (11.2%)	-3.0% (-6.3% to 0.4%)
Death	4 (0.6%)	3 (0.4%)	0.2% (-0.7% to 1.1%)
Endotracheal intubation	8 (1.2%)	13 (2.2%)	-0.9% (-2.4% to 0.6%)
Vasopressors	5 (0.8%)	11 (1.8%)	-1.0% (-2.4% to 0.3%)
Renal failure	2 (0.4%)	2 (0.3%)	0.1% (-0.7% to 0.8%)
Lung abscess / empyema	2 (0.4%)	4 (0.7%)	-0.3% (-1.2% to 0.6%)
Pneumonia development in non-CAP patient	2 (0.4%)	4 (0.7%)	-0.3% (-1.2% to 0.6%)
Hospital readmission	36 (5.9%)	49 (8.1%)	-2.2% (-5.1% to 0.7%)
≥65 years of age	**n = 218**	**n = 227**	
Overall adverse outcome	47 (21.4%)	42 (18.4%)	3.0% (-4.5% to 10.4%)
Death	12 (5.5%)	7 (3.3%)	2.2% (-1.7% to 6.2%)
Endotracheal intubation	6 (2.7%)	7 (3.1%)	-0.5% (-3.7% to 2.8%)
Vasopressors	6 (2.7%)	10 (4.6%)	-2.0% (-5.6% to 1.6%)
Renal failure	1 (0.2%)	2 (0.8%)	-0.5% (-2.1% to 1.0%)
Lung abscess / empyema	1 (0.7%)	1 (0.2%)	0.4% (-1.1% to 2.0%)
Pneumonia development in non-CAP patient	6 (2.6%)	5 (2.1%)	0.5% (-2.5% to 3.4%)
Hospital readmission	27 (12.3%)	21 (9.4%)	2.9% (-3.0% to 8.8%)
Male	**n = 357**	**n = 354**	
Overall adverse outcome	51 (14.3%)	59 (16.6%)	-2.3% (-7.6% to 3.0%)
Death	10 (2.7%)	3 (1.0%)	1.8% (-0.3% to 3.8%)
Endotracheal intubation	7 (1.9%)	12 (3.3%)	-1.4% (-3.8% to 1.0%)
Vasopressors	5 (1.3%)	9 (2.7%)	-1.4% (-3.5% to 0.8%)
Renal failure	1 (0.4%)	2 (0.6%)	-0.3% (-1.4% to 0.9%)
Lung abscess / empyema	0 (0.1%)	2 (0.7%)	-0.5% (-1.5% to 0.4%)
Pneumonia development in non-CAP patient	5 (1.5%)	4 (1.2%)	0.3% (-1.4% to 2.1%)
Hospital readmission	34 (9.4%)	38 (10.6%)	-1.2% (-5.6% to 3.2%)
Female	**n = 469**	**n = 476**	
Overall adverse outcome	46 (9.7%)	50 (10.6%)	-0.9% (-4.8% to 3.0%)
Death	6 (1.3%)	7 (1.4%)	-0.1% (-1.7% to 1.5%)
Endotracheal intubation	7 (1.4%)	8 (1.8%)	-0.4% (-2.1% to 1.4%)
Vasopressors	6 (1.2%)	12 (2.5%)	-1.3% (-3.1% to 0.6%)
Renal failure	1 (0.3%)	2 (0.3%)	-0.0% (-0.9% to 0.9%)
Lung abscess / empyema	4 (0.8%)	2 (0.5%)	0.3% (-0.9% to 1.4%)
Pneumonia development in non-CAP patient	3 (0.6%)	4 (0.9%)	-0.4% (-1.7% to 0.9%)
Hospital readmission	29 (6.2%)	33 (6.9%)	-0.7% (-3.9% to 2.5%)

Hispanic	**n = 108**	**n = 104**	
Overall adverse outcome	6 (5.6%)	10 (9.6%)	-4.1% (-11.2% to 3.1%)
Death	0 (0.0%)	1 (1.0%)	-1.0% (-2.8% to 0.9%)
Endotracheal intubation	0 (0.0%)	2 (1.9%)	-1.9% (-4.6% to 0.7%)
Vasopressors	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Renal failure	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Lung abscess / empyema	0 (0.0%)	1 (1.0%)	-1.0% (-2.8% to 0.9%)
Pneumonia development in non-CAP patient	0 (0.0%)	0 (0.0%)	0.0% (0.0% to 0.0%)
Hospital readmission	6 (5.6%)	7 (6.7%)	-1.2% (-7.6% to 5.3%)
African-American	**n = 296**	**n = 297**	
Overall adverse outcome	28 (9.3%)	38 (12.6%)	-3.3% (-8.3% to 1.8%)
Death	5 (1.6%)	0 (0.1%)	1.5% (-0.1% to 3.0%)
Endotracheal intubation	2 (0.8%)	7 (2.2%)	-1.4% (-3.4% to 0.7%)
Vasopressors	0 (0.1%)	6 (2.2%)	-2.0% (-3.8% to -0.3%)
Renal failure	0 (0.1%)	1 (0.4%)	-0.3% (-1.2% to 0.6%)
Lung abscess / empyema	0 (0.1%)	1 (0.4%)	-0.3% (-1.2% to 0.6%)
Pneumonia development in non-CAP patient	0 (0.1%)	1 (0.4%)	-0.3% (-1.2% to 0.6%)
Hospital readmission	21 (6.9%)	27 (9.0%)	-2.0% (-6.4% to 2.4%)
White	**n = 455**	**n = 470**	
Overall adverse outcome	62 (13.6%)	66 (14.0%)	-0.4% (-4.8% to 4.1%)
Death	11 (2.4%)	9 (2.0%)	0.5% (-1.5% to 2.4%)
Endotracheal intubation	10 (2.2%)	13 (2.8%)	-0.6% (-2.7% to 1.5%)
Vasopressors	9 (2.0%)	14 (3.1%)	-1.1% (-3.2% to 1.0%)
Renal failure	3 (0.6%)	2 (0.5%)	0.1% (-1.0% to 1.1%)
Lung abscess / empyema	4 (0.8%)	3 (0.7%)	0.1% (-1.1% to 1.3%)
Pneumonia development in non-CAP patient	8 (1.7%)	7 (1.6%)	0.1% (-1.6% to 1.9%)
Hospital readmission	36 (7.9%)	38 (8.2%)	-0.3% (-3.8% to 3.3%)

CAP - community-acquired pneumonia, COPD - chronic obstructive pulmonary disease; PSI - pneumonia severity index, IQR – interquartile range, LRTI – lower respiratory tract infection.

We defined renal failure as Kidney Disease: Improving Global Outcomes stage 3 – new renal replacement therapy, tripling of baseline creatinine, or serum creatinine ≥4.0 mg/dL.[12]

* Numbers (%) presented are derived from the primary intention-to-treat analysis, including imputation for missing data.

Table S6. Secondary safety outcomes

	Procalcitonin (n = 826)	Usual Care (n = 830)	Difference (95% CI)
ICU admission, n (%)	39 (4.7%)	40 (4.8%)	-0.2% (-2.2% to 1.9%)
Subsequent ED visits, n (%)	161 (19.5%)	162 (19.5%)	0.02% (-3.8% to 3.9%)
Quality of life (mean ± SD)			
Day 15	5.8 ± 6.0	6.0 ± 6.0	-0.2 (-0.7 to 0.4)
Day 30	5.7 ± 6.0	6.0 ± 6.0	-0.3 (-0.9 to 0.3)

ICU – intensive care unit; ED – emergency department, SD – standard deviation
Quality of life was measured using the Airway Questionnaire 20.

Table S7. Serious adverse events

Adverse event*	Procalcitonin (n = 826)	Usual Care (n = 830)	p-value
Total events	**14**	**9**	**0.30**
Respiratory, thoracic and mediastinal disorders	7	2	
General disorders and administration site conditions	4	0	
Gastrointestinal disorders	1	1	
Infections and infestations	0	1	
Nervous system disorders	0	1	
Cardiac disorders	0	3	
Blood and lymphatic system disorders	1	0	
Immune system disorders	0	0	
Injury, poisoning and procedural complications	0	0	
Renal and urinary disorders	1	0	
Vascular disorders	0	1	

*All reported adverse events were reviewed by the site Principal Investigator and none was deemed study-related.

Table S8. Intervention effect, by procalcitonin tier

Procalcitonin tier (ug/L)	Procalcitonin (n = 826)	Usual Care (n = 830)	Difference (99.86% CI)
	Antibiotic-days to day 30 mean (SD)		
I (< 0.1)	3.7 (5.5)	3.7 (5.3)	-0.08 (-1.1 to 0.9)
II (0.1 – 0.25)	4.4 (5.5)	6.4 (6.8)	-2.0 (-4.8 to 0.8)
III (≥ 0.25 – 0.5)	7.3 (6.2)	6.6 (6.3)	0.7 (-5.2 to 6.6)
IV (> 0.5)	10.2 (7.7)	7.6 (6.5)	2.7 (-2.5 to 7.9)

There was a possible interaction between study group and procalcitonin tier (p=0.02 for interaction term).
We display 99.86% CIs to adjust for multiple comparisons of antibiotic exposure outcomes between groups.

Table S9. Diagnostic and therapeutic interventions, by study group

Characteristics	Procalcitonin (n = 826)	Usual Care (n = 830)
All participants (intention to treat)	**n = 826**	**n = 830**
Diagnostic - mean ± SD		
Chest X-ray	1.3 ± 1.8	1.2 ± 1.4
Chest CT	0.2 ± .4	0.2 ± .5
Chest ultrasound	0.03 ± .2	0.04 ± .2
Therapeutic – n (%)		
Corticosteroids	436 (52.8)	425 (51.3)
Bronchodilators	574 (69.6)	598 (72.2)
Diuretics	132 (16.0)	141 (17.0)
Asthma	**n=310**	**n=336**
Diagnostic - mean ± SD		
Chest X-ray	1.1 ± 1.2	1.1 ± 0.9
Chest CT	0.1 ± .4	0.1 ± .4
Chest ultrasound	0.02 ± .1	0.04 ± .2
Therapeutic – n (%)		
Corticosteroids	228 (73.5)	230 (68.5)
Bronchodilators	260 (83.9)	284 (84.5)
Diuretics	31 (10.0)	45 (13.4)
COPD	**n=265**	**n=259**
Diagnostic - mean ± SD		
Chest X-ray	1.6 ± 2.7	1.2 ± .9
Chest CT	0.2 ± .5	0.2 ± .5
Chest ultrasound	0.03 ± .2	0.05 ± .2
Therapeutic – n (%)		
Corticosteroids	224 (84.5)	210 (81.1)
Bronchodilators	241 (90.9)	236 (91.1)
Diuretics	73 (27.5)	76 (29.3)
Acute bronchitis	**n = 208**	**n = 190**
Diagnostic - mean ± SD		
Chest X-ray	1.1 ± .7	1.1 ± .9
Chest CT	0.1 ± .4	0.1 ± .4
Chest ultrasound	0.03 ± .2	0.02 ± .1
Therapeutic – n (%)		
Corticosteroids	39 (18.8)	36 (18.9)

Bronchodilators	91 (43.8)	98 (51.6)
Diuretics	18 (8.7)	14 (7.4)
Community-acquired pneumonia	**n = 167**	**n = 161**
Diagnostic - mean ± SD		
Chest X-ray	1.7 ± 3.0	1.8 ± 2.7
Chest CT	0.3 ± .6	0.4 ± .6
Chest ultrasound	0.1 ± .2	0.1 ± .3
Therapeutic – n (%)		
Corticosteroids	80 (47.9)	68 (42.2)
Bronchodilators	125 (74.9)	116 (72.0)
Diuretics	43 (25.7)	49 (30.4)

CT - computed tomography, COPD - chronic obstructive pulmonary disease

Table S10. Distribution of procalcitonin tiers, by final diagnoses

	Procalcitonin tier (ug/L)			
	I (< 0.1)	II (0.1 - 0.25)	III (≥ 0.25 - 0.5)	IV (> 0.5)
n (%)				
All participants	1236 (77.4%)	230 (14.4%)	50 (3.1%)	80 (5.0%)
Asthma	528 (85.3%)	65 (10.5%)	11 (1.8%)	15 (2.4%)
COPD	389 (76.7%)	73 (14.4%)	18 (3.6%)	27 (5.3%)
Acute bronchitis	303 (77.5%)	63 (16.1%)	8 (2.1%)	17 (4.4%)
CAP	182 (58.0%)	62 (19.7%)	25 (8.0%)	45 (14.3%)

COPD – chronic obstructive pulmonary disease, CAP – community-acquired pneumonia
Procalcitonin level data were available for 96.4% of the overall cohort (1596 of 1656 pts), 95.8% of asthma patients (619 of 646), 96.8% of COPD patients (507 of 524), 98.2% of acute bronchitis patients (391 of 398), and 95.7% of CAP patients (314 of 328).

Table S11. Antibiotic type, number, and mode in emergency department, by study group and final diagnoses*

	Procalcitonin (n = 826)	Usual Care (n = 830)
All patients (intention-to-treat)	**n = 826**	**n = 830**
Antibiotic type		
Azithromycin	146 (17.7%)	170 (20.5%)
Ceftriaxone	58 (7.0%)	62 (7.5%)
Levofloxacin	49 (5.9%)	54 (6.5%)
Doxycycline	20 (2.4%)	26 (3.1%)
Vancomycin	20 (2.4%)	20 (2.4%)
Cefepime	12 (1.5%)	15 (1.8%)
Moxifloxacin	12 (1.5%)	12 (1.5%)
Number of antibiotics		
1	200 (24.2%)	216 (26.0%)
2	54 (6.5%)	72 (8.7%)
3 or more	14 (1.7%)	15 (1.8%)
Mode		
Intravenous	119 (14.4%)	133 (16.0%)
Asthma	**n = 310**	**n = 336**
Antibiotic type		
Azithromycin	48 (15.5%)	56 (16.7%)
Ceftriaxone	10 (3.2%)	17 (5.1%)
Levofloxacin	15 (4.8%)	22 (6.6%)
Doxycycline	9 (2.9%)	12 (3.6%)
Vancomycin	5 (1.6%)	7 (2.1%)
Cefepime	4 (1.3%)	5 (1.5%)
Moxifloxacin	5 (1.6%)	3 (0.9%)
Number of antibiotics		
1	64 (20.6%)	77 (22.9%)
2	11 (3.6%)	17 (5.1%)
3 or more	8 (2.6%)	6 (1.8%)
Mode		
Intravenous	27 (8.7%)	38 (11.3%)
COPD	**n = 265**	**n = 259**
Antibiotic type		
Azithromycin	53 (20.0%)	60 (23.2%)
Ceftriaxone	20 (7.6%)	20 (7.7%)
Levofloxacin	17 (6.4%)	22 (8.5%)
Doxycycline	11 (4.2%)	13 (5.0%)
Vancomycin	13 (4.9%)	7 (2.7%)
Cefepime	6 (2.3%)	6 (2.3%)
Moxifloxacin	5 (1.9%)	5 (1.9%)
Number of antibiotics		

1	78 (29.4%)	82 (31.7%)
2	18 (6.8%)	28 (10.8%)
3 or more	7 (2.6%)	3 (1.2%)
Mode		
Intravenous	49 (18.5%)	54 (20.8%)
Acute bronchitis	**n = 208**	**n = 190**
Antibiotic type		
Azithromycin	19 (9.1%)	41 (21.6%)
Ceftriaxone	5 (2.4%)	7 (3.7%)
Levofloxacin	4 (1.9%)	4 (2.1%)
Doxycycline	3 (1.4%)	2 (1.1%)
Vancomycin	2 (1.0%)	1 (0.5%)
Cefepime	1 (0.5%)	1 (0.5%)
Moxifloxacin	0 (0.0%)	1 (0.5%)
Number of antibiotics		
1	27 (13.0%)	44 (23.2%)
2	5 (2.4%)	7 (3.7%)
3 or more	0 (0.0%)	4 (2.1%)
Mode		
Intravenous	10 (4.8%)	10 (5.3%)
Community-acquired pneumonia	**n = 167**	**n = 161**
Antibiotic type		
Azithromycin	55 (32.9%)	49 (30.4%)
Ceftriaxone	37 (22.2%)	39 (24.2%)
Levofloxacin	28 (16.8%)	34 (21.1%)
Doxycycline	5 (3.0%)	11 (6.8%)
Vancomycin	13 (7.8%)	16 (9.9%)
Cefepime	8 (4.8%)	12 (7.5%)
Moxifloxacin	9 (5.4%)	4 (2.5%)
Number of antibiotics		
1	76 (45.5%)	64 (39.8%)
2	33 (19.8%)	47 (29.2%)
3 or more	10 (6.0%)	9 (5.6%)
Mode		
Intravenous	73 (43.7%)	79 (49.1%)

*n (%) is shown for all variables.

Displayed are the top seven antibiotics prescribed in the emergency department, representing 89.2% of all instances of emergency department antibiotic prescription. The antibiotics not shown encompass 19 unique antibiotics, each of which was received by 15 or less patients.

Table S11. Clinician adherence to procalcitonin-guided antibiotic prescription, by center.

Center	PCT group patients (n)	PCT guideline adherence (%)
1	54	83.3
2	26	80.8
3	85	78.8
4	97	72.2
5	26	69.2
6	61	68.9
7	111	67.6
8	33	66.7
9	26	65.4
10	42	64.3
11	64	59.4
12	73	43.8
13	56	42.9
14	38	39.5

PCT – procalcitonin. PCT guideline adherence defined as clinicians followed the guideline at all timepoints.

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