Pneumonia in Hospitalized Patients

Update in Hospital Medicine

October 7, 2024

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Disclosures

- Grant funding
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
  - Massachusetts Department of Public Health
- Royalties
  - UpToDate for chapters on pneumonia

Outline

- How accurate are clinical signs for pneumonia?
- Is pneumonia in hospitalized patients viral or bacterial?
- What kind of imaging should we get?
- Is there a role for procalcitonin?
- Do we need to get cultures?
- Do we need to start antibiotics right away?
- What should we treat with?
- Do we need to include atypical coverage?
- How long should we treat for?

AMERICAN THORACIC SOCIETY DOCUMENTS

Released in 2019

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

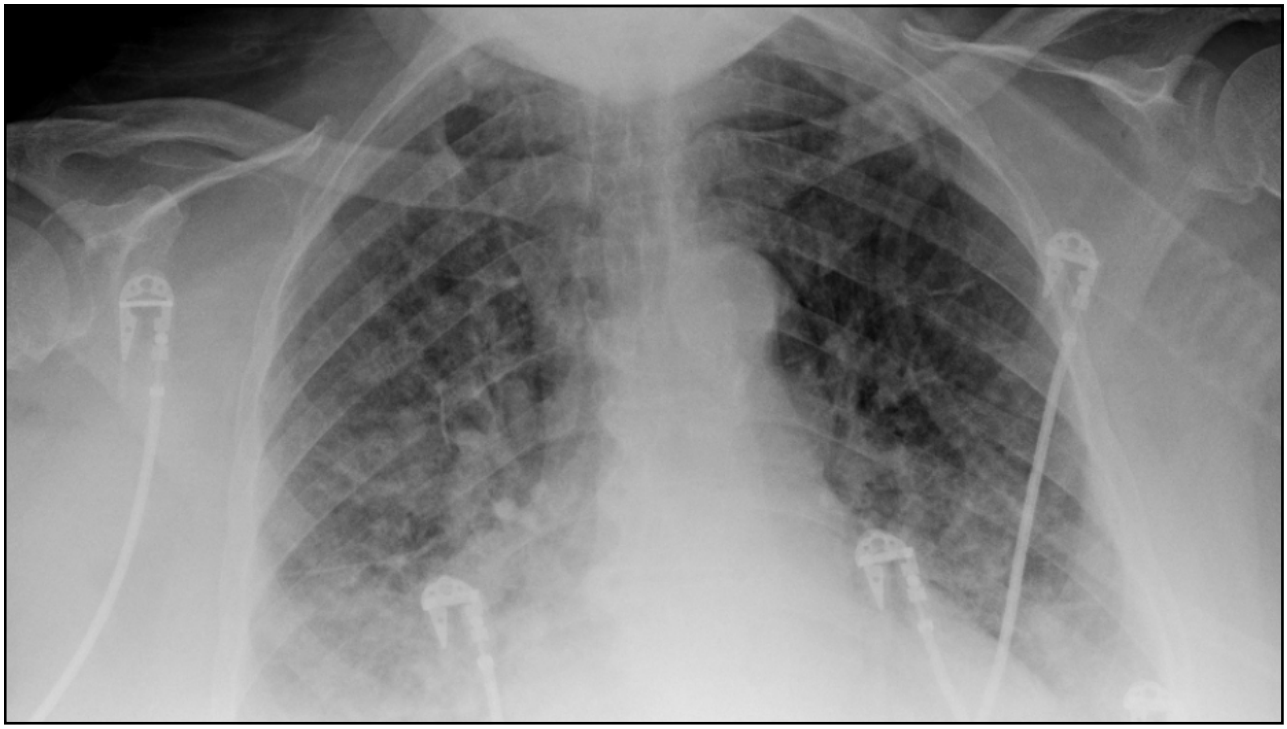
THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2019 AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA AUGUST 2019

Background: This document provides evidence-based clinical practice guidelines on the management of adult patients with community-acquired pneumonia.

management decisions. Although some recommendations remain unchanged from the 2007 guideline, the availability of results from new therapeutic trials and epidemiological investigations led to

Case Study

- A 72-year old man with a history of rapid atrial fibrillation and COPD is admitted to hospital from assisted living with confusion. His breathing is labored and he has an intermittent non-productive cough.
- On exam, he is lethargic but easily arousable. Temperature 100, HR 120 and irregular, BP 98/64, resp rate 28, SaO2 88% RA. JVP difficult to see. Wheezing and possible crackles in the bases. Mild lower extremity edema.
- Labs are notable for WBC count of 9.8, hematocrit 31, platelets 154, Na 130, creatinine 2.0, LFTs normal.
- Urinalysis with 4-6 WBC/hpf
- Portable chest x-ray with edema +/- LLL infiltrate



Does this patient have pneumonia?*

A. Yes

B. No

Would you start antibiotics?*

A. Yes

B. No

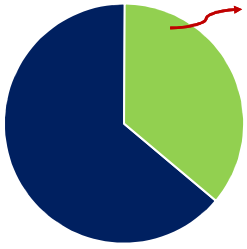
Why is Pneumonia So Difficult to Diagnose?

- Many medical conditions in hospitalized patients present with the same clinical signs as pneumonia
  - Radiographic opacities
  - Fever
  - Abnormal white blood cell count
  - Impaired oxygenation
  - Increased pulmonary secretions

Diagnostic Uncertainty in Pneumonia

Analysis of ED vs discharge diagnoses in 2,383,899 patients admitted to 118 VA hospitals, 2015-2022

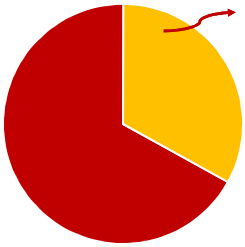
ED Diagnosis of Pneumonia



36% did not have a discharge diagnosis of pneumonia

- ED Pneumonia +, Discharge Pneumonia +
- ED Pneumonia +, Discharge Pneumonia -

Discharge Diagnosis of Pneumonia



33% did not have an ED diagnosis of pneumonia

- Discharge Pneumonia +, ED Pneumonia +
- Discharge Pneumonia+, ED Pneumonia -

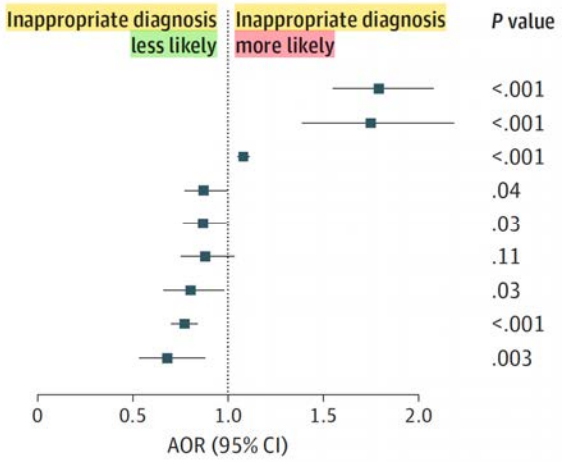
Uncertainty common: *uncertainty expressed in clinical notes for 51-58% of patients; 24% treated with diuretics, 38% treated with corticosteroids, 10% treated with all 3 of diuretics, steroids, and antibiotics*

Jones, *Ann Intern Med* 2024; doi:10.7326/M23-2505

Predictors of Inappropriate Diagnosis

Analysis of 17,290 patients admitted to 48 Michigan hospitals, 2017-2020.
Inappropriate diagnosis defined as <2 signs or symptoms of CAP or negative chest imaging.

Measure	AOR (95% CI)
Dementia	1.79 (1.55-2.08)
Altered mental status, no dementia	1.75 (1.39-2.19)
Age, per 10 y	1.08 (1.05-1.11)
Home oxygen	0.87 (0.77-1.00)
Chronic kidney disease	0.87 (0.76-0.99)
Respiratory viral panel negative	0.88 (0.75-1.03)
Respiratory viral panel positive	0.80 (0.66-0.98)
≥2 SIRS criteria plus end organ dysfunction	0.77 (0.70-0.84)
History of pulmonary cancer	0.68 (0.53-0.88)

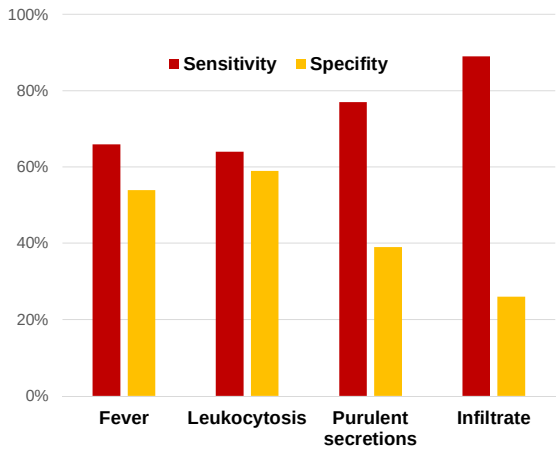


Gupta, *JAMA IM* 2024;ePub

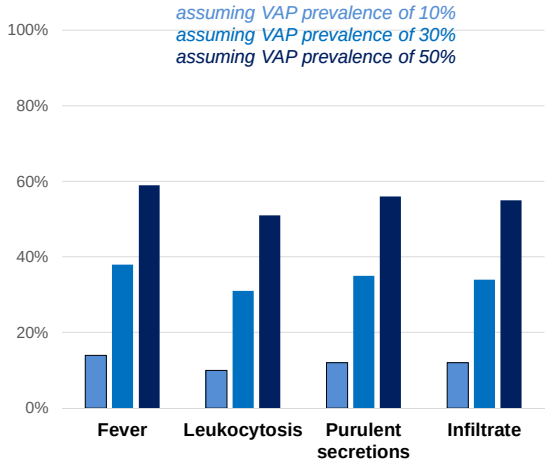
Accuracy of Clinical Signs for VAP

Meta-analysis of 25 studies examining accuracy of clinical signs for VAP relative to histology, N=75 to 336 per sign

Sensitivity and Specificity



Positive Predictive Value

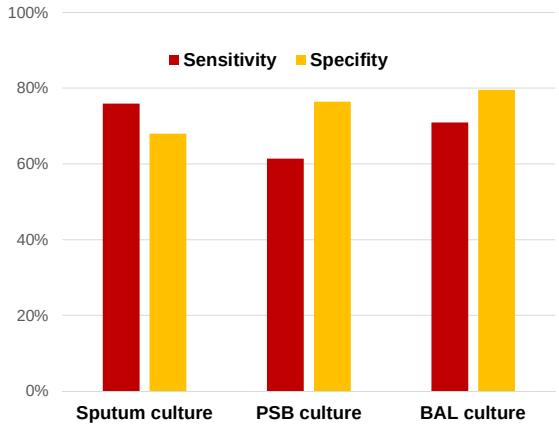


Fernando, *Intensive Care Med* 2020;46:1170-9

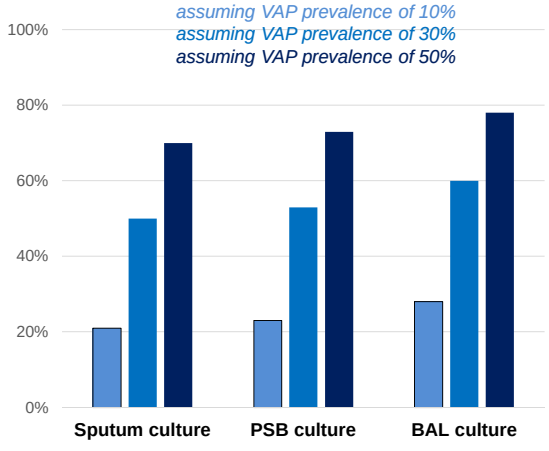
Accuracy of Respiratory Cultures for VAP

Meta-analysis of 25 studies examining accuracy of clinical signs for VAP relative to histology, N=75 to 336 per sign

Sensitivity and Specificity



Positive Predictive Value



Fernando, *Intensive Care Med* 2020;46:1170-9

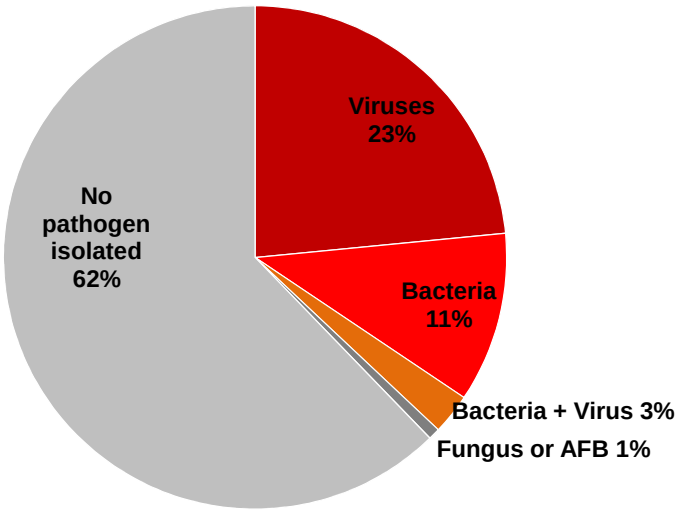
If the patient does have pneumonia, is it more likely bacterial or viral?*

A. Bacterial

B. Viral

Etiology of Community-Acquired Pneumonia

2,259 adults admitted to 5 hospitals in Chicago and Nashville, Jan 2010-Jun 2012



Jain, *N Engl J Med* 2015;373:415-427

Etiology of Community-Acquired Pneumonia

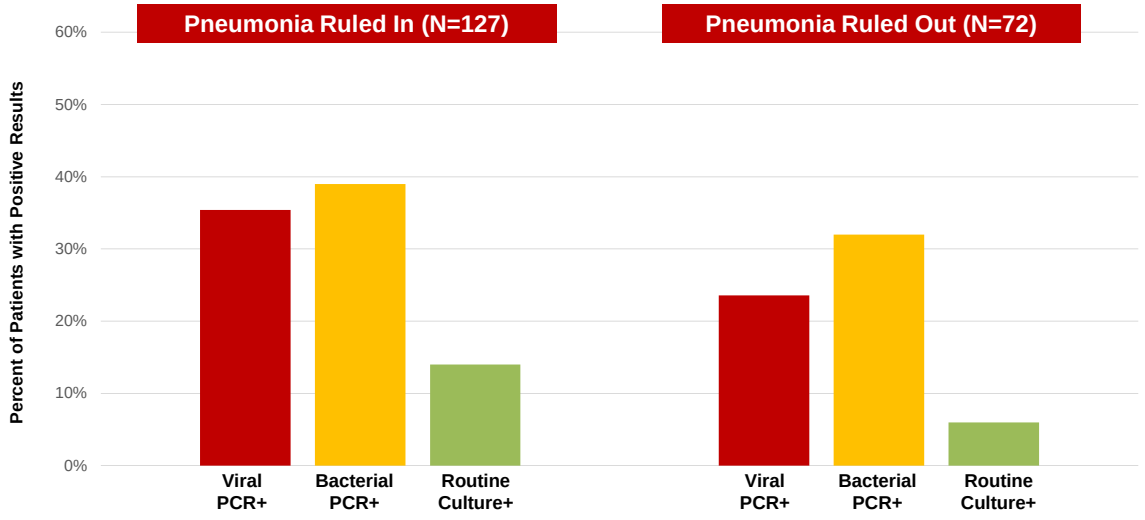
2,259 adults admitted to 5 hospitals in Chicago and Nashville

Rhinovirus	8.6%
Influenza	5.8%
Strep. pneumoniae	5.1%
Metapneumovirus	3.9%
RSV	3.0%
Parainfluenza	3.0%
Coronavirus	2.3%
Mycoplasma pneumoniae	1.9%
Staph. aureus	1.6%
Adenovirus	1.4%
Legionella pneumophila	1.4%
Enterobacteriaceae	1.4%
Haemophilus influenzae	0.5%
Chlamydia pneumoniae	0.4%
Other	2.3%

Jain, *N Engl J Med* 2015;373:415-427

Not every positive test indicates pneumonia…

199 elderly patients started on antibiotics for suspected pneumonia; pneumonia then ruled in or out by chest CT



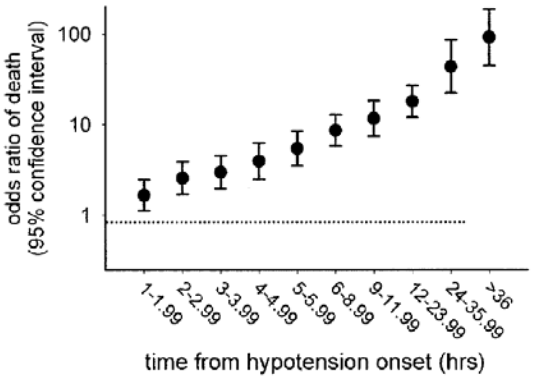
Prendki, *Eur Respir J* 2018; 51:1702375

Do we have to start antibiotics right away?*

A. Yes

B. No

In Septic Shock, Time Matters…

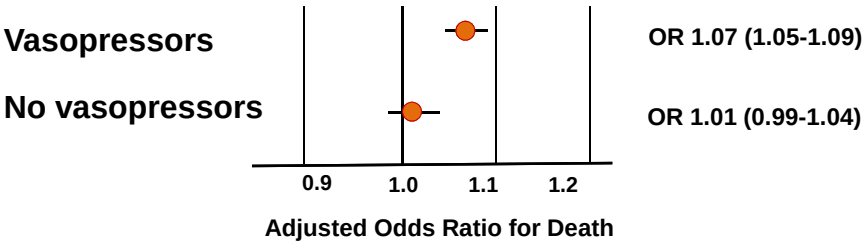


Kumar, *Crit Care Med* 2006;34:1589-1596

But are antibiotics equally urgent for sepsis without shock?

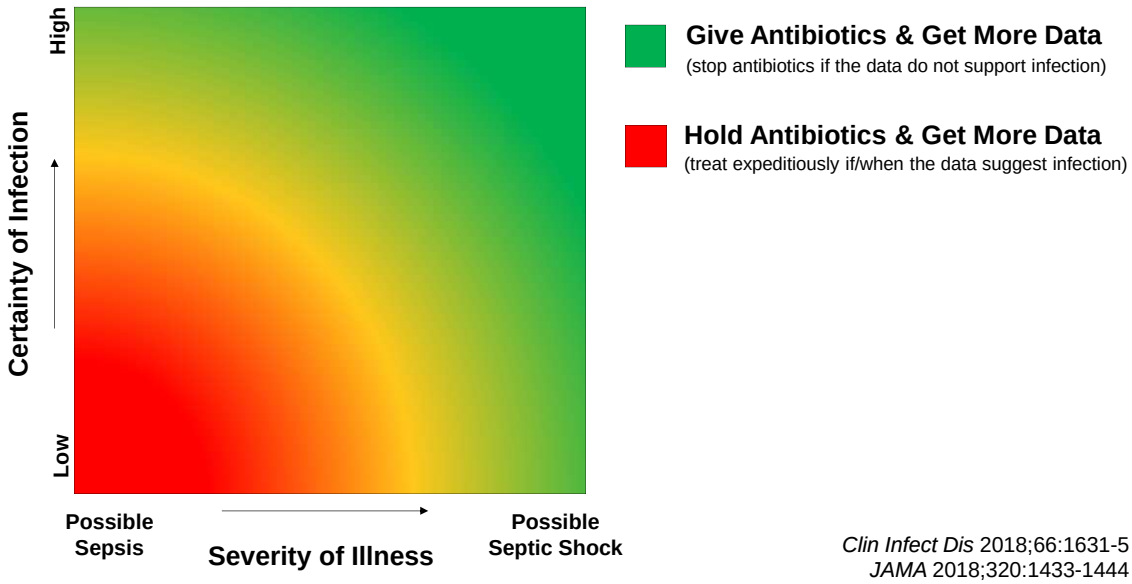
Association between each hour of delay until broad-spectrum antibiotics and in-hospital death amongst 49,331 patients in New York State

New York State



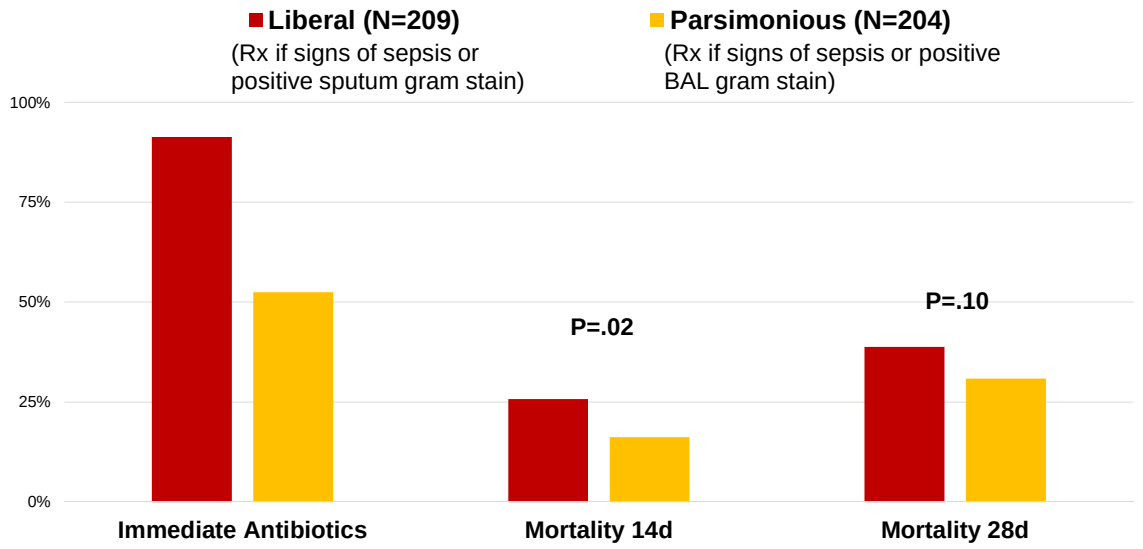
Seymour, *N Engl J Med* 2017;376:2235-2244

Tailor Immediacy of Treatment to Certainty of Infection and Severity of Illness



Clin Infect Dis 2018;66:1631-5
JAMA 2018;320:1433-1444

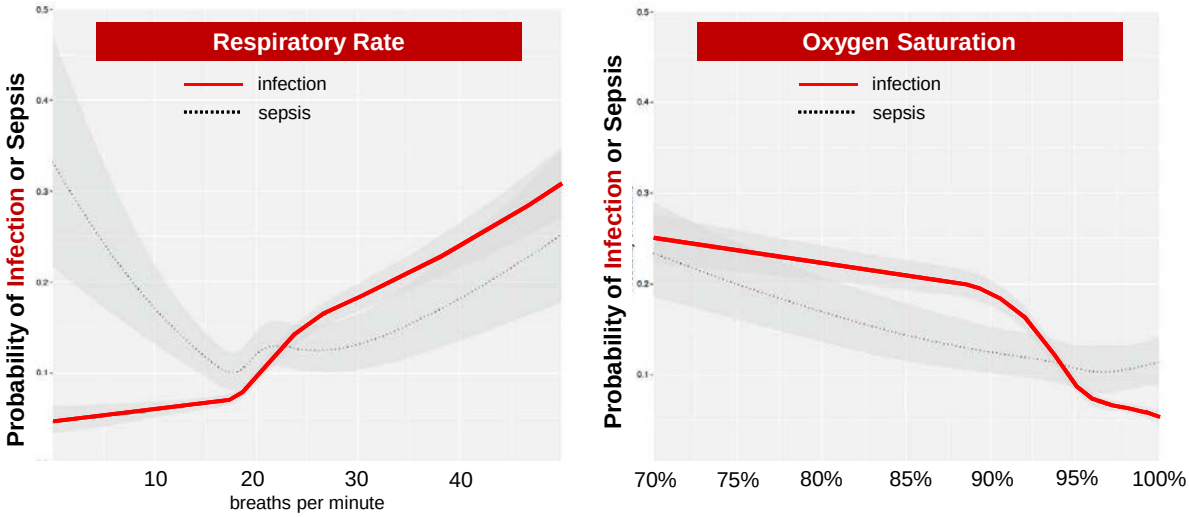
Liberal vs Parsimonious Treatment for Suspected VAP



Fagon et al. *Ann Intern Med* 2000;132:621-630

Association between Clinical Signs & Likelihood of Infection

Analysis of 131,475 patients transported by EMS in Alberta, 2015-2016



Lane, *Intensive Care Med* 2020;46:1394-1403

Clinical Signs in Patients Starting Antibiotics for Pneumonia

9,540 patients admitted to 4 Boston hospitals & started on antibiotics for pneumonia, 2015-2018

79% had a temperature <38º C

82% had a median respiratory rate <22 breaths/min

55% had a WBC count >4,000 and <12,000 cells/mm^3

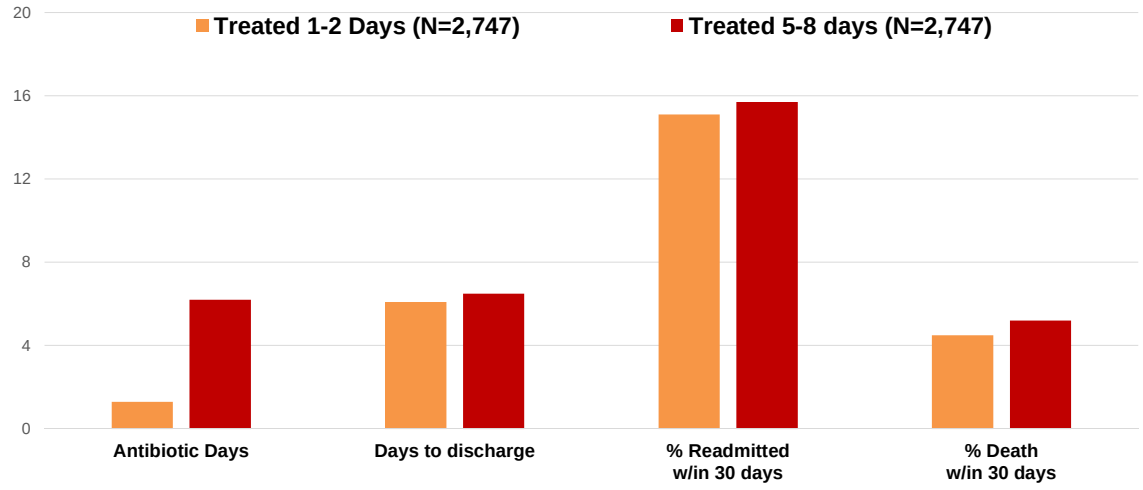
39% had O_2 sat > 95% on ambient air

Klompas, *JAMA Network Open* 2020;3(7):e2010700

All signs normal in 19% !!!

Short vs long treatment for pneumonia with normal O2 sat

4,494 propensity-matched patients with O2 Sat ≥95% on ambient air treated for pneumonia, 4 hospitals, 2017-2021



Klompas, *Clin Infect Dis* 2023;76:e1217-e1223

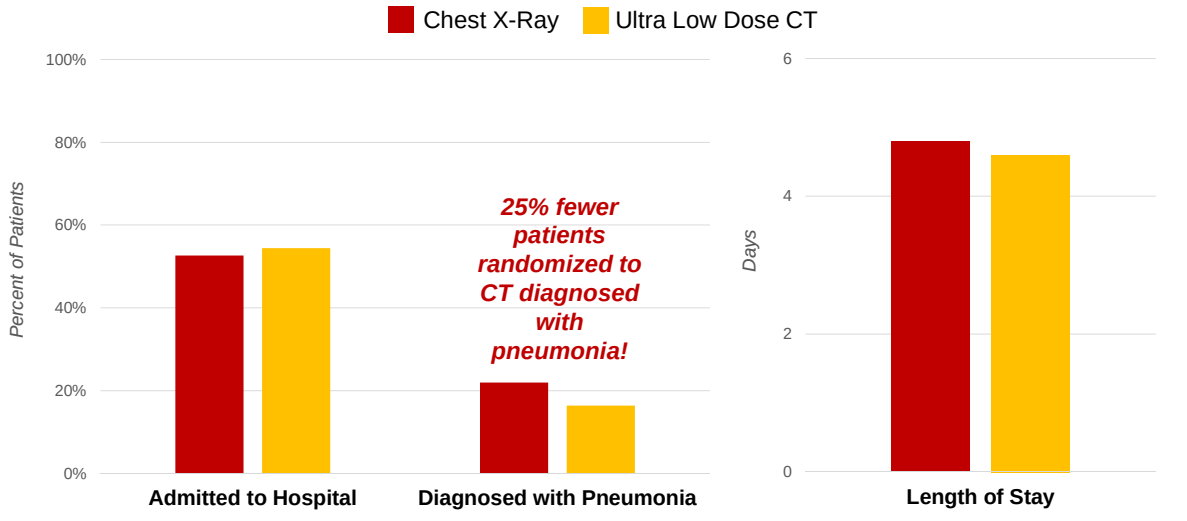
Could further imaging help?*

A. Yes

B. No

CT vs CXR for Suspect Pulmonary Disease in the ED

2,418 ED patients with suspected pulmonary disease randomized to ultra-low dose CT vs CXR, Netherlands, 2017-8

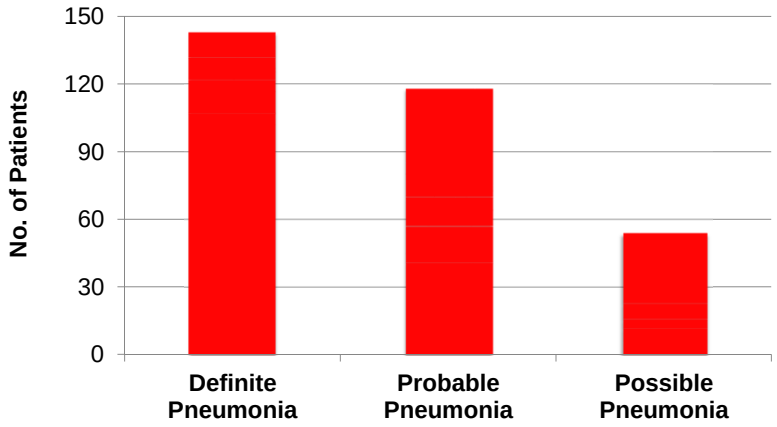


van den Berk, *Thorax* 2023;78:515-522

Chest X-Ray vs CT Scan

319 patients with clinically suspected pneumonia

Initial pneumonia classification following chest x-ray

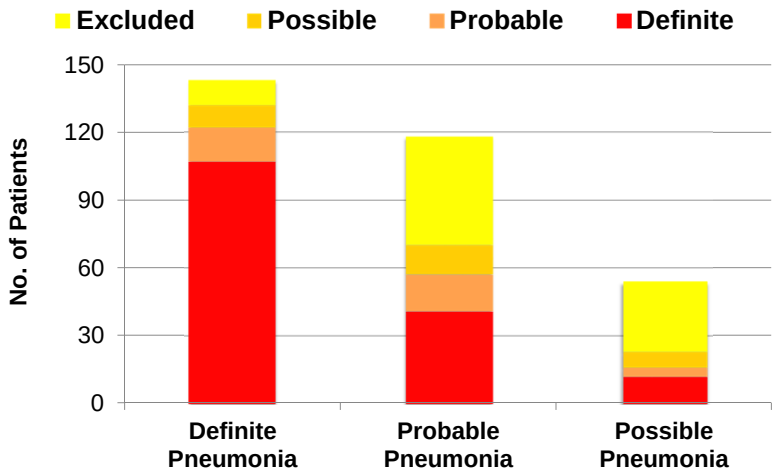


Claessens, *AJRCCM* 2015;192:974-982

Chest X-Ray vs CT Scan

319 patients with clinically suspected pneumonia

Revised pneumonia classification following CT chest



Claessens, *AJRCCM* 2015;192:974-982

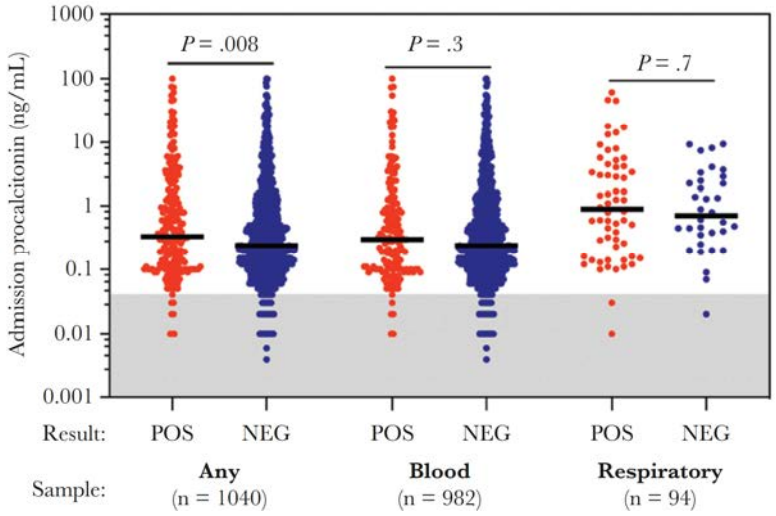
Could procalcitonin help?*

A. Yes

B. No

Limited correlation between procalcitonin and bacterial cultures

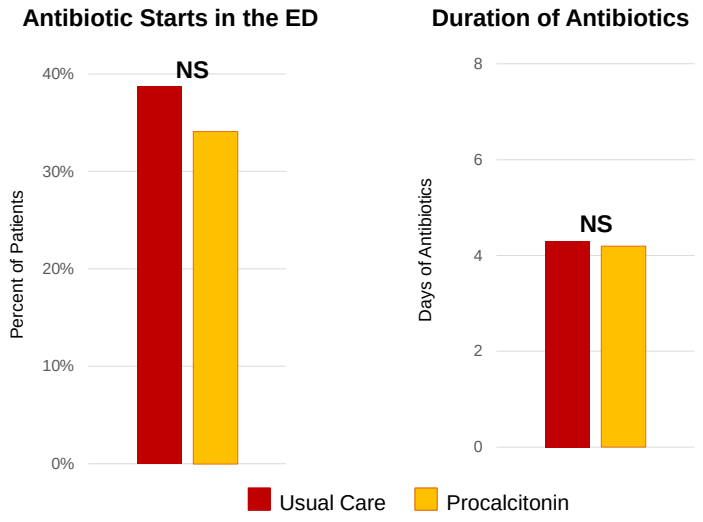
1,040 patients admitted to 260 UK hospitals with COVID-19; PCT & blood or respiratory cultures obtained within 48h of admission



Ralph, *Open Forum Infect Dis* 2022; doi.org//10.1093/ofid/ofac179

Procalcitonin for ?Pneumonia

1656 patients with possible pneumonia randomized to procalcitonin vs routine care



Huang, *N Engl J Med* 2018;379:236-249

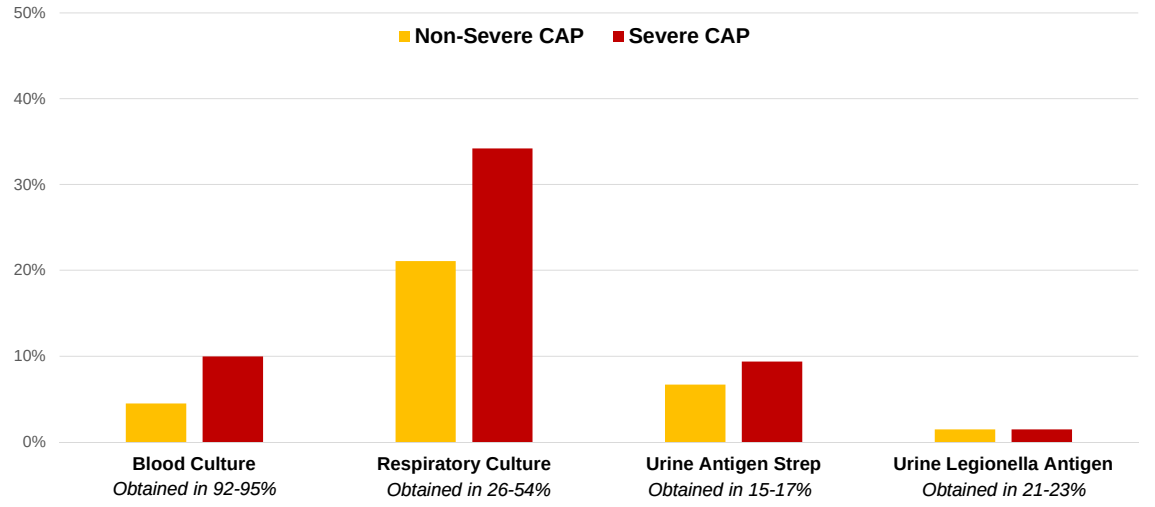
Should we culture for bacteria and test for viruses?*

A. Yes

B. No

Yield by Specimen Type

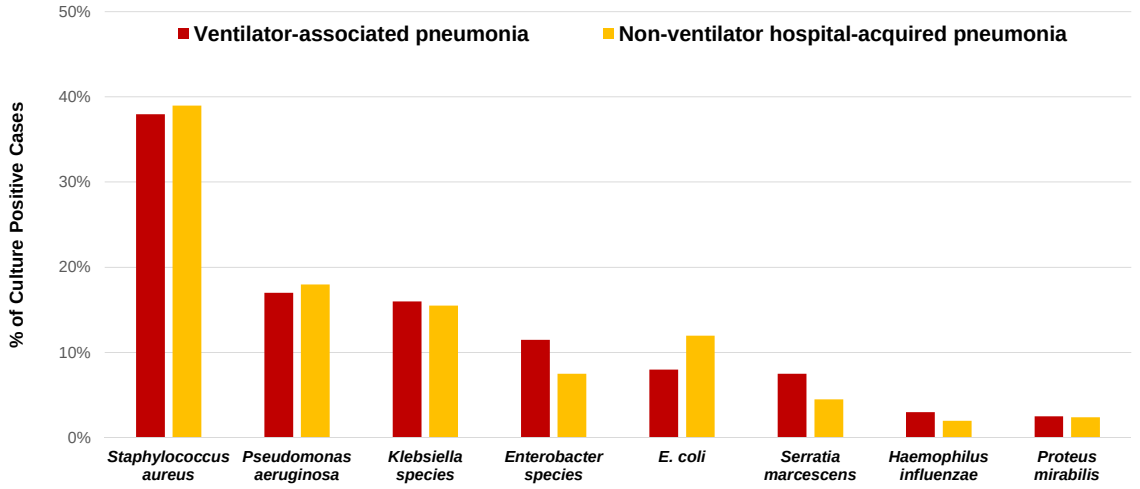
154,799 patients admitted to 177 U.S. hospitals with community acquired pneumonia, 2010-2015



Haessler, *Crit Care Med* 2022; 10.1097/CCM.0000000000005498

Pathogens!

13,258 cases of culture-positive hospital-acquired pneumonia from 253 hospitals, 2012-2019



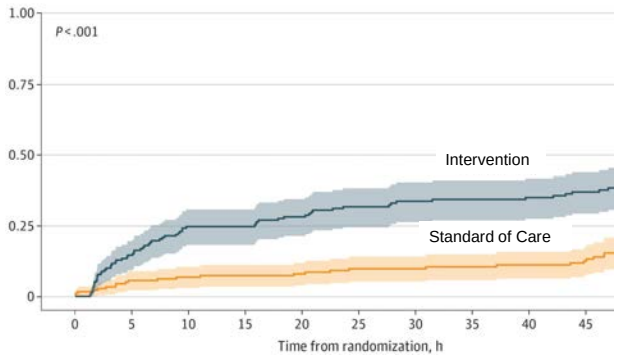
Zilberberg, *Infection Control & Hospital Epidemiology* 2022;43:277-283

Impact of Multiplex Respiratory PCR on Outcomes

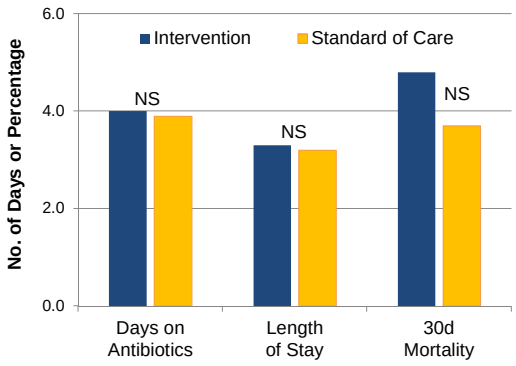
374 patients with suspected CAP in a large Norwegian hospital randomized to multiplex PCR vs routine care

More patients randomized to multiplex received pathogen-directed therapy (35% vs 13%)
and in less time (35h vs 44h) but no difference in antibiotic days, length-of-stay, readmissions, or deaths

Proportion of Patients with Pathogen Directed Therapy



Outcomes



Markussen, *JAMA Network Open* 2024;7(3):e240830

Check for updates

AMERICAN THORACIC SOCIETY DOCUMENTS

Released May 2021

Nucleic Acid–based Testing for Noninfluenza Viral Pathogens in Adults with Suspected Community-acquired Pneumonia

An Official American Thoracic Society Clinical Practice Guideline

Outpatients: we suggest not performing routine NAAT testing for respiratory viral pathogens other than influenza.

Inpatients: we suggest performing NAAT testing for respiratory viruses other than influenza in patients with severe CAP or immunocompromised state

ATS/IDSA Guidelines

Obtain sputum gram stain & culture in inpatients if:

Any of the following:

- the patient has severe pneumonia
- you believe empiric coverage for MRSA or Pseudomonas is necessary
- the patient has a prior history of MRSA or Pseudomonas infection
- patient was been hospitalized and received IV antibiotics within the preceding 90 days

Test for influenza if influenza is circulating in the community. Test for other respiratory viruses if severe pneumonia or immunocompromised.

My Opinion

Obtain sputum gram stain & culture + viral studies in all inpatients

My reasons:

- Risk factors for resistant organisms are ill defined
- Positive cultures can help you tailor treatment
- Negative cultures can facilitate stopping antibiotics early
- Culture data is critical to generate hospital antibiograms to inform future empiric treatment choices
- Many viruses cause pneumonia & they circulate year-round (Covid!)
- Viral diagnosis has infection control implications

Which antibiotics should we use?

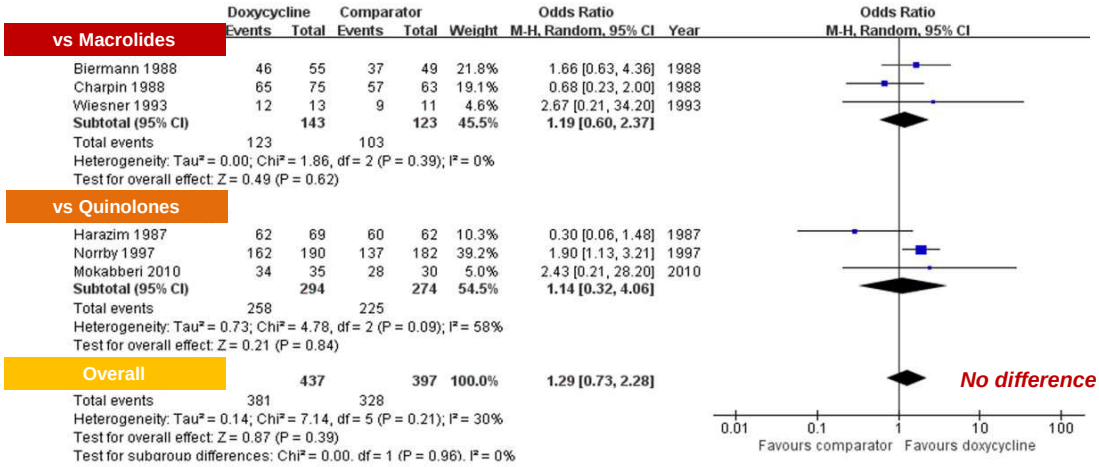
Treatment Strategy for Inpatients with CAP

	Standard Regimen	MRSA coverage?	Pseudomonas coverage?
Mild disease	**B-lactam + macrolide or Fluoroquinolone**	If prior history of respiratory MRSA then cover for MRSA If risk factors alone, get cultures & nasal PCR. Only cover MRSA if cultures or nasal PCR positive	If prior history of respiratory Pseudomonas then cover for Pseudomonas If risk factors alone, get cultures. Only cover for Pseudomonas if cultures positive
Severe disease	**B-lactam + (macrolide or fluroquinolone)**	If prior history of respiratory MRSA or risk factors for MRSA then get cultures and cover MRSA upfront	If prior history of respiratory Pseudomonas or risk factors for Pseudomonas get cultures and cover for Pseudomonas upfront

AJRCCM 2019;7:e45-e67

What about doxycycline?

*Meta-analysis of 6 randomized trials of doxy vs comparator for **mild-to-moderate** CAP*



Caveats: old trials, most comparators no longer used, 4/6 trials at increased risk of bias

Choi, *Clin Infect Dis* 2023;76:683-691

Nasal MRSA Culture/PCR

- Can a nasal swab screen MRSA predict the presence or absence of MRSA pneumonia?
- Meta-analysis of 22 studies, 5163 patients

Sensitivity	**85%**
Positive predictive value	**57%**
Negative predictive value	**98%**

Parente, *Clinical Infectious Disease* 2018;67:1-7

Can the Gram Stain guide antibiotic choice?

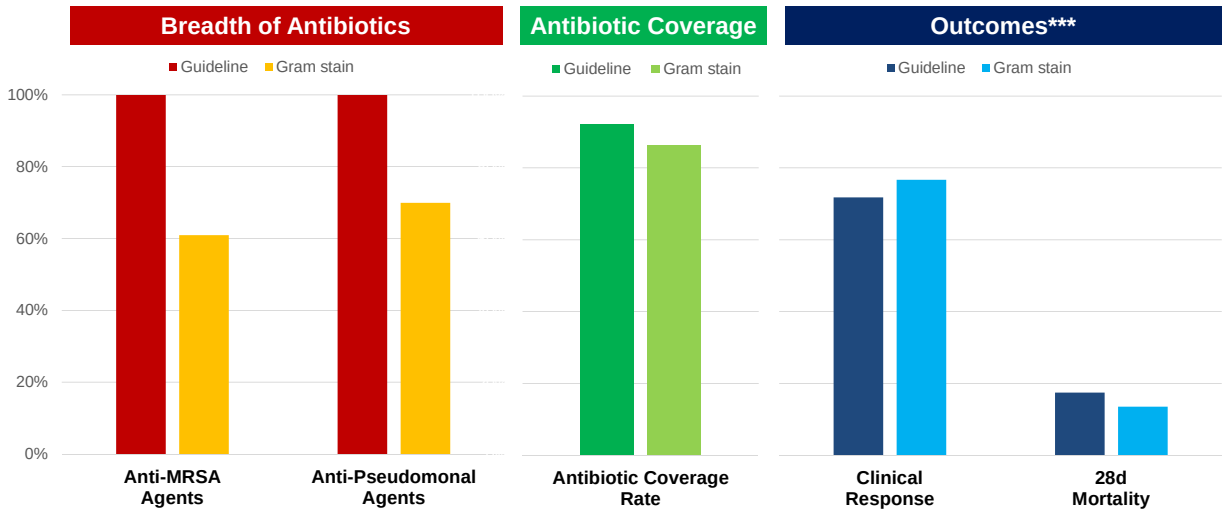
206 patients with suspected VAP randomized to Gram stain-guided vs guideline-based empiric antibiotics

	GNRs present	GNRs not seen
GPCs in clusters	Cover for MRSA & Pseudomonas	Cover for just MRSA
GPCs in chains or pairs	Cover for just Pseudomonas	Non-Pseudomonal beta lactam
GPCs not seen	Cover for just Pseudomonas	Cover for MRSA & Pseudomonas

Yoshimura, *JAMA NO* 2022;5(4):e226136

Can the Gram Stain guide antibiotic choice?

206 patients with suspected VAP randomized to Gram stain-guided vs guideline-based empiric antibiotics

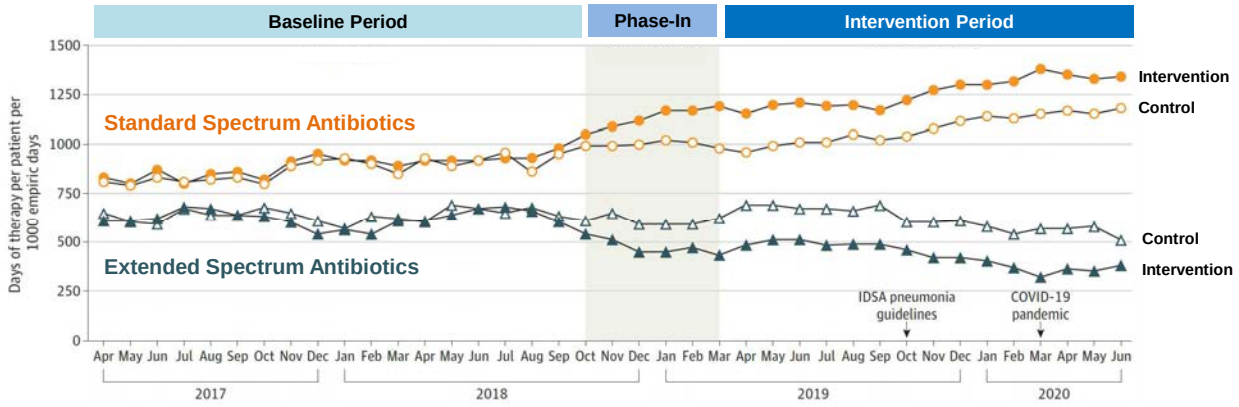


*** Caveat: only 5% of patients infected with Pseudomonas, 11% with MRSA

Yoshimura, *JAMA NO* 2022;5(4):e226136

Quantifying MDR Risk Can Decrease Antibiotic Overuse

Cluster randomized trial of EHR-based stewardship bundle with education, real-time MDRO risk estimates, and feedback. Clinicians prompted to choose standard spectrum antibiotics if MDR risk <10%. 96451 pneumonias, 59 hospitals, 2017-2020



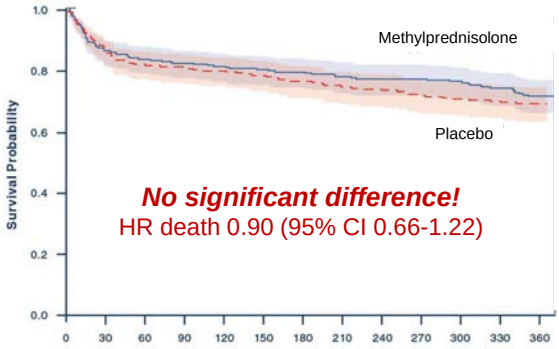
Gohil, JAMA 2024;331:2007-2017

Should we add steroids?

Two Recent RCTs

584 ICU & intermediate care patients with CAP randomized to methylprednisolone 40mg/day x7d then 13d taper

Treatment started up to 96h after admission
96% of participants were male
~10% of patients had influenza

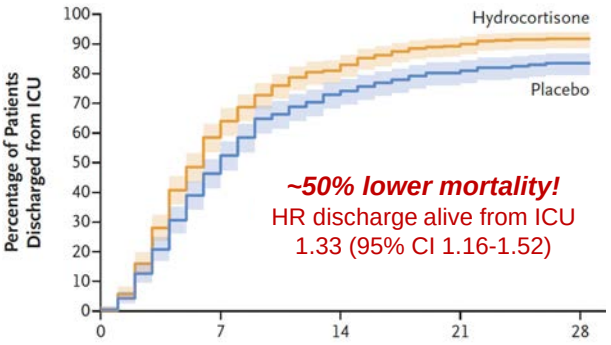


No significant difference!
HR death 0.90 (95% CI 0.66-1.22)

Meduri, Intensive Care Med 2022;48:1009–1023

795 patients ICU patients with severe CAP randomized to hydrocortisone 200mg/day x 4-8d

Treatment started within 24h after admission
31% of participants were female
Excluded patients with influenza

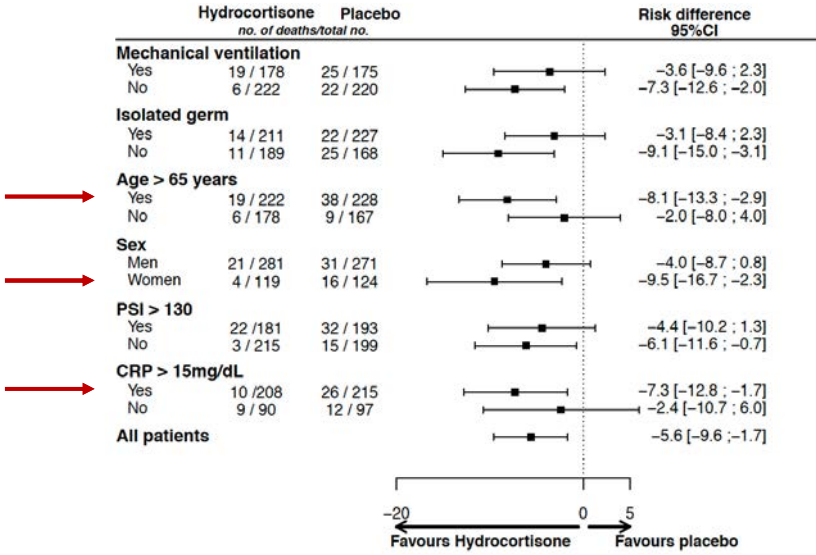


~50% lower mortality!
HR discharge alive from ICU
1.33 (95% CI 1.16-1.52)

Dequin, NEJM 2023;288:1931-1941

Who Is Most Likely to Benefit?

795 patients ICU patients with severe CAP randomized to hydrocortisone 200mg/day x 4-8d vs placebo



Bottom Line

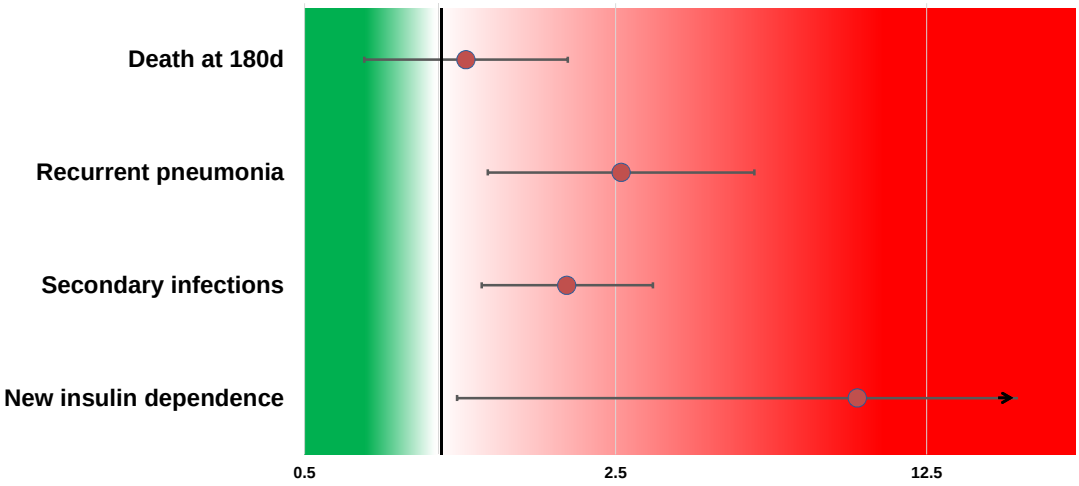
Consider steroids for:

- **severe CAP (ICU)**
  and
- **<24h since admission**
  and
- **CRP >150mg/L**

Dequin, NEJM 2023;288:1931-1941

Long-term impact of steroids for CAP

785 patients hospitalized with CAP randomized to prednisone 50mg PO x 7d vs placebo, 180-day outcomes



Blum, *BMC Pulm Med* 2023;23:500

Do we need to cover for atypicals?*

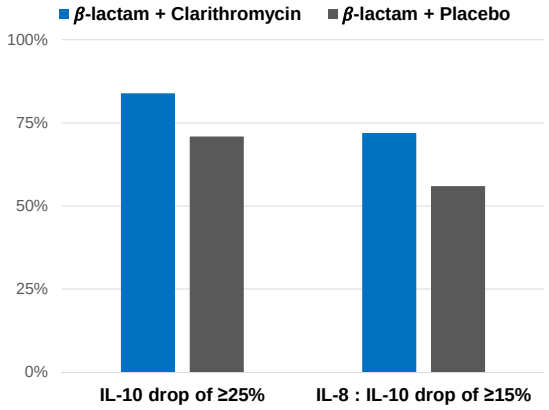
A. Yes

B. No

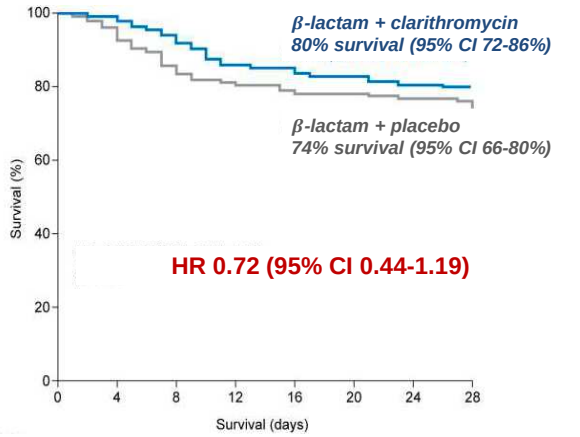
β-lactam alone vs β-lactam+macrolide

278 patients hospitalized with CAP in Greece randomized to β-lactam + placebo vs β-lactam + clarithromycin.
Greater drop in inflammatory markers, less sepsis, less hospital death but no difference in 28d or 90d mortality

Inflammatory Markers



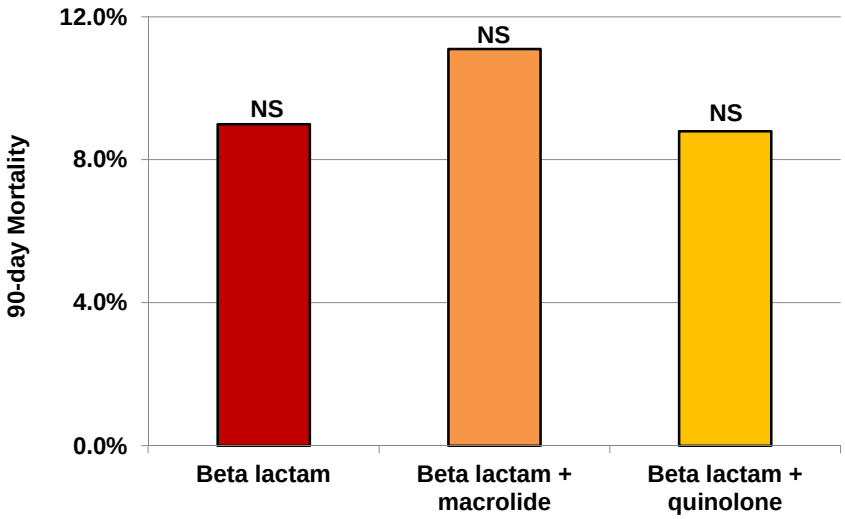
28d Survival



Giamarellos-Bourboulis, Lancet Respir Med 2024;12:294–304

βlactam vs βlactam+macrolide vs βlactam+quinolone

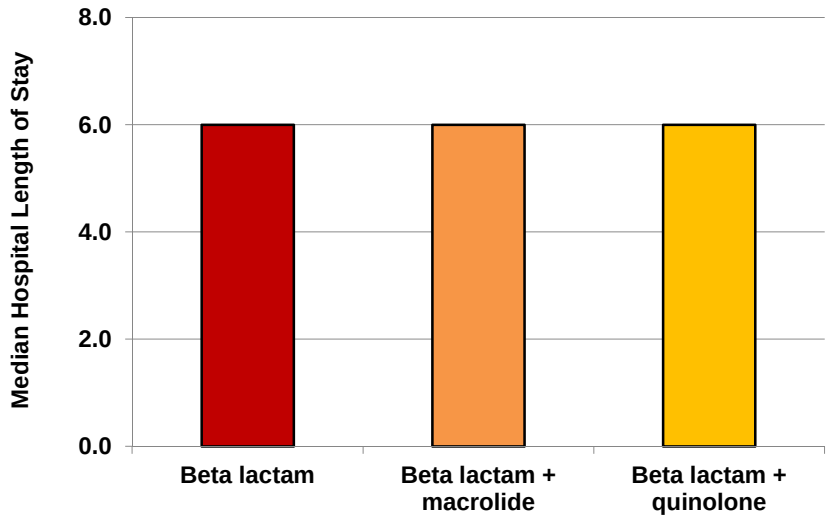
Cluster randomized trial of 2,283 non-ICU patients with CAP in the Netherlands



N Engl J Med 2015;372:1312-23

βlactam vs **βlactam+macrolide** vs **βlactam+quinolone**

Cluster randomized trial of 2,283 non-ICU patients with CAP in the Netherlands



N Engl J Med 2015;372:1312-23

Do patients who aspirate need antibiotics?*

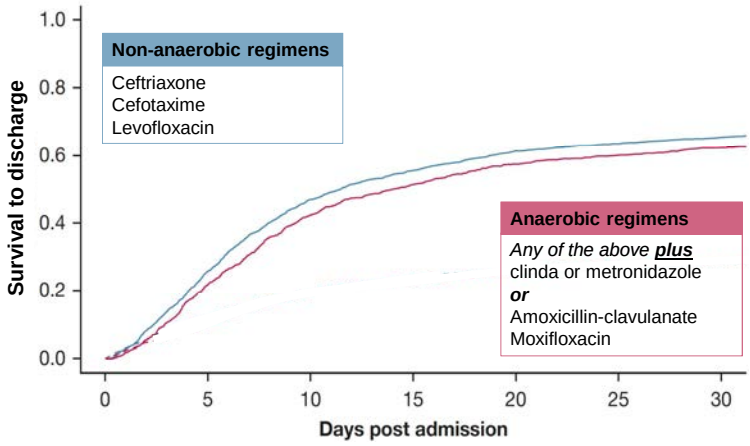
A. Yes

B. No

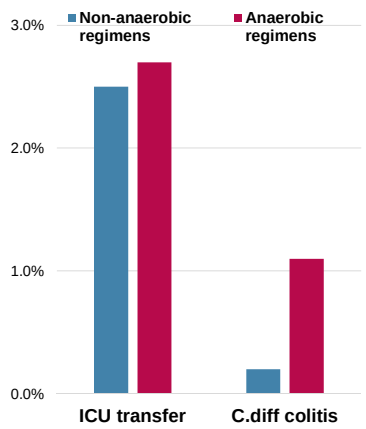
Adding anaerobic coverage: Same Outcomes, More *C.diff*

Propensity-matched comparison of anaerobic vs non-aerobic regimens for aspiration pneumonia, 18 hospitals, Ontario

Survival to Discharge



Complications



Bai, *Chest* 2024;166:39-48

How long should we treat for?*

A. 3 days

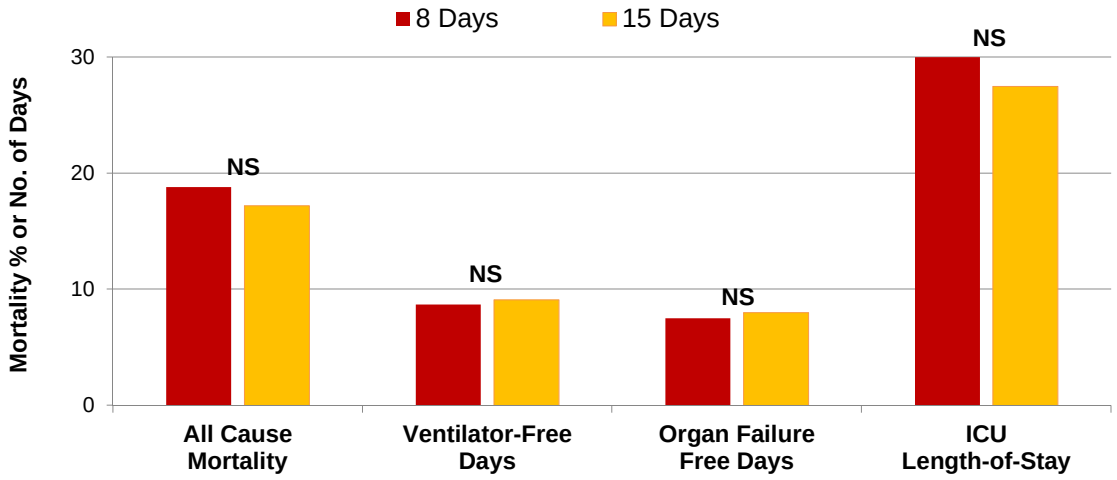
B. 5 days

C. 7 days

D. 10 days

Ventilator Associated Pneumonia

401 patients with ventilator-associated pneumonia randomized to 8 vs 15 days of antibiotics

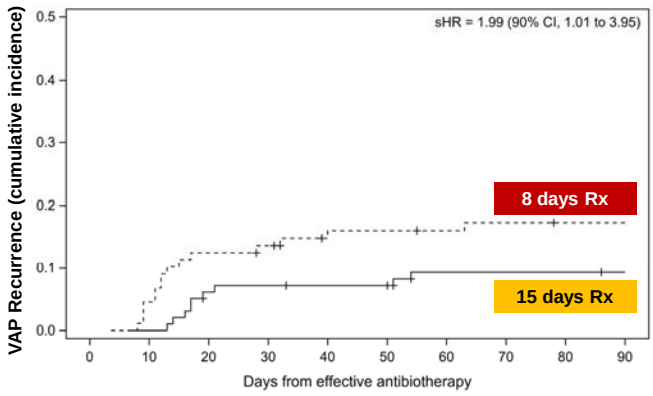


Chastre, *JAMA* 2003;290:2588-2598

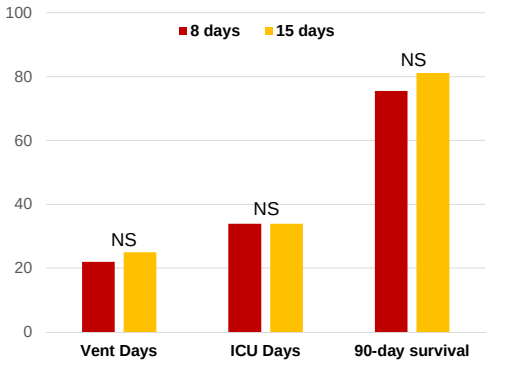
What about Pseudomonas???

186 patients with VAP due to non-fermenting gram negatives randomized to 8 vs 15 days of antibiotics

Recurrent Pneumonia



Length of Stay and Mortality

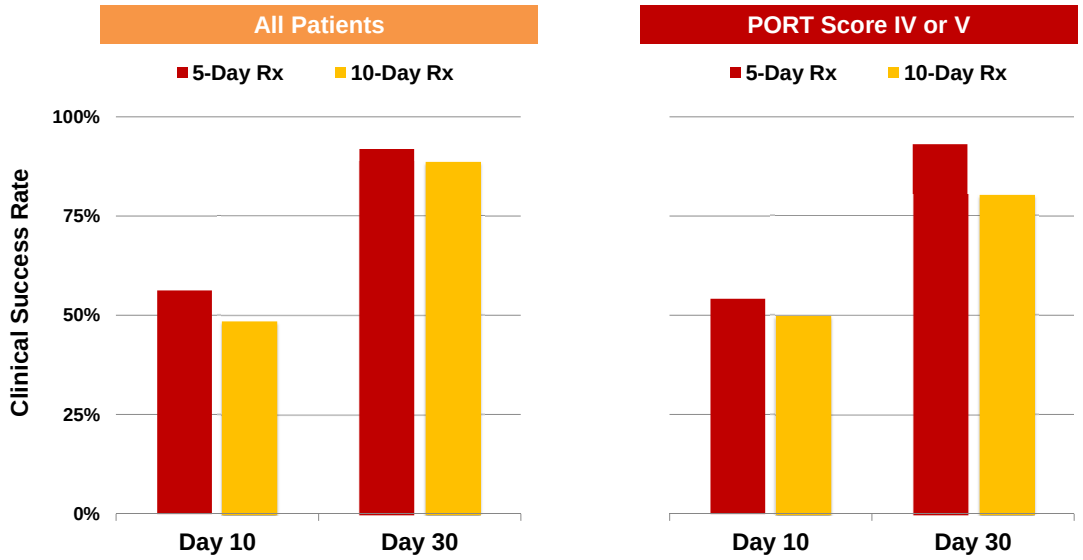


Bougle, *Intensive Care Med* 2022;48:841-849

Is less than 8 days feasible?

5 vs 10 Days for Community Acquired Pneumonia

Randomized controlled trial, 312 patients, 4 hospitals in Spain



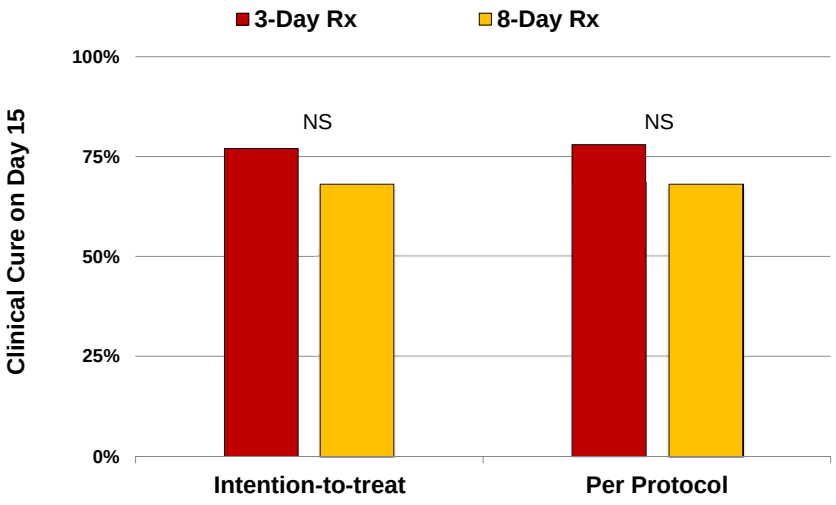
Uranga, JAMA Internal Medicine 2016;176:1257-1265

Is less than 5 days feasible?

Image: www.she.stir.ac.uk/env-carbon-management/challenge.php

3 vs 8 Days for Community Acquired Pneumonia

Randomized double-blind multicenter trial, 310 patients, 20 hospitals in France



Dinh et al. *Lancet* 2021;397:1195-1203

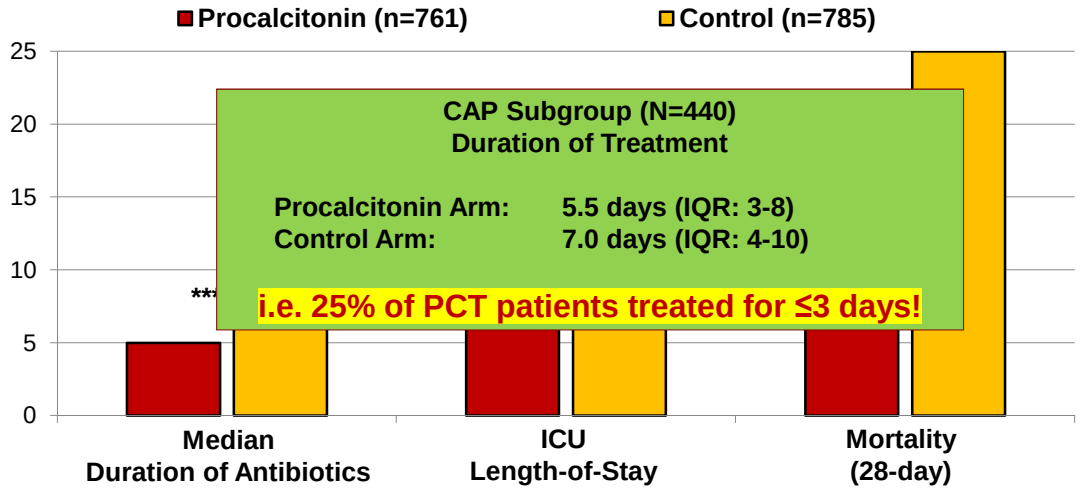
Could procalcitonin help?*

A. Yes

B. No

Procalcitonin Surveillance: SAPS

1575 critically ill patients, open label RCT, 15 ICUs, Netherlands



de Jong, *Lancet Infect Dis* 2016;16:819-827

ATS/IDSA Guidelines	My Opinion
Treat all patients for a minimum of 5 days	**If patient is immunocompetent, hemodynamically stable, and clearly improving then <5 days is fine.** **My reasons:** • Diagnosis of pneumonia is often questionable. Even when the diagnosis is correct, a third or more are caused by viruses • 2 RCTs showing 3 days as good as 8 days for both mild and severe CAP

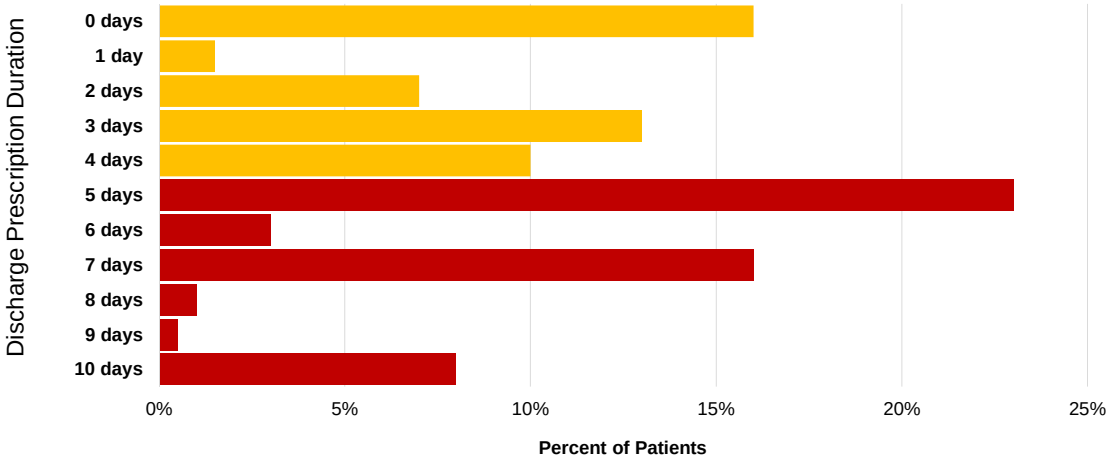
How many days of antibiotics does the patient need after discharge?

Typical Treatment Durations at Discharge

6,481 patients treated for pneumonia in 43 Michigan hospitals

68% Overtreated. Discharge antibiotics accounted for 93% of unnecessary antibiotic days

Each additional day of treatment associated with 5% increase in risk of adverse events

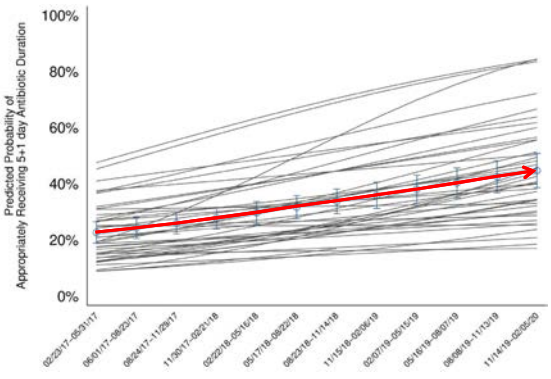


Ann Intern Med 2019;171:153-163

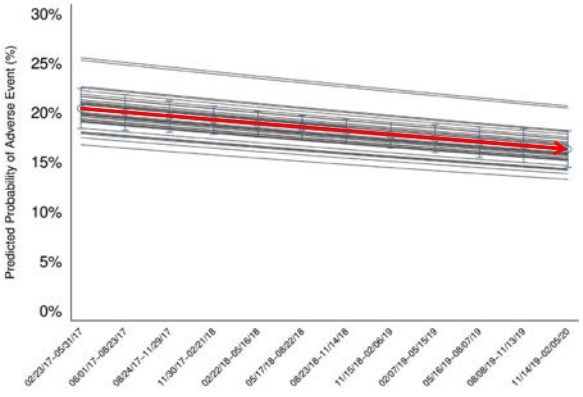
Shorter courses associated with fewer adverse effects

Statewide collaborative to decrease duration of antibiotics for uncomplicated CAP, 41 hospitals in MI, 2017-2020

Proportion of patients getting ≤6 days Rx



Adverse Effects



Vaughn, *Clin Infect Dis* 2022; doi.org/10.1093/cid/ciab950

Summary

- Diagnosing pneumonia is challenging. **We're often wrong.** CT may help.
- Many (?most) pneumonias are caused by **viruses.** Test for them.
- Tailor the **urgency of treatment** to **severity of illness** and **certainty of infection**. If you're on the fence and the patient is stable **get more data** before starting antibiotics.
- Know your antibiogram. **Vancomycin not necessary** for most patients. If you start it, stop if MRSA not found. **Atypical coverage most important** for patients with severe disease or compromised immune systems
- **Short course regimens (3-5 days) usually adequate**. Serial procalcitonin measures may enable shorter courses. **Don't reset the clock at discharge!**