PRO/CON debate: should ”atypical coverage” be added empirically as part of CAP therapy?

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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

Question 9: In the Inpatient Setting, Which Antibiotic Regimens Are Recommended for Empiric Treatment of CAP in Adults without Risk Factors for MRSA and *P. aeruginosa*?

Recommendation 9.1

In inpatient adults with non-severe CAP without risk factors for MRSA or *P. aeruginosa*, we recommend the following empiric treatment regimens:

1. Combination therapy with a β-lactam and a macrolide (strong recommendation, high quality of evidence), or

2. Monotherapy with a respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin 400 mg daily) (strong recommendation, high quality of evidence).

Metlay et al. Amer J Resp and Crit Care Med, 2019

Some definitions

Severe pneumonia

Validated definition includes either one major criterion or three or more minor criteria
Minor criteria
Respiratory rate ≥ 30 breaths/min
Pa_{O2}/F_{IO2} ratio ≤ 250 → SpO_2 of ~86% on RA
Multilobar infiltrates
Confusion/disorientation
Uremia (blood urea nitrogen level ≥ 20 mg/dl)
Leukopenia* (white blood cell count < 4,000 cells/μl)
Thrombocytopenia (platelet count < 100,000/μl)
Hypothermia (core temperature < 36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Septic shock with need for vasopressors
Respiratory failure requiring mechanical ventilation
*Due to infection alone (i.e., not chemotherapy induced).

Atypical coverage = antibacterial coverage of *Mycoplasma pneumoniae*, *Legionella* spp, *Chlamydia pneumoniae*, typically with a macrolide, fluoroquinolone, or a tetracycline

Metlay et al. Amer J Resp and Crit Care Med, 2019

Some confessions

1. I think we overuse atypical coverage
2. I think guidelines are worth debating
3. I also like to win
4. I’m not going to use any arguments I don’t believe

PRO: atypical coverage **should** be added for CAP

I AGREE that:

- Detected Legionella is rare and that other “atypical” causes of pneumonia likely don’t need treatment in most patients

BUT

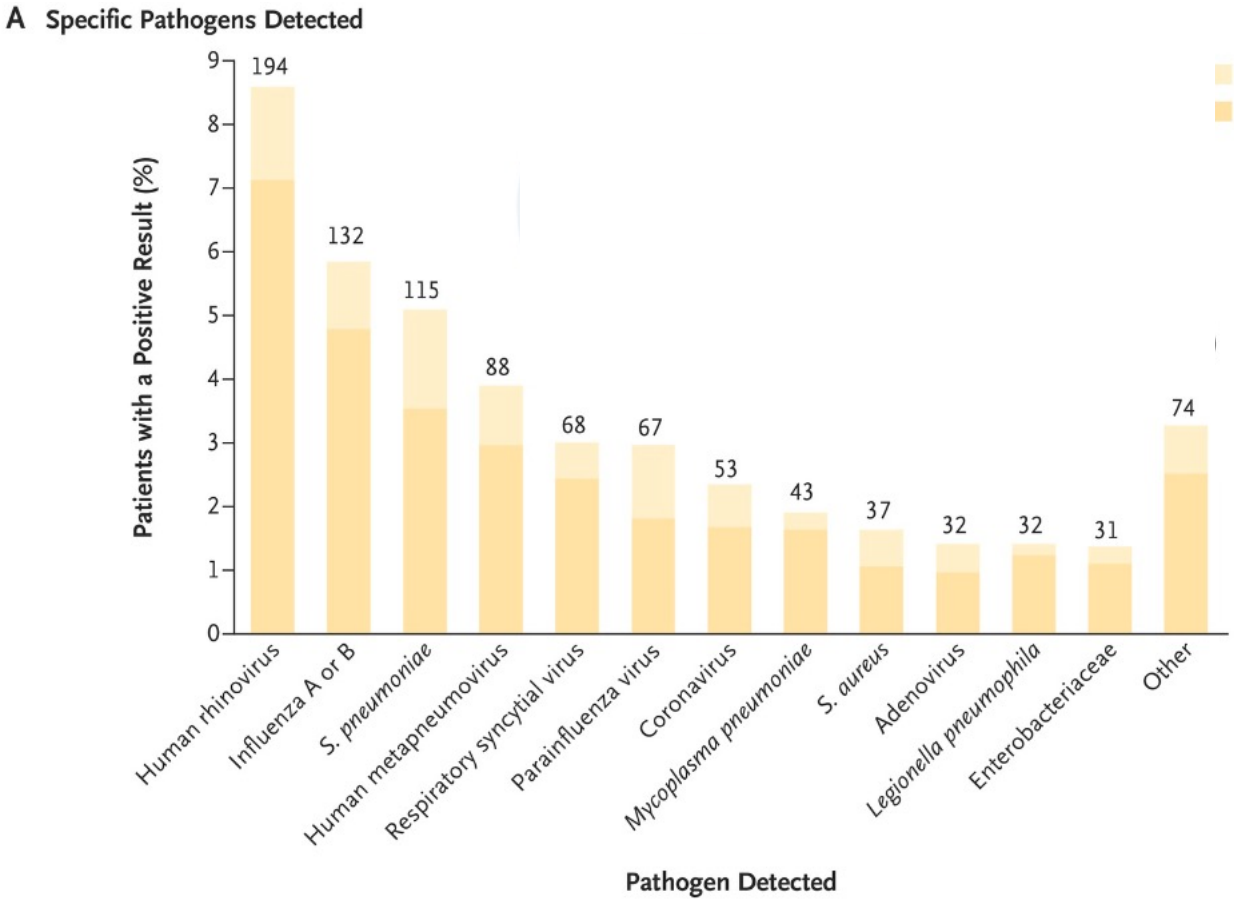
1. Diagnostic accuracy of pneumonia is poor
2. For the patients who **do** have atypicals, earlier therapy is better
3. Pneumonia benefits from empiric atypical coverage
4. Risks of atypical coverage are small

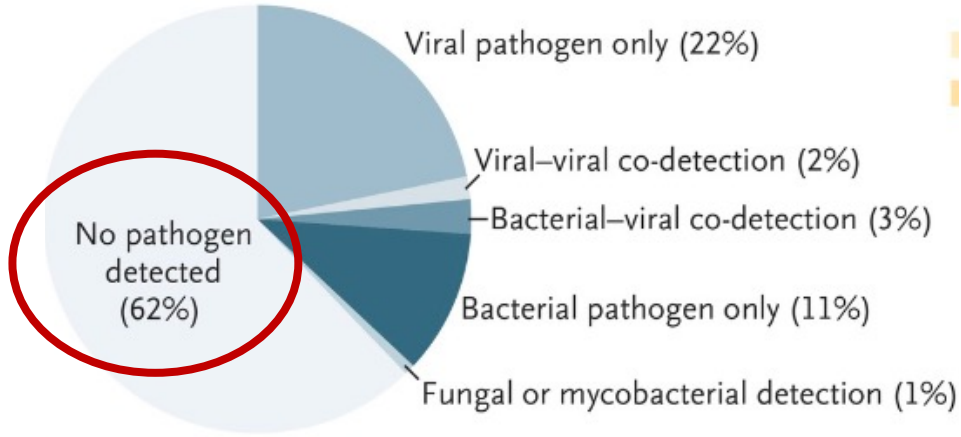
1. Diagnostic accuracy of pneumonia is poor

- EPIC study: Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults
  - 2320 patients w radiologic evidence of pneumonia requiring hospitalization enrolled into prospective observational multicenter trial
  - Blood, urine, respiratory specimens collected for diagnostic testing
- Pathogen detected in 38%

Jain et al. NEJM, 2015. doi: 10.1056/NEJMoa1500245

1. Diagnostic accuracy of pneumonia is poor





What does no pathogen mean?

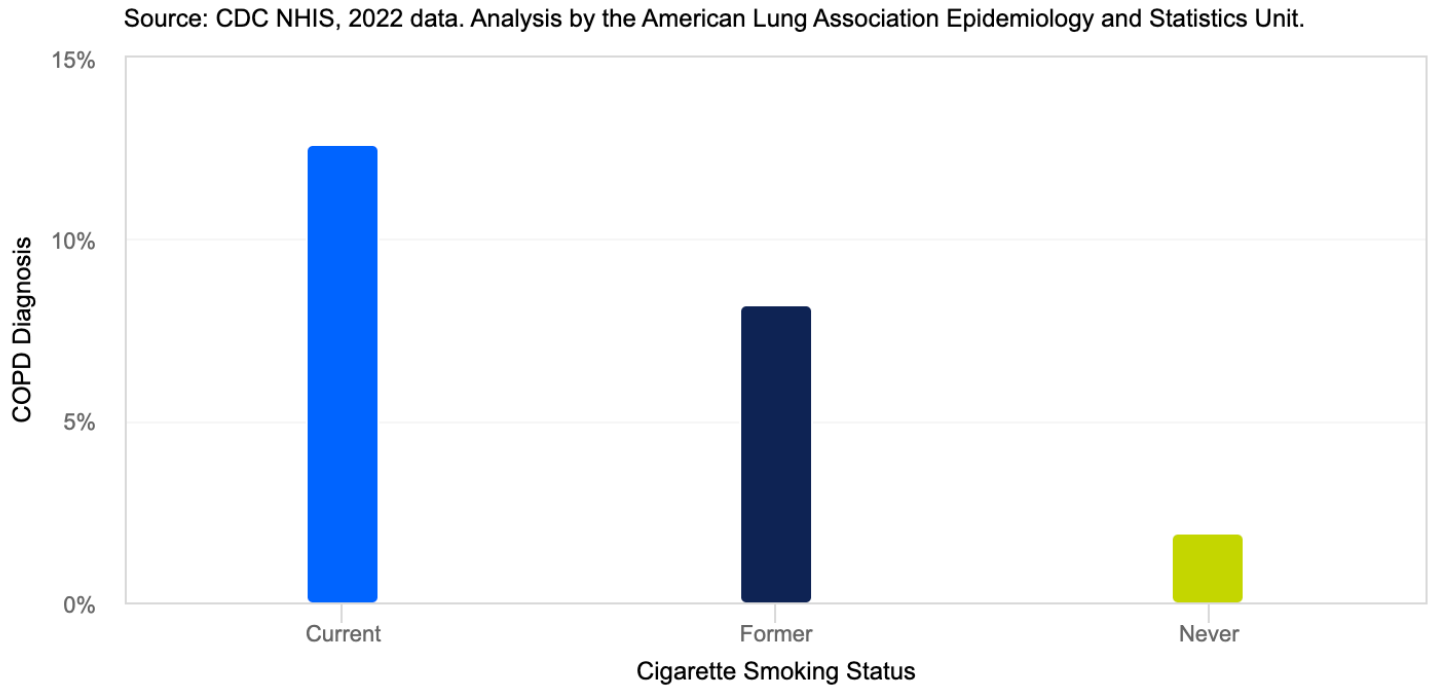
- Not actually pneumonia
- We did the wrong tests
- **Bacteria/viruses are there but escaped detection**

1.5 Legionella testing does not cover all species or serotypes

- Common testing: Urine Legionella antigen
  - pneumophila only
  - Serogroup 1 only

- Other testing exists but not often obtained on “floor” patients
  - Biofire Legionella pneumophila PCR
  - Legionella spp PCR (lab-developed)

1.75 Other indications for atypical coverage for respiratory infection are common



4.6% of adults in 2022 reported a diagnosis of COPD, chronic bronchitis, or emphysema

- 9.7% of adults 65+
- Subclinical/unknown diagnoses may be double known diagnoses

American lung association, 2024

2. For the patients who DO have atypicals, it is better to give active therapy up front

β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia
A Randomized Noninferiority Trial

- 580 patients enrolled in open-label RCT
- Treated for CAP with beta lactam+macrolide vs beta lactam
  - Study team sought out cases of Legionella and added macrolide for them (urine antigen testing)
  - All patients also had *C.pneumoniae* and *M.pneumoniae* testing (not told to clinical team)
- Primary outcome: clinical stability at 7 days

Garin et al. JAMA Intern Med, 2014 doi:10.1001/jamainternmed.2014.4887

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A Randomized Noninferiority Trial

Primary outcome: 41% in mono tx vs 34% in combo tx had NOT reached clinical stability by day 7 (not non-inferior)

- Numerically worse if pneumonia was severe
  [HR for stability=0.81 in mono vs combo (0.59 – 1.10)]
- Numerically worse if an atypical was identified
  [HR for stability=0.33 in mono vs combo (0.13 – 0.85)]

Garin et al. JAMA Intern Med, 2014 doi:10.1001/jamainternmed.2014.4887

2. For the patients who DO have atypicals, it is better to give active therapy up front

	Monotherapy (n=291)	Combination therapy (n=289)
Legionella pneumophila (n, %)	12 (4.1)	4 (1.4)
Mycoplasma pneumoniae (n, %)	6 (2.1)	9 (3.1)

eTable 5. Secondary Outcomes in Patients Infected With Atypical Pathogens

	Monotherapy (n=18)	Combination therapy(n=13)	P value
In-hospital death (n, %)	0	0	
Intensive care unit admission (n, %)	3 (16·7)	0	0·12
Complicated pleural effusion† (n, %)	1 (5·6)	0	0·39
Length of stay in days (median, IQR)	8·5 (6·8-11·3)	8·0 (6·0-9·0)	0·38
30-days death (n, %)	2 (11·1)	0	0·21
30-days readmission (n, %)	0	1 (7·7)	0·23
90-days death (n, %)	3 (16·7)	0	0·12
90-days readmission (n, %)	1 (5·6)	1 (7·7)	0·81
New pneumonia within 30 days (n, %)	0	0	

† need for thoracic drainage or surgery

Garin et al. JAMA Intern Med, 2014 doi:10.1001/jamainternmed.2014.4887

2.5 Urine Legionella testing not always available -> benefit of empiric atypical coverage

3. Pneumonia does benefit from empiric atypical coverage

Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial

- ACCESS RCT
  - 278 patients admitted to hospital with CAP whose SOFA score was ≥2 (median 3-4)
  - Clarithromycin vs placebo given x 7 days along with standard of care
    - Ceftriaxone, IV piptaz, or amp-sulbactam
    - If Legionella or atypicals identified, treatment switched to moxifloxacin
  - Primary outcome: assessed at day 4
    - Any ≥50% dec in respiratory severity score relative to day 1
    - AND Any ≥30% decrease in SOFA score OR ≥80% decrease in procalcitonin/procal <0.25
  - Secondary endpoints: multiple
    - Clinical success at end of treatment (resolution of CAP sx), 28- and 90-day mortality

Giamarellos-Bourboulis et al. Lancet Resp Med, 2024, doi:10.1016/S2213-2600(23)00412-5

ACCESS study - Results

	SOC + clarithro	SOC + placebo	P-value
Composite primary endpoint	91 (68%)	51 (38%)	<0.001
≥50% decrease in respiratory symptom severity score at day 4	97 (72%)	64 (48%)	<0.001
≥30% decrease in SOFA score at day 4	91 (68%)	54 (41%)	<0.001
Resolution of CAP sx at day 8	43 (32%)	23 (17%)	0·0067
28 day mortality	27 (20%)	35 (26%)	0.25
90 day mortality	46 (34%)	50 (38%)	0.61

Giamarellos-Bourboulis et al. Lancet Resp Med, 2024, doi:10.1016/S2213-2600(23)00412-5

ACCESS study – Results cont'd

Most common pathogens		
Staphylococcus aureus	32 (24%)	22 (17%)
Streptococcus pneumoniae	8 (6%)	8 (6%)
Haemophilus influenzae	16 (12%)	23 (17%)
Klebsiella pneumoniae	8 (6%)	10 (8%)
Legionella pneumophila	1 (1%)	3 (2%)

- Pretty high rate of microbiologic detection (55% vs 53%)
- Impact was similar for patients with or without microbiologically documented infection (for bacterial or non bacterial pathogens)
- TEAEs by day 90 occurred in 43% in clarithro group vs 53% in placebo group – mostly driven by septic shock [9% in clarithro group vs 17% in placebo group]

Giamarellos-Bourboulis et al. Lancet Resp Med, 2024, doi:10.1016/S2213-2600(23)00412-5

4. Risks of empiric coverage are small

TEAEs on RCTs of combo vs monotherapy coverage

- Giamarellos-Bourboulis et al: TEAEs higher in monotherapy arm
- Garin et al: no significant AEs in either arm
- Postma et al: similar rates of minor or major complications (80% in each arm with no complications)

Risks smaller if negative diagnostic testing allows you to stop early

Conclusions: we SHOULD empirically add atypical coverage to CAP therapy for hospitalized adults