Combination Therapy is Required for Community-Acquired Pneumonia (CAP): Of COurse Not (CON)

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University of Utah Health and Salt Lake City VA

Outpatient CAP

Summary of the evidence. RCTs of antibiotic treatment regimens for adults with CAP provide little evidence of either superiority or equivalence of one antibiotic regimen over another, because of small numbers and the rare occurrence of important outcomes such as mortality or treatment failure resulting in hospitalization. Several published trials

Combination therapy for those with comorbidities based on more vulnerable status and "risk factors for antibiotic resistance by virtue of contact with healthcare system"…no references provided.

and more severely ill. As observational data suggest that inpatient and outpatient CAP are due to the same pathogens (69, 71–73, 82), except for *Legionella* and gram-negative bacilli, which are rarely documented in outpatient settings, it seems reasonable that an antibiotic regimen that was effective for inpatients would be effective for outpatients.

Studies of high-dose oral amoxicillin have demonstrated efficacy for inpatients with CAP (86–88). Similarly, there is evidence supporting amoxicillin-clavulanic acid in outpatient CAP (71, 73) and inpatient CAP (89, 90).

Metlay JP, et al. Am J Resp Crit Care Med. 2019 Oct 1;200(7):e45-e67

1998 IDSA Guideline	β-lactam **with or without** a macrolide or a fluoroquinolone alone	B-II	"Guidelines for the selection of these regimens are based largely on clinical experience and/or invitro activity."
2000 IDSA Guideline	β-lactam **PLUS** a macrolide or a fluoroquinolone alone	B-II	• Based on a retrospective evaluation of nearly 13,000 Medicare database patients that found the addition of a macrolide to a β-lactam was associated with a lower 30-day mortality compared to a β-lactam alone. • Due to the limitations, the authors acknowledged that future randomized controlled trials would be needed to confirm these findings before they are adopted into clinical practice.
2003 IDSA Guideline	β-lactam **PLUS** a macrolide or a fluoroquinolone alone	A-I	Recommendation remained the same, however, no randomized controlled trials noted in guidelines to support level of evidence switch from B-II to A-I.

Credit to Whitney Hartlage, PharmD

CAP: Etiology

”Classic” etiologies:

- ***S. pneumoniae***
- *H. influenzae*
- *M. pneumoniae*
- *S. aureus*
- *Legionella* species
- *Moraxella*
- *Chlamydia species*

- In modern era, more than half of clinical cases will have no etiology identified
- *S.pneumoniae* causes a minority of cases

Clinical Infectious Diseases

REVIEW ARTICLE

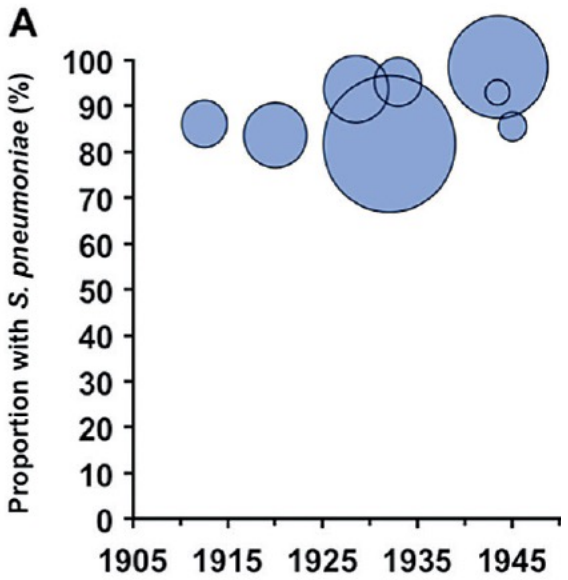
IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Evolving Understanding of the Causes of Pneumonia in Adults, With Special Attention to the Role of Pneumococcus

Daniel M. Musher,[1,2] Michael S. Abers,[3,4] and John G. Bartlett[5]

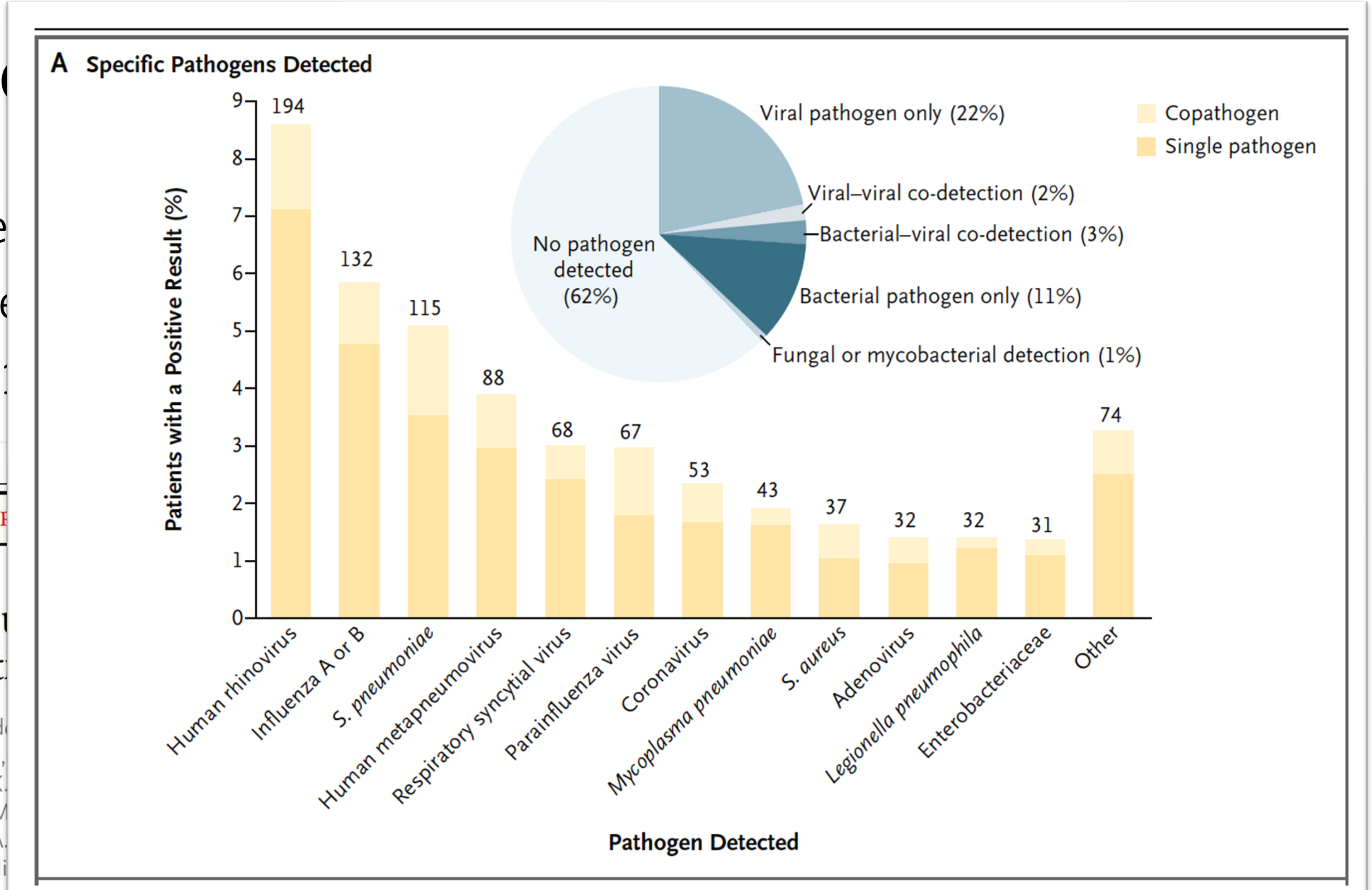
[1]Departments of Medicine and Molecular Virology and Microbiology, Baylor College of Medicine, and [2]Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; [3]Massachusetts General Hospital and [4]Harvard Medical School, Boston, Massachusetts; and [5]Johns Hopkins University School of Medicine, Baltimore, Maryland

Musher, Clin Infect Dis 2017



CAP: Etiol

- Prospective
- Virus recove
- Bacteria in



Community-Acqu
Hospitalizat

S. Jain, W.H. Self, R.G. Wund
C.G. Grijalva, E.J. Anderson,
F. Carroll, C. Trabue, H.K.
K. Ampofo, G.W. Waterer, M
D. Erdman, E. Schneider, L.A.
and L. Finelli

Jain, NEJM 2015

Over-Diagnosis of CAP

- Retrospective study of patients treated for UTI and CAP at 46 hospitals across Michigan Hospital Medicine Safety (HMS) Consortium
- Over-diagnosed with CAP if they did not meet published diagnostic criteria (*reviewers agreed on 94% of over-diagnosis classifications*)
- 11.4% (n=1602) of 14,085 patients treated for CAP were over-diagnosed
- Varied across hospitals (3.6% to 27.8%)

Gupta A, et al. BMJ Qual Saf. 2022 May; 31(5): 383–386.

Ultra-Short-Course Antibiotics for Suspected Pneumonia With Preserved Oxygenation

Michael Klompas,[1,2] Caroline McKenna,[1] Aileen Ochoa,[1] Wenjing Ji,[3] Tom Chen,[1] Jessica Young,[1,4] and Chanu Rhee[1,2]; for the Prevention Epicenters Program, Centers for Disease Control and Prevention

- Patients started on antibiotics for pneumonia in 4 hospitals with oxygen saturations ≥95% on ambient air
- May 2017 – February 2021
- Propensity-matched patients treated 1–2 days vs 5–8 days
- Primary outcome: Hospital mortality and time to discharge

Results

- 10,012/39,752 patients on ambient air
- 2871 treated 1–2 days vs. 2891 for 5–8 days
- Hospital mortality
  - (2.1% vs 2.8%, short vs. long)
- Shorter time to discharge
  - (6.1 vs 6.6 days; SHR, 1.13 [95% CI, 1.07–1.19])
- No difference in 30-day readmission, 30-day mortality or 90-day *C. difficile*

Clin Infect Dis. 2023 Feb 8;76(3):e1217-e1223. doi: 10.1093/cid/ciac616.

Take Home

- Large population (25-30%) with “possible pneumonia” who could stop early
- Not pneumonia vs. viral vs. mild bacterial case
- Review of oxygenation may be an ASP strategy to reduce duration

Why would we recommend atypical coverage for all when atypical infection is so uncommon and diagnostic accuracy is so unclear/poor?

Outcome Data

Trial	Design (n)	Patient population	Clinical Outcomes
Eliakim-Raz N, et al. 2012	Meta-analysis 28 trials 5939 patients	-RCTs of adult patients hospitalized due to CAP -Atypical coverage vs. regimen without atypical antibiotic coverage -Mostly FQ monotherapy vs. β-lactam monotherapy	Primary: Mortality and proportion with treatment failure **No difference** in mortality between the atypical arm and the non-atypical arm (RR 1.14; 95% CI 0.84 to 1.55) or clinical success Clinical success for the atypical arm was significantly higher for *Legionella pneumophilae* (43 patients) and non-significantly lower for pneumococcal pneumonia

Garin N, et al. JAMA Intern Med. 2014 Dec;174(12):1894-901.
Postma DF, et al. N Engl J Med. 2015;372(14):1312.
Eliakim-Raz N, et a. Cochrane Database Syst Rev. 2012 Sep 12;2012(9):CD004418.

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Garin N, et al. 2014	Open label non-inferiority RCT N = 580 β-lactam monotherapy vs. β-lactam + macrolide	Immunocompetent adults admitted with CAP	Outcome: Proportion not meeting clinical stability by day 7 **No difference**: (41.2%) in the monotherapy arm vs. 7 of 289 (33.6%) in the combination arm (7.6% difference, P = .07) **Patients infected with atypical pathogens or PSI IV disease drove the outcome* Mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the 2 arms

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Postma DF, et al. 2015	Cluster-randomized, crossover, non-inferiority trial 1) β-lactam monotherapy vs. 2) β-lactam + macrolide v. 3) Fluoroquinolone N = 656 β-lactam monotherapy N = 739 β-lactam + macrolide N = 888 Fluoroquinolone	Adults admitted to non-ICU wards with CAP	90-day mortality: **No difference** No difference in length of stay or complications

Garin N, et al. JAMA Intern Med. 2014 Dec;174(12):1894-901.
Postma DF, et al. N Engl J Med. 2015;372(14):1312.
Eliakim-Raz N, et a. Cochrane Database Syst Rev. 2012 Sep 12;2012(9):CD004418.

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

- Different question than ”Should all get atypical coverage”.

- Respiratory symptom severity score subjective (cough, SOB, chest pain, sputum production)
  - 28 and 90-day mortality no different
  - Seems to make people feel better more quickly

- 701/979 screened were excluded (27% because they didn’t meet 2 SIRS criteria)
  - Authors acknowledge this is a sicker population

- Legionella only isolated 1-2% of patients

- Clarithro vs. Azithro?

- *My conclusion: May support immunomodulatory role for patients with severe CAP (ICU) and maybe some on the floor but not all floor CAP patients look like this. Depends on your goal…*

Lancet Respir Med . 2024 Jan 3:S2213-2600(23)00412-5.

Azithromycin Toxicity

ORIGINAL ARTICLE

Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

- TN Medicaid beneficiaries who took Azithromycin x 5 days
- Increased risk of cardiovascular death (hazard ratio, 2.88; 95% confidence interval [CI], 1.79 to 4.63; P<0.001)

FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms

Original Investigation

June 4, 2014

Association of Azithromycin With Mortality and Cardiovascular Events Among Older Patients Hospitalized With Pneumonia

- Retrospective VA cohort of those ≥ 65 admitted with CAP
- Propensity matched those receiving azithromycin vs. other standard CAP therapy
- Small ↑ risk of MI but reduced 90-day mortality

Ray WA, et al. N Engl J Med 2012;366:1881-90.
https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-azithromycin-zithromax-or-zmax-and-risk-potentially-fatal-heart
Mortensen EM, et al. JAMA. 2014;311(21):2199-2208. doi:10.1001/jama.2014.4304

Journal of the American Heart Association

ORIGINAL RESEARCH

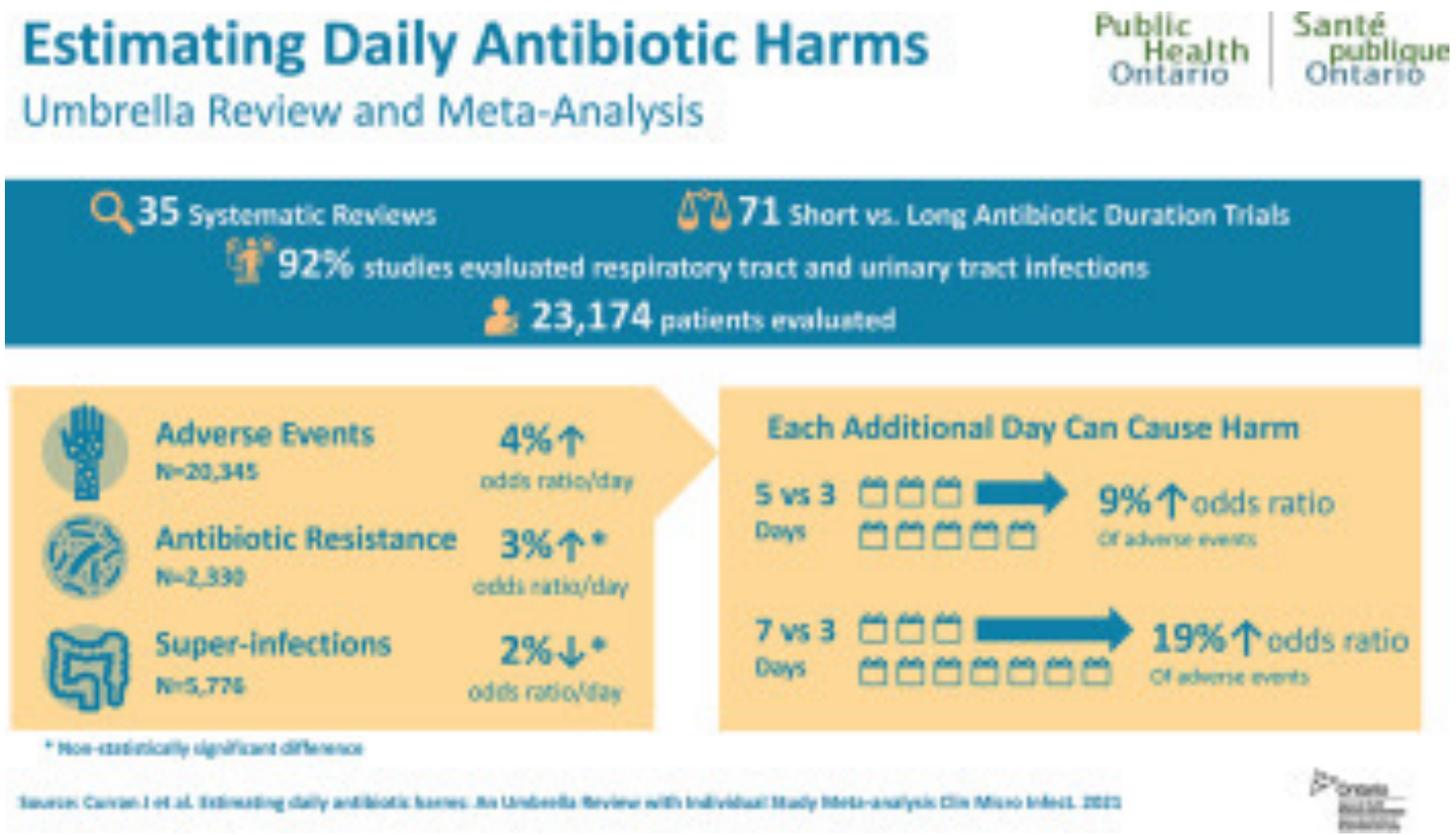
Relationship Between Azithromycin and Cardiovascular Outcomes in Unvaccinated Patients With COVID-19 and Preexisting Cardiovascular Disease

- Data from the ISACS-COVID-19 (International Survey of Acute Coronavirus Syndromes-COVID-19) registry across 5 European countries

- 793 patients exposed to azithromycin within 24 hours from hospital admission and 2141 patients who received standard care

- Azithromycin therapy was associated with an increased risk of acute heart failure in patients with preexisting CVD (risk ratio [RR], 1.48 [95% CI, 1.06–2.06])

J Am Heart Assoc. 2023 Jul 18;12(14):e028939.



•Six studies with 2238 patients evaluated adverse events due to macrolides

•Macrolides were associated with significant increases in the odds of developing adverse events with each day of therapy (OR 1.01, 95% CI 1.01-1.10)

Clin Microbiol Infect . 2022 Apr;28(4):479-490.

Conclusions

- Atypical infection uncommon and CAP over-diagnosed
- NO clear impact on survival or clinical efficacy with empirical atypical coverage in typical hospitalized floor patients (maybe immunomodulatory effect for sicker patients)
- Potential toxicities with azithromycin not worth the benefit
- Not a proponent of empiric atypical for all…consider for more severe cases, high clinical suspicion of Legionella, limited diagnostics

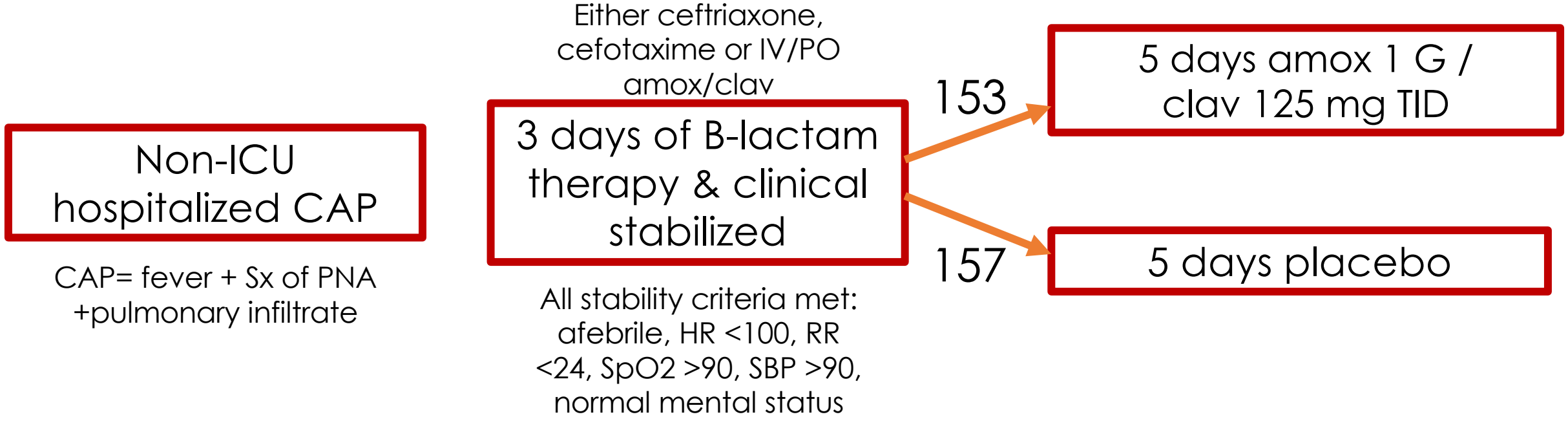
CON: Rebuttal

Points

- Other RCT and real world clinical outcome data do not support need for atypical coverage in floor CAP patients

- Newer rapid diagnostics increase ability to exclude atypical pathogens at time of empiric therapy

Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial



Dinh A, et al. Lancet . 2021 Mar 27;397(10280):1195-1203.

Lancet 3 vs 8 Days for CAP

No difference in any outcomes

- Primary outcome: cure at 15 days
  - Cure was defined as afebrile, resolution of signs/symptoms, no additional antibiotics
  - 77% (3 day) vs. 68% (8 days); difference of 9·44% [95% CI –0·15 to 20·34]→ non-inferior
- Adverse events (14% vs. 19%)
- Mortality (2% vs. 1%)

Dinh A, et al. Lancet . 2021 Mar 27;397(10280):1195-1203.

We've Seen This Before

- RCT of patients with mild to moderate/severe CAP
- All pts. received IV amoxicillin for 3 days
- At 3 days pts. were randomized into two groups if they had improvement, become afebrile, and were able to take oral therapy:
  - Amoxicillin 750 mg PO TID x 5 days
  - Placebo TID x 5 days

Research

BMJ

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

	3 Days	8 Days
Clinical cure at 10 days	93%	93%
Clinical cure at 28 days	90%	88%
Adverse events	11%	21%

Moussaoui, *BMJ* 2006

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CAP Treatment Options

Floor (CURB 65 score 0-2 / Drip score less than 4) - For most patients (not at an increased risk for drug-resistant pathogens)

- [x] Antibiotics
  - Preferred Antibiotics
    - azithromycin (ZITHROMAX) 500 mg in sodium chloride 0.9 % 250 mL IVPB
      500 mg, Intravenous, at 250 mL/hr, Administer over 60 Minutes, Once, Today at 1000, For 1 dose, STAT

And

- cefTRIAXone (ROCEPHIN) 2 g in sodium chloride 0.9% IVPB Mini-bag Plus
  2 g, Intravenous, at 200 mL/hr, Once, Today at 1000, For 1 dose, STAT

And

- cefuroxime axetil (CEFTIN) tablet 500 mg
  500 mg, Oral, 2 times daily, First Dose Tomorrow at 1000, For 8 doses
  Routine

- [x] Labs
  - [x] Streptococcus Pneumoniae Antigen,Urine
    Once - Routine - Lab First occurrence Today at 0921, Urine, Urine-General
    Collection Method Override: Unit Collect
  - [x] Legionella Pneumophilia Antigen, Urine
    Once - Routine - Lab First occurrence Today at 0921, Urine
    Collection Method Override: Unit Collect
  - [x] Procalcitonin
    Once - Routine - Lab First occurrence Today at 0921
    Do you want to change the specimen collection from what it shows in the banner bar? No
  - [ ] Culture, Blood - 1st of 2 Perpheral Draw
    STAT - Lab, 1st of 2 Peripheral Draw. Phleb to determine site
  - [ ] Culture, Blood - 2nd of 2 Peripheral Draw
    STAT - Lab, 2nd of 2 Peripheral Draw. Phleb to determine site
  - [ ] Aerobic Respiratory Culture with Gram Stain
    Once - Routine - Lab, Sputum, Sputum Induced

***Daily ASP Prospective Audit and Feedback**

A Pathway for Community-Acquired Pneumonia With Rapid Conversion to Oral Therapy Improves Health Care Value

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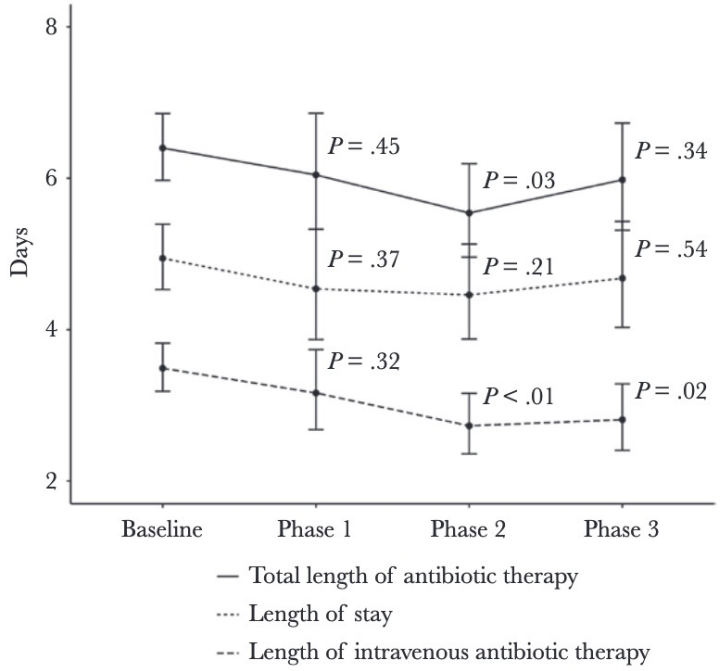
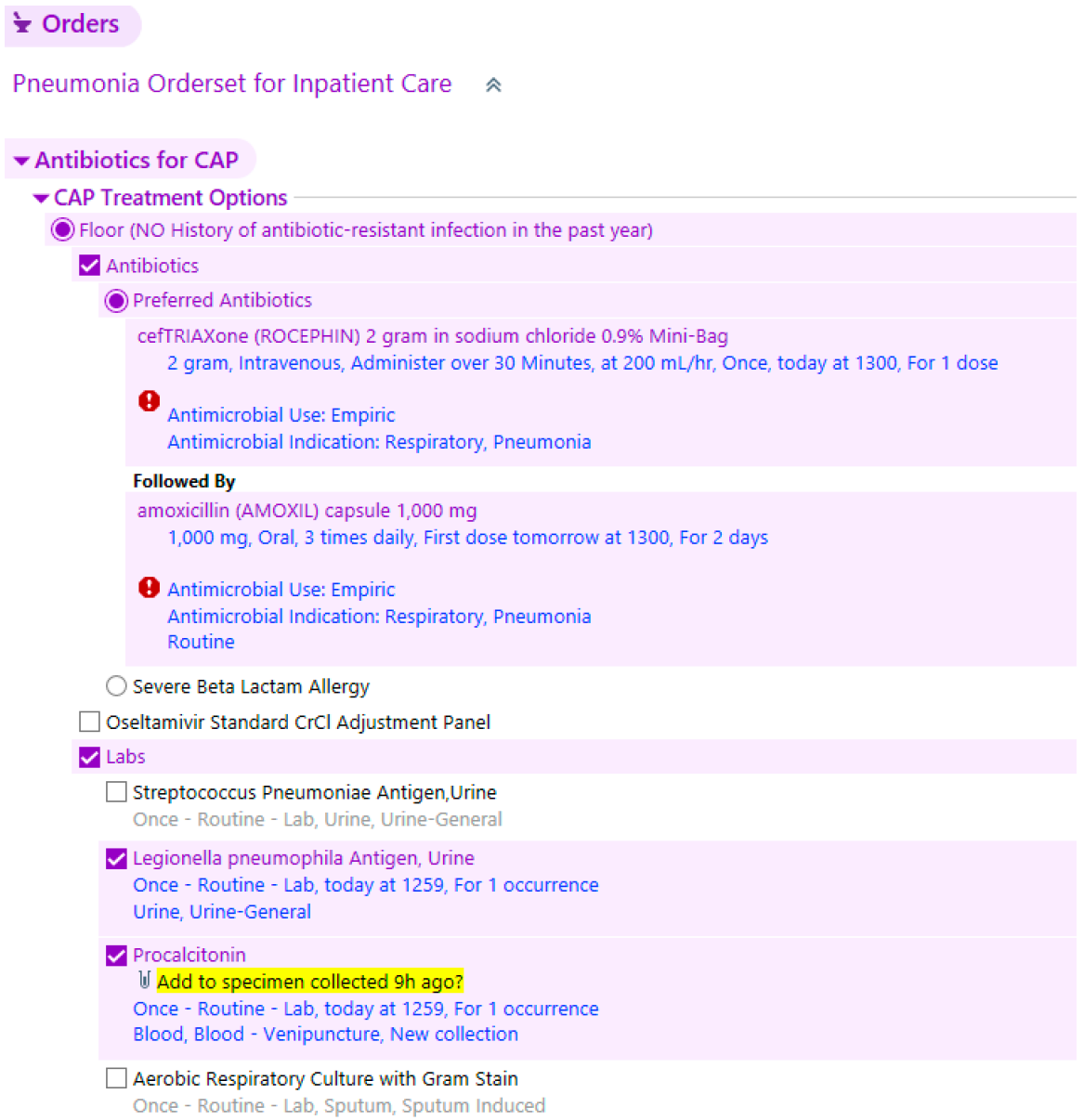
- Sustained reductions in atypical antibiotic duration
- Median cost per case decreased by 20%
- Total length of antibiotic duration decreased by 1 day
- IV duration of antibiotics decreased by 22%
- No change in 30-day readmission rate, length of stay or inpatient mortality



Ciarkowski CE, et al. Open Forum Infect Dis. 2020 Oct 19;7(11):ofaa497.

New Order Set (Rolled out 11/11/21)



Infectious Disease Clinics of North America
Volume 27, Issue 1, March 2013, Pages 99-114

Does Empiric Therapy for Atypical Pathogens Improve Outcomes for Patients with CAP?

Thomas M. File Jr. MD, MSc [a b], Thomas J. Marrie MD [c]

- *"The present controversy regarding the need to cover atypical pathogens in the empiric therapy of community-acquired pneumonia is related to several issues, including the relevance of terminology, imprecise diagnostic methods, and perceived contradictory results of published evidence… until there is the availability of accurate, cost-effective, and easily interpreted laboratory tests to provide the etiologic diagnosis at the time of point of care, empiric therapy of atypical pathogens is supported."*

BioFire® FilmArray® PNA Panel

BACTERIA: (Semi-Quantitative)	ATYPICAL BACTERIA: (Qualitative)	VIRUSES:	ANTIMICROBIAL RESISTANCE GENES:
● Acinetobacter calcoaceticus-baumannii complex ● Enterobacter cloacae complex ● Escherichia coli ● Haemophilus influenzae ● Klebsiella aerogenes ● Klebsiella oxytoca ● Klebsiella pneumoniae group ● Moraxella catarrhalis ● Proteus spp. ● Pseudomonas aeruginosa ● Serratia marcescens ● Staphylococcus aureus ● Streptococcus agalactiae ● Streptococcus pneumoniae ● Streptococcus pyogenes	● Chlamydia pneumoniae ● Legionella pneumophila ● Mycoplasma pneumoniae	● Adenovirus ● Coronavirus ● Human metapneumovirus ● Human rhinovirus/enterovirus ● Influenza A virus ● Influenza B virus ● Parainfluenza virus ● Respiratory syncytial virus	Carbapenemases: ● IMP ● KPC ● NDM ● OXA-48-like ● VIM ESBL: ● CTX-M Methicillin resistance: ● mecA/C and MREJ (MRSA)

BioFire® FilmArray® Pneumonia Panel. 2021.

More Sensitive Than Culture

Rand KH, et al. *Open Forum Infect Dis.* 2021;8(1):ofaa560.	
Sensitivity 98.55%	Specificity 69%
NPV 98.9%	PPV 63%

Based on BAL and endotracheal aspirate

Kolenda C, et al. *Open Forum Infect Dis.* 2020;7(11):ofaa484.	
Sensitivity 100%	Specificity 88.4-100%*

Based on BAL and endotracheal/bronchial aspirate
* Varied based on pathogen

<u>Limitations</u>: specificity, limited clinical experience suggests doesn't impact antibiotic use, likely needs significant stewardship intervention