DukeHealth

Atypical De-escalation Pathway

1. START EMPIRIC THERAPY

Adults with suspected CAP:
Start β-lactam therapy
*Add atypical coverage in select patients (e.g azithromycin^)

^or doxycycline in setting of macrolide allergy or elevated QTc > 500

Incidence of atypical pathogen in CAP is rare[1,2]

- 1.4% *Legionella* pneumophila
- <3% *Mycoplasma/Chlamydia* combined

Because atypical infections are uncommon, and atypical coverage may increase cardiovascular risk and macrolide resistance, routine continuation of atypical coverage in all patients is NOT recommended

2. ATYPICAL COVERAGE IN SELECT PATIENTS*

Initiating empiric atypical coverage is reasonable if ONE or MORE of the following are present:

- Severe CAP (see criteria below)
- High suspicion for *Legionella* (eg. known outbreak or exposure, recent travel or hotel/cruise stay to endemic areas, healthcare water exposure)
- Positive atypical pathogen testing (*Mycoplasma*, *Chlamydia pneumoniae*, or

Severe community acquired pneumonia (CAP) is defined as[3]

<u>One major criterion OR ≥ 3 minor criteria</u>

Major Criteria:

- Shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Minor Criteria (≥ 3 qualifies as severe):

- RR ≥ 30 breaths/min
- PaO2/FiO2 ratio ≤ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN ≥ 20 mg/dL)
- Leukopenia (WBC < 4 K/μL)
- Thrombocytopenia (Plt < 100 K/μL)
- Hypothermia (core temp < 36 C)
- Hypotension requiring aggressive fluid resuscitation

3. REASSESS AT 24 HRS*

*or earlier if rapid diagnostic results

- Clinical response and diagnostic results
- Microbiology: Blood/sputum cultures, respiratory panel and/or *Legionella* urine antigen if obtained
- Alternative diagnosis or pathogen identified?

Testing Performance

- **eRVP:**[4] Sensitivity 93-99% and specificity 99% for *Mycoplasma/Chlamydia pneumoniae*
- ***Legionella* urine antigen (serogroup 1):**[5,6] Moderate sensitivity 79% and high specificity 100%; negative predictive value 99%

Can atypical coverage be discontinued?

DISCONTINUE WHEN

Atypical coverage can be discontinued if the expanded respiratory PCR panel (eRVP) and/or *Legionella* urine antigen are negative and suspicion is low

- Stop azithromycin or doxycycline at 48-72 hr

CONTINUE WHEN

- Positive *Legionella* urine antigen or PCR
- Positive *Mycoplasma* or *Chlamydia* PCR
- High suspicion for *Legionella* despite negative urine antigen test

Why de-escalate atypical coverage?

- **Potential harms**: increased risk of cardiovascular death (highest in first 5 days of azithromycin use[7]), development of macrolide resistance
- No difference in ICU admission, length of stay (LOS), mortality, or 90-day readmission in RCT of β-lactam monotherapy vs. β-lactam+macrolide in moderate-severe CAP except in proven atypical infections[8]
- Incidence of atypical pathogens in CAP is low. Most CAP cases have no pathogen identified (62%); 23% are viral and 11% are bacterial[2]

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References: 1. Graham FF, et al. Global Perspective of Legionella Infection in Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis of Observational Studies. *International Journal of Environmental Research and Public Health*. 2022; 19(3):1907. https://doi.org/10.3390/ijerph190319072. Jain S, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015;373(5):415-427. doi:10.1056/NEJMoa1500245. 3. Metlay JP, et al. on behalf of the American Thoracic Society and Infectious Diseases Society of America, 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, *American Journal of Respiratory and Critical Care Medicine*, Volume 200, Issue 7, October 2019, Pages e45–e67, https://doi.org/10.1164/rccm.201908-1581ST. 4. Babady NE, et al. Multicenter Evaluation of the ePlex Respiratory Pathogen Panel for the Detection of Viral and Bacterial Respiratory Tract Pathogens in Nasopharyngeal Swabs. J Clin Microbiol. 2018;56(2):e01658-17. Published 2018 Jan 24. doi:10.1128/JCM.01658-17. 5. Peci A, et al. Evaluation and Comparison of Multiple Test Methods, Including Real-time PCR, for Legionella Detection in Clinical Specimens. *Front Public Health*. 2016;4:175. Published 2016 Aug 31. doi:10.3389/fpubh.2016.00175. 6. Kawasaki T, et al. Diagnostic accuracy of urinary antigen tests for legionellosis: A systematic review and meta-analysis. *Respir Investig*. 2022;60(2):205-214. doi:10.1016/j.resinv.2021.11.011. 7. Zaroff JG, et al. Association of azithromycin use with cardiovascular mortality. JAMA Netw Open. 2020;3(6):e208199. doi:10.1001/jamanetworkopen.2020.8199 8. Garin N. β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia: A Randomized Noninferiority Trial. *JAMA Intern Med*. 2014;174(12):1894–1901. doi:10.1001/jamainternmed.2014.4887