S.N.A.P.

RCT: Postma DF, et al. "Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults." The New England Journal of Medicine. 2015. 372(14):1312-23.

Take-Home Message:
In suspected community acquired pneumonia not requiring treatment in the ICU, empiric treatment with beta-lactam monotherapy was not inferior to beta-lactam plus macrolide or fluoroquinolone monotherapy for 90 day mortality.

Executive Summary:
Published in April 2015, Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults was a cluster-randomized, non-inferiority trial designed to test whether beta-lactam monotherapy could be used as empiric treatment for community acquired pneumonia. The study randomized 7 large medical centers in the Netherlands to 3 different empiric antibiotic regimens for patients admitted to non-ICU wards with community-acquired pneumonia: beta-lactam monotherapy, beta-lactam plus a macrolide, or respiratory fluoroquinolone monotherapy. Each medical center rotated through the three antibiotic regimens in a randomly-assigned order, and physicians at each center preferentially treated with the assigned empiric antibiotic regimen unless medical reasoning led them to choose an alternate therapy. Each hospital completed the antibiotic rotation twice with each antibiotic strategy being used for 4 months at a time. The primary outcome of 90 day mortality was 9.0% in the beta-lactam monotherapy group, 11.1% in the beta-lactam plus macrolide group, and 8.8% in the respiratory fluoroquinolone group; therefore, beta-lactam monotherapy demonstrated an absolute risk reduction of 2.1% vs beta-lactam plus macrolide and an absolute risk increase of 0.2% vs respiratory fluoroquinolones. 90% confidence intervals did not cross the pre-selected 3% non-inferiority standard, suggesting that beta-lactam monotherapy is non-inferior to current guideline therapies. Secondary outcomes, including time to transition to oral antibiotics, length of hospital stay, and occurrence of minor or major complications during hospitalization were not significantly different between any of the groups (with the exception of the fluoroquinolone group whose time to starting oral treatment was 1 day shorter, which did attain statistical significance). The results were not affected by controlling for the severity of pneumonia or patient comorbidities, suggesting non-inferiority of beta-lactams even in populations with a greater burden of comorbidities and with more severe infections.

This trial was unique in that it was a pragmatic study, so rather than testing particular antibiotics head-to-head, it designated a favored strategy for empiric antibiotic therapy while still allowing the clinician to deviate based on medical reasoning (most often for antibiotic allergies, concern over previous antibiotic failure, or suspicion for atypical infection) and analysis was done as intention-to-treat. This allowed for lower patient exclusion, improving generalizability, reducing indication bias, and more closely matching real-world practice. However, it has been criticized for the amount of treatment crossover between groups as a result of the allowance of deviation for "medical reasoning" (for example, 27% of patients in the beta-lactam monotherapy group actually received initial atypical coverage). Crossover increases the similarity between the groups and weakens the non-inferiority conclusion. Still, total atypical antibiotic use was still reduced by nearly 70% during the beta-lactam monotherapy strategy period. Others have criticized the study's selected non-inferiority margin of 3%, which is arbitrarily selected by the study authors and the use of 90% rather than 95% confidence intervals, as the 95% CI fails to demonstrate non-inferiority to fluoroquinolones when employed. It should also be noted that this study had low rates of documented atypical pathogens and beta-lactam resistant pathogens, so these results may not be generalizable in areas with significant beta-lactam resistance or with high levels of atypical pneumonia.

Guidelines
Current IDSA/ATS consensus guidelines for community-acquired pneumonia in patients admitted to the hospital but not requiring ICU level care recommend:

- A respiratory fluoroquinolone (strong recommendation, level I evidence) *or*

- A beta-lactam **plus** a macrolide (strong recommendation, level I evidence) or doxycycline as a macrolide alternative (level III evidence)

They suggest monotherapy with a macrolide can be used in carefully selected patients who have non-severe disease and are at low risk for drug-resistant pathogens. They do not comment on beta-lactam monotherapy.

Practice changer?

This study, while imperfect, is fairly convincing that beta-lactams can successfully be used to treat community-acquired pneumonia in non-critical hospitalized patients without placing them at increased risk of mortality, complications, or extended duration of IV or oral antibiotic treatment. Given the potential benefits of restricting atypical antibiotic coverage (namely reducing adverse drug events and improving antibiotic stewardship), this study improves my confidence to treat patients who reside in communities without a high prevalence of beta-lactam resistance and in whom I have a low clinical suspicion for atypical infection with beta-lactam monotherapy.

The following will be included as a linked attachment in the weekly announcements:

Design (this is a bulleted-list summary of your trial's design)

- Study design: Multicenter, cluster-randomized, crossover non-inferiority trial
- Patients: N= 2,283
    - Intervention: Beta-lactam monotherapy (n=656)
    - Control: Beta-lactam-macrolide (n=739) or fluoroquinolone monotherapy (n=888)
- Setting: 7 hospitals in the Netherlands
- Enrollment: February 2011 to August 2013
- Analysis: intention-to-treat
- Mean follow-up: 90 days

- **Population**
- **Inclusion Criteria**
    - 18 years old or older
    - Clinically suspected CAP (based on symptoms or imaging) requiring hospitalization in a non-ICU ward

- **Exclusion Criteria**
    - Patients with cystic fibrosis
    - One hospital excluded patients with a CURB-65 score of 2 or less

- **Baseline Characteristics**
    - Mean age: 70 years
    - Mean PSI score: 85
    - Median CURB-65 score: 1
    - Radiology confirmed CAP: 76%

Interventions

- Each hospital was randomly assigned a sequence for administration of three empiric antibiotic strategies (beta-lactam monotherapy, beta-lactam + macrolide, and fluoroquinolone monotherapy). Each strategy was given to patients as the preferred empiric treatment patients admitted to the non-ICU ward with CAP for two designated 4 month periods during the two year study. An alternate antibiotic could be used at the provider's discretion if the assigned regimen was medically contraindicated (i.e. antibiotic intolerance) or

medical reason dictated use of alternate therapy (i.e. suspicion for or knowledge of organism with susceptibilities requiring use of an alternate antibiotic).

- Patients were followed for 90 days

Outcomes: Comparisons are beta-lactam monotherapy (BL) vs beta-lactam-macrolide (BLM) therapy and beta-lactam monotherapy (BL) vs fluoroquinolone monotherapy (FQL)

- **Primary Outcomes**
    - All-cause 90 day mortality
        - Intention-to-treat analysis, crude numbers
            - BL vs BLM: 9.0% vs 11.1% (ARR 2.1%; 90% CI -0.2 to 5.0)
            - BL vs FQL: 9.0% vs 8.8% (ARI 0.2%; 90% CI -2.5 to 2.4)
            - BL non-inferior to BLM and FQL based on 3% acceptable risk difference
        - Intention-to-treat analysis, adjusted for Pneumonia Severity Index (PSI) and comorbidities
            - BL vs BLM: ARR 1.9%; 90% CI -0.6 to 4.4
            - BL vs FQL: ARI 0.6%; 90% CI -2.8 to 1.9
            - BL non-inferior to BLM and FQL based on 3% acceptable risk difference
        - Antibiotic-adherent analysis, crude
            - BL vs BLM: ARR 1.3%; 90% CI -1.3 to 4.8
            - BL vs FQL: ARI 1.7%; 90% CI -4.1 to 1.1
            - BL non-inferior to BLM but inferior to FQL crossing 3% acceptable risk difference, based on lower bound of the 90% CI which is -4.1%
        - Antibiotic-adherent analysis, adjusted
            - BL vs BLM: ARR 2.1%; 90% CI -0.5 to 5.0
            - BL vs FQL: ARI 0.4%; 90% CI -2.7 to 2.2
            - BL non-inferior to BLM and FQL based on 3% acceptable risk ratio
- **Secondary Outcomes**
    - Time to starting oral treatment
        - Intention to treat, crude
            - BL vs BLM: median 4 days for both; rate ratio 0.95 (95% CI 0.84-1.08)
            - BL vs FQL: median 4 vs 3 days; rate ratio 1.28 (95% CI 1.13-1.44)
            - Similar in intention-to-treat and antibiotic-adherent; similar crude and adjusted
            - Bottom line: no significant difference with BLM; slightly longer in BL vs FQL
    - Length of hospital stay
        - Intention to treat, crude – rate ratio difference (95% CI)
            - BL vs BLM: median 6 days for both; rate ratio 0.86 (95% CI 0.77-0.96)
            - BL vs FQL: median 6 days for both; rate ratio 1.03 (95% CI 0.93-1.15)
            - Similar in intention-to-treat and antibiotic-adherent; similar crude and adjusted
            - Bottom line: no significant difference between any of the groups
    - Occurrence of minor or major complications during the hospital stay
        - BL vs BLM: OR 1.06 (95% CI 0.76-1.48)
        - BL vs FQL: OR 1.02 (95% CI 0.73-1.41)
        - Bottom line: No significant difference between any of the groups

- **Adverse Events –** minor and major complications assessed as a secondary outcome. No significant differences were noted.

- **Subgroup Analysis**
    - The authors conducted a separate sensitivity analysis of 30 day mortality on patient's with radiologically-proven CAP with similar effect estimates.

Criticisms

- The treatment many patients received was different from the group to which they were randomized, including 38.7% in the beta-lactam monotherapy group who did receive atypical coverage during their stay because it was added for "medical reasons." Some have asked that the authors report results on patients who completed the beta-lactam monotherapy to those who did not, but the authors argue that this would result in confounding by indication. Furthermore, the authors argue that this is a more realistic approach to antibiotic administration where the intent is to adhere to a guideline but clinical judgement can be used to treat differently if felt necessary.
- The study uses 90% confidence intervals to declare non-inferiority; when extended to 95% confidence intervals, the line of non-inferiority is crossed with comparison to fluoroquinolones (though not with beta-lactam-macrolides).
- Some criticize that the selected non-inferiority margin of 3% was too large when the expected mortality from CAP over 90 days is 5%.
- Blinding was not possible in this study, though this was not felt to be significant given that death was the objective primary outcome.
- The study demonstrated low rates of beta-lactam resistance and the prevalence of atypical pathogens was low, which may limit the generalizability and applicability of the study.

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