

**Rory Stuart**

### **Block 3 CAT**

**Reference:** Garin N, Genné D, Carballo S, et al.  $\beta$ -Lactam Monotherapy vs  $\beta$ -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.

**Question:** Is  $\beta$ -lactam monotherapy noninferior to  $\beta$ -lactam and macrolide combination therapy in moderately severe community-acquired pneumonia?

**Introduction:** Community acquired pneumonia (CAP) represents a significant cause of morbidity and mortality in both inpatient and outpatient settings. Treatment regimens, in the United States, are tailored to cover both “typical” and “atypical” organisms. *Streptococcus pneumoniae* is the most common bacterial pathogen in most settings and is adequately covered with a  $\beta$ -lactam class antibiotic. Atypical organisms, however, represent a significant portion of CAP pathogens and necessitate the addition of a macrolide antibiotic for adequate coverage. The data behind these tenants of treatment is not straightforward which has resulted in conflicting clinical guidelines.  $\beta$ -lactam and macrolide combination therapy is the standard in the US, while European guideline recommend combination therapy only in more severely ill patients. The addition of a macrolide is not without additional risk; there are known adverse cardiovascular side effects, as well as the ever present risk of increased antibiotic resistance. On the other hand failing to adequately cover atypical organisms could lead to increased morbidity and mortality.

**Methods:** This was an open-label, noninferiority, randomized trial that took place at 6 acute care hospitals in Switzerland from January 2009 through Jan 2013. All patients 18 years or older with presence of at least 2 clinical findings suggestive of pneumonia, and a new infiltrate on CXR, who required hospital admission were consecutively enrolled. Patients were randomized to initial treatment with a  $\beta$ -lactam alone or combination therapy with a  $\beta$ -lactam and a macrolide. Cefuroxime or amoxicillin and clavulanic acid were the  $\beta$ -lactam used while clarithromycin was the lone macrolide. Urine screening for legionella was performed to ensure atypical coverage was appropriately added if indicated for this specific pathogen. The primary outcome was the proportion of patients who failed to reach “clinical stability” a day 7. Clinical stability was defined using a set of clinical variables that included heart rate, respiratory rate, temperature, systolic BP and oxygen saturation on room air.

**Results:** A total of 580 patients (291 in monotherapy arm & 289 in combination arm) were enrolled. After 7 days of treatment, 120 patients (41.2%) in the monotherapy arm had not reached clinical stability as compared to 97 (33.6%) in the combination arm. These numbers failed to achieve the studies predefined boundary and noninferiority could not be demonstrated.

**Discussion:** This study failed to demonstrate that when treating CAP  $\beta$ -lactam monotherapy is noninferior to  $\beta$ -lactam and macrolide combination therapy. Furthermore some the adverse drug effects of the macrolide antibiotics, namely adverse cardiac events, were not observed in their study population. The larger and arguably more globally relevant question of antibiotic resistance was mentioned but was beyond the scope of this particular investigation. One obvious clinical limitation of this study was the need to screen all patients for legionella – a practice that is largely negated in the US due to routine combination therapy. While urine screening did ultimately identify those patients with legionella, initial appropriate antibiotic therapy was delayed. Unfortunately cohort analysis was not performed on this patient set and data describing clinically

significant outcomes based on treatment delay was not available. While responsible antibiotic stewardship will continue to be an increasingly relevant clinical consideration this study certainly will not change practice guidelines, at least not here in the United States.

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