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Is macrolide and beta-lactam combination therapy associated with early clinical stability or 30 day mortality in hospitalized patients with pneumonia? An assessment of confounding by indication.

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IS MACROLIDE AND BETA-LACTAM COMBINATION THERAPY ASSOCIATED WITH EARLY CLINICAL STABILITY OR 30 DAY MORTALITY IN HOSPITALIZED PATIENTS WITH PNEUMONIA? AN ASSESSMENT OF CONFOUNDING BY INDICATION

By

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ABSTRACT

IS MACROLIDE AND BETA-LACTAM COMBINATION THERAPY ASSOCIATED WITH IMPROVEMENT IN HOSPITALIZED PATIENTS WITH PNEUMONIA? AN ASSESSMENT OF CONFOUNDING BY INDICATION

Evangeline Pierce

October 31, 2018

Pneumonia and influenza are one of the leading causes of infectious disease-related deaths worldwide. Current guidelines for the treatment of hospitalized patients with community acquired pneumonia (CAP) include empiric antimicrobial therapy with a macrolide and a beta-lactam. There is little consensus among studies as to which antimicrobial regimen is best. The confusing results seen may very well be due to lack of assessment of confounding by indication (CBI). This analysis was a secondary analysis from Hospitalized Adults with Pneumococcal Pneumonia: Incidence Study (HAPPI). The study participants were those in HAPPI who had received either macrolide and beta-lactam combination therapy or fluoroquinolone mono-therapy within the first 24 hours (n= 3141). The outcomes studied were early clinical stability (ECS) and 30 day mortality. No statistically significant association was found between macrolide and beta-lactam use and ECS using any of the methods used for addressing confounding by indication, logistic regression, propensity score

matching, or instrumental variable analysis (Odds Ratio (OR): 0.908, 95% Confidence Interval (CI): 0.780, 1.059; OR: 0.916, 95% CI:0.775, 1.083; OR: 1.551, 95% CI: 0.777, 3.091, respectively). The two methods addressing measured confounding (logistic regression and propensity score matching) had similar OR's while the method addressing unmeasured confounding (instrumental variable analysis) had a contradictory OR, even though the results were all non significant. No statistically significant association was found between macrolide and beta-lactam use and 30 day mortality using logistic regression, propensity score matching, or instrumental variable analysis (OR: 0.926, 95% CI: 0.692, 1.241; OR: 0.885, 95% CI: 0.748, 1.048; OR: 0.958, 95% CI: 0.603, 1.523, respectively). All three methods looking at combination therapy and 30 day mortality were in agreement. When addressing confounding and CBI more than one method for analysis should be used.

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LITERATURE REVIEW

1.1.1 Introduction

The purpose of this dissertation is to determine the efficacy of macrolide and beta-lactam combination therapy versus fluoroquinolone mono-therapy in the treatment of community acquired pneumonia (CAP) through the assessment of early clinical stability (ECS) and 30 day mortality through the comparison of three different statistical approaches to controlling for confounding by indication. Data was extracted from the Hospitalized Adults with Pneumococcal Pneumonia: Incidence Study (HAPPI). Currently, there is a lack of consensus among epidemiological studies as to which antimicrobial regiment is best, due to variation in the variables included and lack of using more than one statistical method to address confounders and thus confounding by indication. There are two specific aims for this dissertation. The first is to evaluate three years of study data and determine whether macrolide and beta-lactam combination therapy usage is appropriate for gold standard treatment in hospitalized community acquired pneumonia though assessment of ECS and 30 day mortality. The second aim is to assess and compare various methods addressing CBI (multivariable logistic regression, propensity score stratification and matching,

instrumental variable analysis) through the assessment of macrolide and beta-lactam combination therapy and its effect on ECS and 30 day mortality in hospitalized patients with community acquired pneumonia.

1.1.2 Community Acquired Pneumonia

Together, pneumonia and influenza are leading causes of infectious disease related deaths worldwide and the eighth leading cause of death in the United States (1, 2). The setting in which pneumonia develops is important as it determines the type of pneumonia: CAP, healthcare associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP) (3, 4). CAP is characterized by acute symptoms such as dyspnea, cough, fever, or chest pain, and is diagnosed by the presence of pulmonary infiltrate seen on radiography. It is distinguished from HAP in that the patient is exposed to causative pathogens in the community and not a hospital setting.

CAP is a common infectious disease with an estimated incidence of 2–11 cases per 1000 adults in the developed world and a mortality rate of 2%–14% (5). It is approximated that, in the US, more than 1.5 million adults infected with CAP are hospitalized annually, with 100,000 deaths occurring during hospitalization (6, 7). Not only are the economic and clinical burdens of CAP high, but there are also long term effects on quality of life that need to be considered when looking at the overall effect of CAP (8).

The risk of CAP increases with age: however those in early childhood are also at increased risk (9, 10). It is estimated that 1 of every 20 persons aged 85 years or greater will have a new episode of CAP each year (10). Those with increased age often have at least one other medical condition which can complicate CAP (11). Elderly patients categorized as frail (i.e. those who need help with daily activities, who have severe multimorbiditiy, polypharmacy, and possible dementia) are at a much higher risk of CAP than those who have who are not frail (11, 12). However, even without comorbidities, age is an independent risk factor for CAP due to the decreased ability of the immune system to protect against pathogens, decreased ability to have a productive cough, and decreased swallowing reflex (13). CAP patients over 65 years of age account for about one third of all cases, but they are also responsible for more than half of all healthcare expenses (14). As the population of the US is aging, the burden of CAP can only be expected to increase (15).

Many diseases and existing health conditions that can also cause greater exposure or greater risk of exposure of heightened severity of CAP-causative pathogens. Chronic lung diseases (i.e. cystic fibrosis, chronic obstructive pulmonary disease (COPD), and lung cancer) that inhibit airflow can lead to increased risk (16). Patients with Diabetes Mellitus, human immunodeficiency virus (HIV), and those on immunosuppressants have increased risk of CAP due to a compromised immune system (17, 18). Patients taking gastric acid suppressants (medication that decreases the production of acid in the stomach), those who smoke, and those who drink alcohol are at an increased risk for CAP

(16, 19). A recent study also found that clusters of patients with CAP were found in areas with low-income and black populations (7). Unlike many respiratory diseases, CAP does not have seasonality (20).

1.1.3 Community Acquired Pneumonia: Etiology

CAP most common results from bacterial pathogens. However viruses, fungi, and parasites are also known to cause CAP (21). Many causative CAP pathogens are associated with specific risk factors. Risk factors for gram-negative bacilli include previous antibiotic therapy, recent hospitalization, immunosuppression, pulmonary comorbidity (e.g., cystic fibrosis, bronchiectasis, or repeated exacerbations of chronic obstructive pulmonary disease that require frequent glucocorticoid and/or antibiotic use), probable aspiration, and multiple medical comorbidities (eg, diabetes mellitus, alcoholism) (3, 22-24). Risk factors associated with drug-resistant microbes include age over 65 years, beta-lactam, macrolide, or fluoroquinolone therapy within the past three to six months, alcoholism, medical comorbidities, immunosuppressive illness or therapy, exposure to a child in a daycare center, prior hospitalization, or residence in a long-term care facility (25).

Unfortunately the actual incidence is difficult to determine due to contamination of samples with colonizing bacteria. *S. pneumoniae* has been found in up to 15 percent of bacterial CAP cases, but the incidence of CAP due to *S. pneumoniae* has been decreasing due to the use of pneumococcal

vaccines in adults, as well as the decreasing prevalence of smoking (26, 27). *S. pneumoniae* is the leading cause of pneumonia in the elderly population (28). Other common bacteria known to cause CAP in adults are *H. influenzae* often occurring in adults with underlying lung disease, *M. pneumoniae* the most common CAP causing atypical bacteria, *C. pneumoniae* which is common in outbreaks, *Legionella* which can occur sporadically or in outbreaks, and *Klebsiella pneumoniae* which is common in those that have severe underlying diseases such as alcoholism or diabetes (29-33).

The bacterial organisms are often split into two groups, typical and atypical. Bacteria causing typical pneumonia include *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, group A streptococci, *Moraxella catarrhalis*, anaerobes, and aerobic gram-negative bacteria . Atypical bacteria leading to atypical pneumonia include *Legionella* spp, *M. pneumoniae*, *C. pneumoniae*, and *Chlamydia psittaci*.

The incidence of viral CAP depends on the diagnostic method used to determine cause (34). The most common and significant virus is Influenza. Infection with Influenza A or B can not only cause CAP, but it can also predispose a patient to a superimposed bacterial infection which is causative for CAP (35). Parainfluenza and respiratory syncytial virus (RSV) are seen more often in immunocompromised adults; however, RSV can cause respiratory tract illnesses in all age groups (36-38). Other viruses that have been found in patients with CAP are rhinovirus, coronavirus, and human metapneumovirus. However, it is

possible these viruses are not causative for CAP but simply predispose a person to a bacterial co-infection (35).

Fungi are not a common cause of CAP, but they can cause CAP in both immunocompetent and immunocompromised patients who live in or have visited specific endemic areas. Coccidioides fungi are endemic to desert areas including southern Arizona, central California, southwestern New Mexico, and west Texas, and they have been found to cause CAP in patients from this area (39, 40). H. capsulatum is most common in the Midwestern United States located in the Ohio and Mississippi River Valleys; however the development of symptomatic disease depends on the level of exposure (41, 42).

Determining the pathogenicity of CAP often depends on the severity of CAP and the location of treatment, whether in the outpatient or inpatient setting (3, 43). Many cases of CAP are never tested for a pathogen or have no pathogen identified (30, 43). Traditionally, physicians consider lobar consolidation to be due to the "typical" bacteria and interstitial infiltrates to be a result of *Pneumocystis jirovecii* (formerly *P. carinii*) and viruses. Nevertheless, it has been shown that radiologists cannot reliably differentiate bacterial from nonbacterial pneumonia on the basis of a radiographic image (44, 45). Recently a review of Medicare patients hospitalized for CAP in 2009 showed a microbial diagnosis was made in less than 10% of cases (46). Blood cultures, sputum Gram stain and cultures, and urine antigen tests are recommended in hospitalized patients to determine the microbial diagnosis (3, 47).

Blood cultures are positive for a pathogen in only 7 to 16 percent of hospitalized patients with *S. pneumoniae* accounting for two-thirds of the positive results (48, 49). There is a high rate of false positives with blood cultures (10%) and in clinical practice a positive culture rarely leads to changes in antibiotic therapy (48, 50).

Expectorated sputum can be used for testing via a Gram stain and culture, though expectorated sputum can lead to contamination with upper airway flora. Therefore other methods can be used such as transtracheal aspiration, transthoracic aspiration, and the collection of specimens at bronchoscopy (46). The sensitivity and specificity of the sputum Gram stain can vary in different settings, with a meta analysis showing sensitivity of Gram stain compared with culture ranging from 15 to 100 percent and specificity ranging from 11 to 100 percent (51). This variation is most likely from using different thresholds for a positive test. Guidelines recommend that expectorated sputum Gram stain and culture be done only if a good-quality sputum can be obtained (3).

Urinary antigen assays are typically used to detect *S. pneumoniae* and *Legionella*. In a prospective study, the sensitivity of the pneumococcal urinary antigen was 71 percent and the specificity was 96 percent. Interestingly the results of the urinary antigen test led the clinicians in the study to reduce the spectrum of antibiotics in nine percent of patients with CAP (52). It is recommended that the pneumococcal urinary antigen assay be used to augment the standard diagnostic methods of blood culture and sputum Gram stain and culture (53). A new test that has been approved by the US Food and Drug

Administration (FDA) is a polymerase chain reaction (PCR) for detecting *C. pneumoniae*, *M. pneumoniae*, and 14 respiratory tract viruses, and these tests are rapid, sensitive, and specific (54).

1.1.4 Community Acquired Pneumonia: Severity

CAP can be treated inpatient or outpatient. Severity of illness is the strongest factor in the determination of location of treatment, but other factors may taken into account, such as ability to maintain oral intake of fluids and medications, likelihood of medication adherence, history of active substance abuse, mental illness, cognitive or functional impairment, and living or social circumstances (55).

The severity of CAP is oftentimes determined through the Pneumonia Severity Index (PSI) (56). This score is used to predict the need for hospitalization for a patient. PSI ranges from I to V, with a higher score indicating much more severe CAP. The score includes demographic information, comorbidities, initial physical exam results, lab results, and radiographical results (56). PSI scores have low sensitivity and specificity for intensive care unit (ICU) admission, and they do not account for other variables affecting severity such as psychosocial variables, non-common comorbidities, or patient preferences regarding treatment (11).

Another method to determine CAP severity is through CURB-65 scoring (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and

older) (57). CURB-65 scores, ranging from 0 to 5 with the severity of CAP increasing with the score, are easier than the PSI to calculate and interpret as CURB-65 includes only five variables compared to the possible 20 in the PSI. The CRB-65 score provides a four-variable substitute for use where blood testing is not available. The CURB-65 scores do not include data such as hypoxemia, electrolyte disturbance or the inability to take oral medications which could indicate greater severity of CAP (11).

Guidelines are not consistent in the recommendation of which score to use for the determination of severity. The American Academy of Family Physicians (AAFP) guidelines recommend outpatient treatment for PSI risk classes I and II and hospitalization for those in risk classes IV and V. The location of treatment for class III is left to clinical judgement (55, 58). The Infectious Diseases Society of America (IDSA) guideline recommends that physicians consider outpatient treatment for patients in PSI risk classes I, II and III, and hospitalization for those in classes IV and V (3). The British Thoracic Society (BTS) recommends that physicians use the CURB-65 or the CRB-65 when deciding on hospitalization or outpatient treatment, with scores 0-1 being recommended for outpatient treatment and 2-5 recommended for hospitalization. (59). The American Thoracic Society (ATS) guidelines recommend that clinicians use clinical decision scores like the PSI or CURB-65 to support clinical judgment, but the do not define a recommended cutoff for hospital admission (60). Most importantly all of the guidelines recommend that clinicians use PSI and CURB-65 scoring tools to support, not replace, clinical judgment.

1.1.5.1 Community Acquired Pneumonia: Treatment

Treatment recommendations depend on the type of care a patient requires. Once a patient meets the symptom requirements of CAP the necessary level of care is decided. More severe cases will lead to an inpatient setting, which occurs on medical wards or the ICU. Effective empirical treatment involves the selection of an antimicrobial agent with a spectrum of activity that includes the causative pathogen. Often, the causative organism takes a while to be confirmed or is unable to be determined. Therefore empiric antimicrobial therapy is encouraged to begin as soon as possible beginning with a broad-spectrum antimicrobial agent before de-escalating to narrow-spectrum agents dependent on the identification of a pathogen (3, 59, 61-63). It is recommend that antimicrobials be administered as soon as possible after diagnosis of CAP and before leaving the emergency department, especially in those over 65 years of age (3, 64, 65). Patients with sepsis or septic shock should have antibiotics started within one hour.

1.1.5.2 Community Acquired Pneumonia Treatment: Macrolides

Macrolide antimicrobials are used to treat gram-positive bacteria, such as *S. pneumoniae*, and some gram-negative bacteria like *H. influenzae*. Macrolides inhibit protein synthesis in bacteria by binding to the 50S ribosomal subunit and preventing polypeptide elongation and thus protein synthesis (66, 67).

Macrolides also appear to decrease the production of pro-inflammatory cytokines, thereby decreasing inflammation in patients (68, 69). A study assessed the affects of macrolides on the human immune system, ex vivo, using healthy volunteers (70). It was found that there was a neutrophil degranulating effect of azithromycin (a type of macrolide), which was seen in rapid decreases in azurophilic granule enzyme activity in the cells, with corresponding increases in the serum. The oxidative burst response to a particulate stimulus was also enhanced. Both of these inflammatory responses occurred when serum and neutrophil azithromycin concentrations were higher, peaking at the 24-hour mark and then gradually decreasing over the next 27 days. In addition, decreases in chemokines (IL-8 and human growth related oncogene-a) and IL-6 serum concentrations accompanied a down-regulation of the oxidative burst and an increase in neutrophil apoptosis for up to 28 days after. The fact that these anti-inflammatory effects begin to occur so quickly after the start of a treatment regimen could, in theory, correlate with the improved outcomes noted in some CAP patients (69). It has also been suggested that macrolides can assist in the stabilization of the epithelial membrane which contributes to decreased an inflammation (67).

1.1.5.3 Community Acquired Pneumonia Treatment: Beta-Lactam and Macrolides

Beta-lactams are antimicrobials that are effective against gram-positive bacteria and some gram-negative bacteria. They act by inhibiting the synthesis of bacterial walls (71).

In hospitalized patients with CAP empiric therapy with both a macrolide and a beta-lactam is the preferred treatment according to the IDSA (3). Although the mechanism of action is not well understood, it has been suggested that the combination of a macrolide and a beta-lactam can lead to improved clinical outcomes, including lower mortality (72, 73).

1.1.5.5 Community Acquired Pneumonia Treatment: Fluoroquinolone

Fluoroquinolones are direct inhibitors of bacterial DNA synthesis and bind to the complex of specific enzymes within DNA, thus inhibiting progress of the DNA replication, leading to bacterial DNA and cell death (74). Fluoroquinolones work best against aerobic gram-negative bacilli (75). They are contraindicated if a patient has significant QT prolongation, pre-existing CNS lesions or CNS inflammation, or has suffered a stroke (76). Because of the severity of adverse effects and the increased risk for *C. difficile* infection, combination therapy with a beta-lactam plus a macrolide is recommended over mono-therapy with a fluoroquinolone (3, 77). However, fluoroquinolones are an option for treating atypical bacterial pneumonia (3).

1.1.5.6 Community Acquired Pneumonia Treatment: Other Treatments

Antiviral therapy for non-influenza pneumonia has typically been evaluated in immunosuppressed patients and infants. There has been minimal research looking at the use of antivirals for other populations (78-82). Fungal CAP is typically treated with an antifungal like Amphotericin B (or its derivatives) and itraconazole (83).

1.1.5.7 Community Acquired Pneumonia Treatment: Recommendations

The current recommended first line antimicrobial treatment includes a macrolide plus a beta-lactam (3). Respiratory fluoroquinolones are used in patients who cannot take a macrolide or a beta-lactam (84). Strains of drug resistant *S. pneumoniae* bring the current recommendations into question (85).

Even though the guidelines are widely accepted, there is disagreement on the utility of macrolides in the treatment of CAP. The majority of the studies used by the IDSA and the ATS were retrospective cohort studies (3). However, other retrospective studies and some randomized control trials have given evidence to question the benefits of macrolide as they suggest the use of beta-lactam mono-therapy for patients hospitalized with mild CAP (86-93).

1.1.6 Community Acquired Pneumonia: Clinical Outcomes

One way to measure how a patient with CAP is improving in the hospital is to assess clinical stability. In a recent Federal Drug Administration (FDA) paper, emphasis was placed on symptom resolution as objective evidence of clinical improvement in patients with CAP (94). The FDA has also advocated for clinical stability to be an important endpoint in clinical trials comparing different treatment regimens (95). It has been found that the rate of mortality or readmission among patients who had CAP was about 10% when a patient satisfied all conditions of clinical stability (96).

The ATS has a defined set of criteria and guidelines as to what qualifies as clinically stable (97). These criteria include improved symptoms of pneumonia (cough and shortness of breath), lack of fever for at least eight hours, and improving leukocytosis (white blood count decreased at least 10% from the previous day). All of the ATS criteria should be present during the same day compared to the previous day to define clinical stability. The IDSA has another set of criteria for clinical stability (97). The criteria is listed as follows: temperature </= 37.8 C, heart rate </= 100 beats per minute, respiratory rate </= 24 breaths per minute, systolic blood pressure >/= 90 mmHg, arterial oxygen saturation >/= 90% or a partial pressure of oxygen >/= 60 mmHg on room air, and normal mental status. The IDSA criteria should all be present on the same day to qualify as clinically stable. Although the two set of criteria vary, it has been shown that they are clinically equivalent and either can be used for research or clinical practice (97).

ECS occurs when the criteria are met on or before the third day of hospitalization (98). ECS at day three was traditionally based on older studies suggesting that clinical differences in patients treated with antibiotics are apparent earlier than day three of antibiotic treatment. This same time frame is also relevant because the results of the many pathogen tests are usually available within three days (98-100).

Other outcomes typically studied with respect to CAP include in-hospital mortality, 30-day mortality, long-term mortality, and readmission for CAP (3, 56, 101-105). Readmission to the hospital after discharge is typically used as an indicator of vulnerability (106).

1.2.1 Community Acquired Pneumonia and Confounding by Indication

The pathogens and management of CAP have been well studied and many of these studies have assessed antibiotic use for patients with CAP. However these results can be brought into question when assessing for confounding by indication (CBI) (87, 89, 107-115).

Confounding is present when a variable influences both the independent variable (e.g. an antibiotic treatment) and the dependent variable (e.g. a clinical outcome) (116). Confounding by indication (CBI) is a type of confounding that occurs when a treatment (the primary predictor variable) is selected due to a specific characteristic (e.g. history of a particular disease, provider medication preference) and this characteristic also affects the risk of the outcome variable

(117, 118). Not correctly addressing confounding can lead to biased and inaccurate statistical results (117, 119).

1.2.3 Meta Analyses Assessing Antibiotic Usage in Community Acquired Pneumonia

Meta-analyses have been performed to assess the effect of macrolide therapy (both combination and mono therapy) on mortality associated with CAP, Table 1 (88, 120).

Asadi et al, 2012, assessed macrolide based regimens (macrolide mono-therapy, macrolide + beta lactam combination therapy, and fluoroquinolone therapy) and mortality in hospitalized patients with CAP (88). They included both randomized control trials and observational studies in their analysis, for a total of 23 studies, 18 observational cohorts and 5 randomized control trials. They found macrolide use was associated with a statistically significant lower risk of mortality compared with non-macrolide use (RR, 0.78; 95% CI, 0.64–0.95; P = .01). There was a significant amount of heterogeneity among the studies (I^2 = 85%) that was not explained, though it could have been due to confounding by indication that was not addressed equally across studies (i.e. it was noted that confounders were not consistent throughout studies). Heterogeneity could have also resulted from study design differences (e.g. low sample size, differences in inclusion or exclusion criteria, etc.). This seems to be supported when one looks at the effects of macrolide usage on mortality in only the randomized control trials

(comparing macrolide-based regimens and fluoroquinolone treatment, RR, 1.13; 95% CI, 0.65–1.98; P = .66), where the heterogeneity was low (I^2 = 0%). The analysis also found that there was no significant difference of mortality comparing macrolide and beta-lactam combinations and fluoroquinolone use (RR, 1.17; 95% CI, 0.91–1.50; P = .22; I^2 = 43%). They concluded that treatment with a macrolide regiment has a reduction in mortality compared to non-macrolide treatments. However, no difference in mortality between macrolide and beta-lactam combination therapy and fluoroquinolone mono-therapy (both guideline concordant treatments) was seen.

Vardakas et al, 2017, assessed mono-therapy (macrolides, beta-lactams, and fluoroquinolones) and combination therapy (macrolide + beta-lactam, fluoroquinolone + beta-lactam) in community-acquired pneumonia (120). Mono-therapy regimens were not associated with higher mortality when compared with combination therapies (RR 1.14, 95% CI 0.99-1.32, I^2 84%). As seen with Asadi et al, 2012, heterogeneity was lower or non existent in analyses of randomized control trials.They propose that the percentage of patients with heart disease, cancer and severe pneumonia could partly account for the observed heterogeneity, but data for potential confounding factors were not consistently reported across studies. Interestingly, macrolide mono-therapy was associated with lower mortality than macrolide and beta-lactam combination therapy (0.68, 0.51-0.92, I^2 32%), even after removing the two largest studies (0.59, 0.35-1.00, I^2 34%). The authors note that the lower mortality seen with macrolide mono-therapy seems to contradict the increasing prevalence of resistance to macrolide

antibiotics, unless there is an assumption that confounding by indication is occurring, as seen in several of the included studies where macrolide mono-therapy was administered in younger patients and those at a lower risk for death. The authors conclude that this analysis of studies is not conclusive due to the heterogeneity and lack of adjustment for confounding factors.

Table 1. Macrolide and CAP Meta Analyses

Study	Studies Assessed	Therapies Assessed	Results
Asadi et al, 2012	23, included observational ans randomized control trials	Macrolide mono-therapy, macrolide + beta-lactam combination therapy, fluoroquinolone mono-therapy	Macrolide regiment has reduction in mortality compared to non-macrolide treatments. No difference in mortality between macrolide + beta-lactam combination therapy and fluoroquinolone mono-therapy
Vardakas et al, 2017	50, included observational and randomized control trials	Macrolide mono-therapy, beta-lactam mono-therapy, fluoroquinolone mono-therapy, macrolide + beta-lactam combination therapy, fluoroquinolone + beta-lactam combination therapy	Mono-therapy was not associated with higher mortality than combination therapy in North American and retrospective studies. No difference in mortality between fluoroquinolone mono-therapy and beta-lactam + macrolide combination

1.2.4 Randomized Control Trials Assessing Antibiotic Usage in Community Acquired Pneumonia

Randomized control trials are considered the gold standard when evaluating the efficacy of treatments in clinical research. The randomization inherent in this type of study means that when there are observed differences between the treatment types with respect to a particular outcome variable, these differences are due solely to the treatment and not to other variables (e.g. age,

sex, other medications) (121). Randomized control trials also have minimal bias and confounding variables (121). However, not only are randomized control trials expensive, but they are sometimes unethical. As many patients hospitalized with CAP are in critical condition, getting informed consent so the patient can participate in a trial is sometimes impossible (i.e. the medication must be administered immediately and patients are unable to consent).

Even with the complications that come with a randomized control trial, there have been trials assessing the effectiveness of the recommended macrolide and beta-lactam combination therapy against mono-therapy of non-macrolide regimens, Table 3.

Garin et al, 2014, assessed the guideline treatment of macrolide and beta-lactam combination therapy against beta-lactam mono-therapy in a randomized non-inferiority trial, which tests whether the treatment being evaluated is equally as effective as the standard treatment (90). This was an open-label, multicenter, non-inferiority, randomized trial in immunocompetent patients hospitalized with CAP in Switzerland. Patients were treated with a beta-lactam and a macrolide combination therapy or with beta-lactam mono-therapy. It was found after 7 days of treatment, 41.2% of patients receiving combination therapy had not reached clinical stability, compared to only 33.6% of patients receiving mono-therapy (P=0.07). Interestingly, those who were known to have atypical pathogens or had more severe pneumonia (PSI IV) were less likely to reach clinical stability at 7 days with the beta-lactam mono-therapy (HR, 0.99; 95% CI, 0.80-1.22). There were more 30-day readmissions with beta-lactam mono-therapy (7.9%, P = .01).

Additionally, there was no difference between combination therapy and mono-therapy with respect to mortality, intensive care unit admission, complications, length of stay, and recurrence of pneumonia within 90 days.

Postma et al, 2015, did a cluster-randomized, crossover trial assessing patient outcomes in patients in the Netherlands who received guideline concordant treatment, beta-lactam and macrolide combination therapy or fluoroquinolone mono-therapy, and beta-lactam mono-therapy (122). In the intention-to-treat analysis, the risk of death was higher by 1.9% (90% CI, -0.6 to 4.4) with the beta-lactam and macrolide combination therapy when compared to the beta-lactam mono-therapy. The risk of death was lower by 0.6% (90% CI, -2.8 to 1.9) with fluoroquinolone mono-therapy than with beta-lactam mono-therapy. The study concluded that in patients with clinically suspected CAP admitted to non-ICU wards, beta-lactam mono-therapy was non-inferior to beta-lactam and macrolide combination therapy or fluoroquinolone mono-therapy with regard to 90-day mortality.

Figueiredo-Mell et al, 2018 assessed the effects of beta-lactam mono-therapy versus beta-lactam and macrolide combination therapy in patients with HIV and CAP (123). Based in Brazil, patients were given either a beta-lactam and a placebo or a beta-lactam and a macrolide. There was no difference found for in-patient mortality or 14-day mortality between the two groups, Hazard Ratio (HR) 1.22, 95% CI 0.57-2.59 and RR 2.38, 95% CI 0.87-6.53, respectively.

The results of these randomized trials bring into question the current guideline recommendation of macrolide combination therapy (3).

Table 2. Randomized Control Trials and CAP Therapy

Study	Study Type	Therapies Assessed	Results
Garin et al, 2014	Randomized noninferiority trial	Beta-lactam mono-therapy, macrolide + beta-lactam combination therapy	Noninferiority of beta-lactam mono-therapy in patients hospitalized for moderately severe CAP was not found. Patients infected with atypical pathogens or with PSI category IV pneumonia had delayed clinical stability with mono-therapy.
Postma et al, 2015	Cluster-randomized, crossover trial	Beta-lactam mono-therapy, macrolide + beta-lactam combination therapy, fluoroquinolone mono-therapy	Paitents with clinically suspected CAP admitted to non-ICU wards, beta-lactam mono-therapy was noninferior to beta-lactam and macrolide combination therapy or fluoroquinolone mono-therapy with regard to 90-day mortality.
Figueiredo-Mell et al, 2018	Randomized control trial	Beta-lactam mono-therapy, macrolide + beta-lactam combination therapy	There was no difference in patient outcomes in hospitalized patients with HIV/AIDS with CAP, when comparing bera-lactam mono-therapy and macrolide plus beta-lactam combination therapy

1.2.5 Individual Studies Assessing Antibiotic Usage in Community Acquired Pneumonia

Table 2 is an overview of many of the studies that have assessed variations of antibiotic therapy and their effect on CAP (86, 87, 89, 109-114). These studies were selected based on study location (in the United States) and population age (non-pediatric). Some of these studies adjusted for CBI though multivariable logistic regression, but those studies did not have a consensus on the appropriate therapy for CAP (110, 112-114). Of note, logistic regression does

not entirely control for CBI as many times the effects of the variables used are often not truly independent of other individuals variables (124). Only one study used a secondary method to control for CBI through propensity score analysis. No difference in 30-day mortality in either beta-lactam and fluoroquinolone or beta-lactam and macrolide combination therapies was found (89). Note that there was no consensus between these studies regarding the effect of macrolide usage on CAP, and the lack of overall assessment or attention to CBI brings many of their conclusions into question.

Table 3. Macrolide Studies Assessing Confounding By Indication (CBI)

Study	Study Type	Antibiotic Assessed	CBI Addressed	Results
Bratzler et al, 2008	Retrospective Cohort	Macrolide and Cephalosporin, Quinolone	Yes, multivariable logistic regression	Cephalosporin and macrolide combination therapy was associated with decreased in hospital mortality (AOR, 0.6; 95% CI, 0.3–0.9; P p .018)
Frei et al, 2006	Retrospective Cohort	Fluoroquinolone, Beta-lactam and Macrolide	No	Fluoroquinolone therapy was associated with a significantly shorter time to switch therapy than combination therapy (P = 0.01).
Lodise et al , 2007	Retrospective Cohort	Fluoroquinolone, Beta-lactam and Macrolide	Yes, multivariable logistic regression	PSI class V patients had lower 14-day and 30-day mortality rates with beta-lactam and macrolide than with fluoroquinolone, (14-day [P = 0.02]; 30-day [P = 0.05]).
Wilson et al, 2012	Retrospective Cohort	Fluoroquinolone and Beta-lactam, Macrolide and Beta-lactam	Yes - multilevel regression models, propensity score analysis	No significant difference in 30-day mortality between those with a beta-lactam and a fluoroquinolone vs those with a beta-lactam and a macrolide.

Table 3 continued. Macrolide Studies Assessing Confounding By Indication (CBI)

Study	Study Type	Antibiotic Assessed	CBI Addressed	Results
Asadi et al , 2013	Retrospective Cohort	Fluoroquinolone, Macrolide and Beta-lactam	Yes - Multivariable logistic regression	Macrolide and a beta-lactam were associated with increased odds of death or ICU admission vs fluoroquinolone mono-therapy (17.4% vs. 14.4%; aOR, 1.58; 95% CI, 1.09-2.27; p 0.01).
Burgess et al, 2000	Retrospective Cohort	Macrolide and Cephalosporin, Cephalosporin	No	There were no statistical differences between patients who had cephalosporin mono-therapy or combination therapy in mortality (0.9% vs 3.1%, respectively; P = 0.333)
Gleason et al, 1999	Retrospective Cohort	Macrolides and 2nd generation Cephalosporins, Macrolides and 3nd generation Cephalosporins, Macrolides and Beta-lactams, Fluoroquinolones,	No	Treatment with a 2nd generation cephalosporin plus macrolide (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.52-0.96), a 3rd cephalosporin plus macrolide (HR, 0.74; 95% CI, 0.60-0.92), or fluoroquinolone mono-therapy (HR, 0.64; 95% CI, 0.43-0.94) was independently associated with lower 30-day mortality. Use of a beta-lactam plus macrolide (HR, 1.77; 95% CI, 1.28-2.46) were associated with an increased 30-day mortality
Houck et al, 2001	Retrospective Cohort	Macrolides, Fluoroquinolones, Beta-lactam, Macrolide and Beta-lactam	Yes - logistic regression models	In 1995 lower mortality was associated with macrolide mono-therapy (AOR, 0.24; 95% CI, 0.06 to 0.93). In 1997 lower mortality was associated with fluoroquinolone mono-therapy compared with beta-lactam mono-therapy(AOR, 0.27; 95% CI, 0.07 to 0.96).

Table 3 continued. Macrolide Studies Assessing Confounding By Indication (CBI)

Study	Study Type	Antibiotic Assessed	CBI Addressed	Results
Mufson et al, 2006	Retrospective Cohort	Macrolide and Cephalosporin, Macrolide and Beta-lactam, Beta-lactam	No	Compared with beta-lactam mono-therapy, combination macrolide plus additional antibiotic therapy effectively lowered the case-fatality rate among ill adults ⩾50 years of age.

1.3.1 Confounding By Indication

In an observational study, there is a predictor variable, which is the main variable of interest in the study, and an outcome variable, the endpoint of interest in a study. Confounding can appear to strengthen, weaken, or change the effect of a primary predictor variable and the outcome (Figure 1).

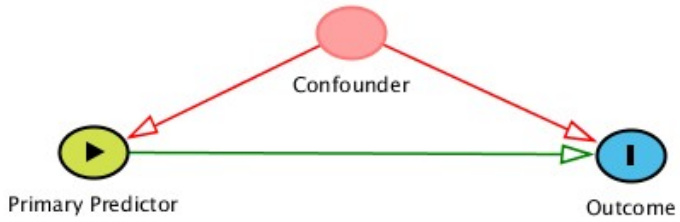

Figure 1. Diagram of Confounding

Three criteria must be met for a variable to be considered a confounder (125, 126). One, a confounder must be an independent risk factor for the outcome. Two, a confounder must be associated with the exposure. Three, a confounder cannot be an intermediate variable between the exposure and the outcome. Confounding variables can be measured or unmeasured (Figure 2).

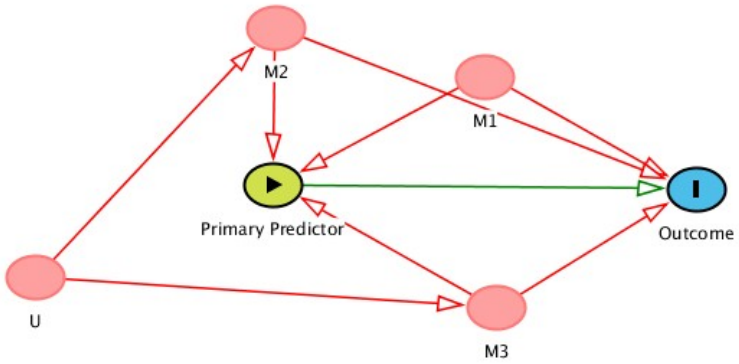

Figure 2. Diagram of Confounding, Measured (M) and Unmeasured (U)

CBI occurs when a specific treatment (primary predictor variable) is selected for a particular characteristic and this characteristic also affects the risk of the outcome variable. CBI is based on confounding bias, which can be described as the differential distribution of a third factor between study groups (127). For example, an investigator may be looking at the effect of anti-depressants in pregnancy and its affect on the development of autism. Depression would be a variable leading to CBI as it would indicate the need for the treatment (via antidepressants) and it can also affect the development of autism in a child, thereby affecting the risk of the outcome (128).

Due to the varying effects CBI can have between the primary predictor variable and the outcome variable, it is important to control for this event through various statistical means. Traditionally, the use of multivariable regression models and propensity score methods are used, but a third lesser known method, instrumental variable analysis is also effective in controlling for CBI (129-132). However no method has been shown to completely control for these CBI outside of true randomization, which is often unfeasible (133).

1.3.2 Multivariable Regression Model

Multivariable regression models are common in statistical analysis of observational studies. Regression models are used to model the likelihood of a binary outcome. The actual model used should fit the data collected and should be able to mathematically answer the questions posed in the study.

Logistic regression can only control for CBI on the condition that all the variables in the model are measured accurately. Logistic regression is limited in its ability to fully adjust a model for CBI because the number of variables that would need to be included in the model is typically more than a study's sample size would allow. Typically in a model with a binary outcome it is assumed that a minimum of ten patients will be needed per each predictor (or confounder) variable in the model, with many studies suggesting 15-20 cases per variable (134, 135). Missing data in any variable can affect the final sample size, so there should be a larger number of patients recruited than are mathematically needed. The multivariable regression model may also ignore complex relationships and may not account for interactions or for nonlinear relationships between the confounding variable and the outcome variable (e.g. if the health status of a patient affects the type of treatment being given). Regression modeling also cannot account for confounders that are unknown or unmeasured (136).

1.3.3 Propensity Scoring

A propensity score is the probability of treatment assignment conditional on observed baseline characteristics (137). Propensity scores are used to balance confounding variables between study groups, mainly for predictor variables (e.g. treatment type) that are provided to a patient in a non random fashion (133, 137-139). Conditional on the propensity score, the distribution of measured baseline covariates is similar between those with the treatment of interest and those without the treatment (139).

A propensity score begins with a multivariable regression model that estimates the joint effects on the primary predictor variable (e.g. the treatment) with variables thought to be associated with the probability of receiving the primary predictor variable (the treatment). A propensity score is usually defined as the estimated probability of receiving the primary predictor variable. There is debate regarding which variables to include in the creation of the propensity score (139-141). However, it is agreed that a misspecified propensity score will not completely balance confounding effects (142, 143).

Using a simplified formula for logistic regression is the first step in developing a propensity score as follows:

$$\text{Primary Predictor (Treatment)} = \alpha + \text{Variable}_1 + \text{Variable}_2 + \ldots \text{Variable}_n$$

The variables included in the regression model will change the likelihood of an individual obtaining the primary predictor variable (e.g. treatment type). For

example, if the predictor is a medication, such as a macrolide, the variables included would be those that are associated with the probability of a patient being prescribed that particular medication (e.g. variables that affect the propensity for receiving the medication).

Each variable included in the propensity score should be theoretically associated with the primary predictor variable and the outcome variable. It has been recommended that models retain non-statistically significant predictors. Also, removing pretreatment variables that are weakly associated with the outcome will have biasing effects (144, 145). If the propensity score is created from only covariates that are statistically significantly different between the primary predictor and comparison groups, the score then fails to take into account the relationship between the non-predictor variables and the outcome. Relying heavily on sample size and not practical relevance causes covariates to be considered in isolation rather than collectively (146, 147). Also, if iterative model-building algorithms such as stepwise regression are used to select the variables included in the propensity score, important confounders that may are strongly related to the outcome but only weakly seen in the stepwise regression, may not be included (147). Simulation studies have suggested that when analyzing moderate-sized data sets, researchers should not exclude any variable from the propensity score model unless it is well established that the variable has no relationship to the outcome (142). Other studies have suggested that only variables that are potential confounders and true confounders should be added into the propensity score (148). It has also been suggested that variables

included in the propensity score should affect the outcome but not the primary predictor variable, and that including variables that affect the primary predictor and not the outcome can increase the variance of the estimated treatment effect without a reduction in bias (142, 147).

Given the lack of consensus on which variables to include in the model, and knowing that it is difficult to correctly classify variables into the true confounders (i.e. those that only affect the outcome, those that only affect primary predictor, and those that affect neither treatment nor the outcome) it is advisable to include all measured baseline characteristics in the creation of a propensity score (147).

Once variable selection is made, the propensity score is then calculated as the logit probability (which tends to be normally distributed) or the predicted probability. The score is in the form of a continuous value, from 0 to 1, for each individual in the study (139, 149).

Once the propensity score has been calculated for each of the patients in the study, there are a variety of methods used to balance confounding. Regression adjustment, stratified regression, or matching models are all common approaches (137, 139, 150). Regression adjustment with a propensity score occurs when the propensity score is used as an indication variable (indicating the propensity to receive a treatment) that is placed into a regression model including the primary predictor variable (treatment) and outcome. Propensity score stratification occurs when there is stratification of subjects' based on the

individual subjects calculated propensity score. Within each propensity score stratum the effect of a treatment on an outcome can be estimated and a more specific risk can be estimated based on an individual's propensity to receive a treatment. Matching on a propensity score creates sets of exposed and unexposed subjects who share a similar score (a similar indication to receive a medication). Once a matched sample has been formed, the treatment effect can be estimated by directly comparing outcomes between treated and untreated subjects in the matched sample.

The propensity score matching approach should fit the research question and specific hypotheses of the study. There are many forms of matching such as Mahalanobis metric matching, nearest neighbor matching, caliper matching, and nearest neighbor matching within a caliper. Nearest neighbor matching within a caliper is a combination of matching approaches, and it allows for multivariable analysis using the matched sample when the sample is sufficiently large (149, 151). Nearest neighbor matching with a caliper first randomly sorts both the treatment and control groups. Then the first treatment unit is selected to find its closest control match based on the absolute value of the difference between the propensity score and that of the control under consideration. The closest control unit within a certain number, the caliper, is selected as a match (149). Not using a caliper can lead to poor balance between the treated and the control (i.e. those without the treatment of interest) (151).

It is usually always appropriate to adjust for more confounding variables in the final model. However, there may be confounding variables that are not

included in the propensity score due to temporality concerns (149). Using the previous example of antidepressant use in pregnancy and its effects on pregnancy, confounding variables (e.g. diagnosis of depression, maternal age) would be placed into the propensity score. The calculated propensity score would then be used as the matching variable. This balances two non-equivalent groups on observed characteristics thus there will be less biased estimates of the effects of antidepressant use in pregnancy (152).

Propensity scores do not fully control for CBI as they do not account for unmeasured confounding. Propensity scores only account for the confounding variables included in the creation of the score. Since unmeasured variables can influence receipt of the particular predictor variable, propensity scores cannot completely remove the bias (149, 153).

1.3.4 Instrumental Variable Analysis

Although typically used in economics, instrumental variable analysis can be useful in the determination of CBI. Instrumental variable (IV) analyses makes use of an IV or an instrument to control for unmeasured variation between confounders. This is different from propensity score matching, which is used to controlled for measured variation between confounders (129, 154).

An instrument is a seemingly random variable that is strongly associated with the predictor variable under study but not associated with the outcome (Figure 3) (155).

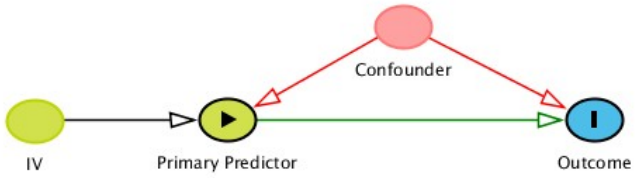

Figure 3. Diagram of Instrumental Variable

Finding an ideal instrument for any particular study is complicated. There are three key assumptions used in the evaluation of an instrument (155). One, the instrumental variable should lead to meaningful differences in the treatment being tested. Two, other than through the specific treatment being tested, there should be no other pathway for the instrumental variable to influence the outcome. Three, the instrumental variable should not cause the patient to receive both the instrument and the outcome. Otherwise stated, the IV should be independent of any possible confounders, should have association with the risk factor, and have independence of the outcome conditional on the risk factor and confounders (156).

IV's can vary in strength. The IV is considered weak when the variable chosen is not a good estimator of the primary predictor variable and does not explain a large proportion of the variation in the primary predictor (157-160). The strength of the IV is typically determined by the F-statistic (161). The closer the F-statistic is to zero, the weaker the instrument. For the maximum bias in IV estimators to be less than 10%, the F-statistic should be greater than 10 (157).

Weak instruments can create biased estimates and confidence intervals that are inaccurate (158). Geographic variables from census data are often used as some sort of an instrument, though the appropriateness of this instrument is based on the dataset being analyzed (162).

Use of instrumental variables is normally done via a specific 2-stage model. This method is recommended as it is based on the fewest assumptions and will generate the most consistent IV estimates, even when the treatment and outcome are binary variables (163-165). However, it can be biased in the direction of the confounded association between the primary predictor variable and outcome (166).

The first stage models the probability of the primary predictor variable as a function of all of the confounding variables and the instrumental variable. In comparison, the second stage again includes the confounding variables along with the predicted probability of the treatment from the first stage (132). The output of the model explains the impact of the probability of treatment on the outcome versus the presence or absence of the treatment (132, 155).

With the previous example of antidepressant use in pregnancy and its effects on pregnancy, an instrumental variable could be health insurance status. Having health insurance could influence a mother's ability to obtain antidepressants during pregnancy, but should have no influence on the development of autism in a child. Health insurance status is then used to remove variation in the treatment so that it is free of the unmeasured confounders. Then

the confounder-free variation in the treatment can be used to estimate the causal effect of antidepressant use in pregnancy on autism development (159, 162, 167).

The inherent limitation for instrumental variable analyses is their strong dependence on the assumption that the instrument is independent of all the variables that have an effect on both the predictor variable and the outcome variable, and that the instrument is independent of the outcome variable (132). Instrumental variable analysis is a large-sample procedure, meaning there is some bias due to sample-size limitations, even if all the assumptions of an appropriate instrument are met (132, 168).

1.5 Conclusions

Current guidelines for the treatment of hospitalized patients with CAP include empiric antimicrobial therapy with a macrolide plus a beta-lactam. There is little consensus among studies as to which antimicrobial regimen is best. The confusing results seen may be due to a lack of assessment of CBI. Thus, the objective of this study is to evaluate the impact of empiric macrolide therapy on early clinical improvement and 30 day mortality of hospitalized patients with CAP.

AIMS AND HYPOTHESES

2.1.1 Aim:

To evaluate three years of study data and determine whether macrolide and beta-lactam combination therapy usage is appropriate for gold standard treatment in hospitalized community acquired pneumonia though assessment of ECS and 30 day mortality.

2.1.2 Hypothesis:

Patients with macrolide and beta-lactam combination therapy will reach ECS and will have decreased 30 day mortality compared to those who have been given a different antibiotic.

2.2.1 Aim:

To assess and compare various methods addressing CBI (multivariable logistic regression, propensity score stratification and matching, instrumental variable analysis) through the assessment of macrolide and beta-lactam combination therapy and its effect on ECS and 30 day mortality in hospitalized patients with community acquired pneumonia.

2.2.2 Hypothesis:

The three methods assessing CBI will show the same effects of macrolide and beta-lactam combination therapy on ECS and 30 day mortality.

MATERIALS AND METHODS

3.1 Study

This is a secondary analysis of years one, two, and three of the Hospitalized Adults with Pneumococcal Pneumonia: Incidence Study (HAPPI). This study was conducted in Jefferson County, Kentucky from 2014 to 2017. It was a prospective population based cohort of adults hospitalized with CAP within the participating hospitals (n=8839) (7).

The study was approved by the Institutional Review Board (IRB) at the University of Louisville Human Subjects Research Protection Program Office (IRB number 11.0613) and by the research offices at each participating hospital. The study was exempt from informed consent.

3.1 Inclusion Criteria

Patients with CAP in one of nine area hospitals in Jefferson County, Kentucky were recruited into the study. The nine area hospitals included Baptist East Hospital, Jewish Hospital, Norton Audubon Hospital, Norton Brownsboro Hospital, Norton Downtown Hospital, Norton Suburban Hospital, St. Mary and

Elizabeth Hospital, University Hospital, and Veteran's Affairs Hospital. A patient was defined as having CAP when the following 3 criteria were met: (1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading; (2) at least 1 of the following: (a) new cough or increased cough or sputum production, (b) fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F), (c) changes in leukocyte count (leukocytosis: >11000 cells/μL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/μL); and (3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2 (7). These criteria were adapted from prior investigations (169, 170). Patients with CAP were included in this analysis upon the determination of antibiotic use within the first 24 hours of admission.

3.2 Exclusion Criteria

Patients were excluded from HAPPI if they did not have a permanent or valid Jefferson County, KY address based on US Census Bureau data, did not have a valid Social Security number (SSN), or were in the correctional system (7). Patients missing data needed to determine ECS were excluded in this analysis. Patients were also excluded from this analysis if they were given both a macrolide and a fluoroquinolone, or a non-macrolide and non-beta-lactam combination therapy with a non-fluoroquinolone substitute in the first 24 hours.

After exclusion and missing data attrition, the study sample size for this analysis was 3142 participants (Figure 4).

3.3 Exposure: Macrolide Usage

Two groups were created from the patients that were included in this analysis. Group 1 consisted of patients who received a macrolide plus a beta-lactam in the first 24 hours of admission but did not receive a fluoroquinolone, n=1904 (Figure 4). Macrolide antimicrobials are as follows: Azithromycin, Clarithromycin, and Erythromycin. Beta-lactam antimicrobials are as follows: Amoxicillin, Amoxicillin/Clavulanate, Ampicillin, Ampicillin/Sulbactam, Cefaclor, Cefazolin, Cefepime, Cefixime, Cefoperazone, Cefoperazone-Sulbactam , Cefotaxime, Cefotetan, Cefpodoxime, Ceftazidime, Ceftriaxone, Cefuroxime, Cephalexin, Cloxacillin, Dicloxacillin, Imipenem/Cilastin, Meropenem, Nafcillin, Penicillin, Penicillin G, Piperacillin, Piperacillin/Tazobactam, and Ticarcillin/ Clavulanic acid.

Group 2 consisted of patients who received a non-macrolide regimen, n=1238 (Figure 4). Quinolone antimicrobials are as follows: Levofloxacin, Gatifloxacin, Moxifloxacin and Ciprofloxacin.

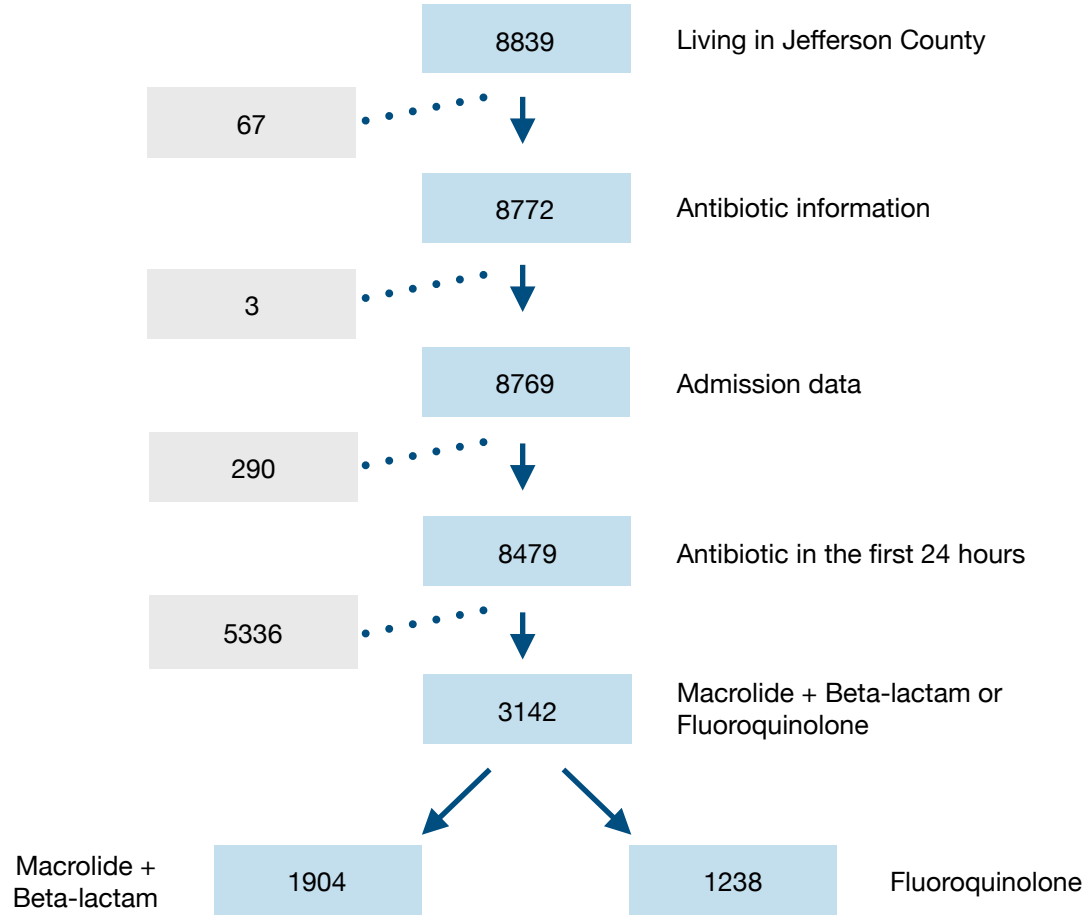

Figure 4. Flow chart showing sample selection for analysis

3.4.1 Outcome: Early Clinical Stability

Clinical stability is defined according to the ATS guidelines published in 2001. The ATS criteria are as follows: improved symptoms of pneumonia (cough and shortness of breath), lack of fever for at least eight hours, improving leukocytosis (decreased at least 10% from the previous day), and ability to take oral medications (97). All the criteria should be present during the same day in

comparison to the previous day to define clinical stability (97). For this study, ECS was to have occurred when the criteria were met on or before the third day of hospitalization. The dependent variable of this study was ECS by day 3 of hospitalization.

3.4.3 Outcome: 30 Day Mortality

The outcome of 30 day mortality was defined as all-cause mortality up to 30 days after hospitalization. Mortality was obtained through medical record abstraction and using data from the Kentucky Department for Public Health Office of Vital Statistics (7).

3.5.1 Other Variables

The original HAPPI study collected more than 600 variables. As analyzing all of these variables is outside the scope of this analysis, a determination of what variables to include was necessary. The variables included in the statistical analysis were important to the risk of CAP, associated with macrolide usage, associated with ECS, factors in clinical presentation, or were demographic variables. Demographic variables included were age, sex and race. Medical history variables included history of intravenous (IV) drug use, alcoholism, asplenia, chronic renal failure, congestive heart failure (CHF), cirrhosis, chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), human

immunodeficiency virus (HIV), diabetes, history of IV steroid use before day 0 of admission, liver disease, history of neoplastic disease within the last year or current neoplastic disease, renal disease, residence in a nursing home, current smoker status, and suspicion of risk for aspiration. Variables that were collected in the initial physical exam in the hospital included body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), temperature, and weight. Variables that were found on the initial physical exam in the hospital included body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR). respiratory rate (RR), temperature, and weight. Initial laboratory finding variables included blood urea nitrogen (BUM), serum glucose, hematocrit percent, and serum sodium. Variables that influenced the level of severity of CAP include altered status on admission, being admitted directly to the intensive care unit from the emergency department, requiring vasopressors on day 0 of admission, and requiring ventilatory support on day 0 of admission. Another variable considered was the classification of “severe”. This variable was created from a score based on the severity criteria recommended by the ATS/IDSA and compiled from the following variables (3, 171):

- Respiratory rate >30 breaths per minute
- Partial pressure of oxygen dissolved in the blood divided by fractional inspired oxygen (PaO2/FiO2) </=250
- Multi-lobar pneumonia as seen on a CT
- BUN >/= 20 mg/dL

- Leukopenia (white blood count >20,000/microL)
- Thrombocytopenia (platelets <100,000/microL)
- Hypothermia (temperature < 36 degrees Celsius)
- Hypotension (SBP<90mmHg and DBP<60mmHg
- Ventilator type (nasal intermittent mandatory ventilation (NMIV))
- Altered mental status on admission
- Septic shock
- Vasopressor medication

Census tract block information from patients was used in the instrumental variable analysis.

3.5.2 Instrumental Variable

Area Deprivation Index (ADI) was assessed as an appropriate instrumental variable. ADI is defined as a geographic area-based measure of the socioeconomic deprivation experienced by a neighborhood and is determined from census information. Higher ADI values represent higher levels of deprivation (172). ADI is based on the following indicators: median family income, income disparity, occupational composition, unemployment rate, family poverty rate, percentage of the population below 150% of the poverty limit, single-parent household rate, home ownership rate, median home value, median gross rent, median monthly mortgage, household crowding, and percentages of households

without access to a telephone, plumbing, or motor vehicles. Factor analysis and principal-components analysis were used in index construction (173).

3.6.1 Sample Size and Statistical Power

The initial study sample had 8839 participants, but after attrition due to exclusion criteria and missing data, the total sample size was 3,142, with 1,904 in group 1 and 1,238 in group 2.

Of those who gained ECS (n=2,018), 57.7% were given macrolide and beta-lactam combination therapy (n=1,205). The risk of ECS among group 1 was 63.29%. The risk of ECS among group 2 was 65.67%. Given the expected frequencies of exposure, an OR of 1.28 at 80% power and 1-alpha of 95% is detectable, the inverse of which is an OR of 0.78. Although, with the given sample size, a post hoc power analysis showed the statistical analysis of ECS was under-powered at 27.81% (174).

Of those who died within 30 days of discharge from the hospital (n=224), 60.3% were given macrolide and beta-lactam combination therapy (n=125). The risk of 30 day mortality among group 1 was 7.09%. The risk of ECS among group 2 was 7.19%. Given the frequencies of exposure, an OR of 1.5 at 80% power and 1-alpha of 95% is detectable, the inverse of which is an OR of 0.67.

However, with the given sample size, a post hoc power analysis showed the statistical analysis for 30 day mortality was under-powered at 2.18% (174).

Further statistical analysis were performed using STATA 14 and R.

Fisher's Exact Test was used on categorical variables and the Mann-Whitney U/ Wilcoxon Sum-rank test was used on continuous variables to understand the characteristics of the population and to assess variables for inclusion in further analysis. Inclusion was determined to occur at a conservative p-value of <0.20. Variables initially included were organized by type - demographic variables, medical history, physical findings on initial exam, laboratory findings on initial exam, and severity of CAP (Table 4).

3.6.2 Statistical Analysis of Confounding and Confounding By Indication

The effect of macrolide usage on ECS was assessed using multiple statistical methods: multivariable logistic regression, stratification using the propensity score, propensity score matching, and instrumental variable analysis. After the primary analysis determining which variables are statistically significantly different between the two groups, using P<= 0.2, the significant variables were placed into the multivariable logistic regression model. The final model was determined through a data-based method for assessment (125). A full model with the statistically significant variables was made. Then starting with the full model each covariate was removed, one at time. When the beta coefficient of

macrolide and beta-lactam therapy was more than 10% different than original full model beta coefficient of macrolide and beta-lactam therapy, the variable will be considered for the full model. The variable that was least significant, the one with the largest P value that did not affect the beta coefficient of macrolide and beta-lactam therapy more than 10%, was removed and the remaining variables went through the same process till only the confounding variables remained. A bidirectional stepwise method was also used, which is a mix of the forward and backward methods. (Forward stepwise regression is when variables are introduced one by one, beginning with the strongest, and then stopping when addition of the next factor does not significantly improve AIC. Backward stepwise regression is where all the variables are initially introduced and then are withdrawn one by one until the overall AIC does not deteriorate (175, 176).) The results of the bidirectional stepwise method were compared to the data-based method for assessment.

Propensity scores were calculated by a logit regression. The propensity score was created using all of the demographic characteristic variables, except for those that were included in the severity score (Table 4) (142, 143). These variables were: age, sex, race, mental status, history of neoplastic disease, CHF, CVA, COPD, renal disease, chronic renal failure, liver disease, cirrhosis, asplenia, alcoholism, suspicion of aspiration, IV steroid use, IV drug use, HIV, nursing home status, smoking status, direct ICU admission, exam HR, exam BMI, hematocrit laboratory values, glucose laboratory values, and sodium laboratory values. The propensity score was established by creating the

predicted probability of receiving the macrolide and beta-lactam combination treatment given the set of variables described above.

Propensity scores were used to stratify the population. Patients were ranked according to propensity score and stratified into propensity score quintiles, an approach that is known to remove the majority of bias in measured covariates (177). Also, patients receiving macrolide and beta-lactam combination therapy (group 1) were matched with patients that did not receive the combination therapy (group 2) according to their propensity scores. The 1:1 matched analysis was performed using caliper width based on the propensity score (178). The caliper width was determined by taking the standard deviation of the propensity score and multiplying it by 0.25.

Instrumental Variable Analysis were performed using the multivariable logistical regression and the two stage probit model with a significant instrument, that was determined by the F-statistic being greater than 10. The probit coefficient created by the model was multiplied by 1.6 and then exponentiated to approximate an Odds Ratio (OR) such that the outcomes of the various methods for addressing confounding by indication could be compared to one another (165).

The results from the different models were compared by placing them into a forest-like plot. A confidence interval that excluded the OR's from other methods was considered significantly different.

RESULTS

4.1 Population

In the original study population, there were 8,839 participants with CAP included who all lived in Jefferson County. 8,772 had antibiotic information listed, with 8,769 of those having admission data. There were only 8,479 participants who received an antibiotic within the first 24 hours. Of these, only 3,141 received either macrolide and beta-lactam combination therapy (N=1,905) or flouroquinolone mono-therapy (N=1,238) (Figure 4).

Table 4 shows descriptive statistics for the study population. Among the demographic variables neither sex nor race were significantly different between the groups. Age was significantly different between the groups, p=0.001, with 65 as the mean age in group 1 and 67 as the mean age in group 2 (Table 4).

Of the medical history variables, history of intravenous drug use, CHF, cirrhosis, COPD, history of IV steroid use before day 0 of admission, residence in a nursing home, and current smoker status were significantly different between the two different groups, given $p<0.2$ (Table 4). Interestingly, nursing home status

was most significant (p=<0.001) with 74 in a nursing home in group 1 (4%) and 102 in a nursing home in group 2 (8%).

Of the variables that were found on the initial physical exam in the hospital DBP, SBP, HR and RR were all significantly different between groups (given p<0.2), with p-values of <0.001, 0.001, 0.002, and <0.001, respectively (Table 4).

From the initial laboratory finding variables, hematocrit percent was found to be significantly different (given p<0.2) between the two groups, (p=0.001) (Table 4). The mean hematocrit percentage was 36.1% in group 1 and 36.9% in group 2. Serum glucose was also noted to be different between the two groups, p=0.012, with 170 mg/dL the mean in group 1 and 160 mg/dL the mean in group 2.

Of the variables that influenced the severity of CAP, ventilator support on day zero was significant (given p<0.2), p=0.032, with 179 (9%) in group 1 and 84 (7%) in group 2 (Table 4).

Severe was a significant variable (given p<0.2), p=0.005, with 602 people in group 1 and 333 in group 2. There were many variables that were included in the severe variable that were also examined. Some of these variables were independently significant while others were not. To prevent variables from being used twice in the analysis, the decision was made to include the severe variable as it carries a wider range of disease information with it.

Other correlated variables were COPD and IV steroid use before day 0 of admission (0.3414, p-value=< 0.001). This correlation is most likely a result of IV steroids given for exacerbations COPD (179).

Table 4. Characteristics of Study Population by Antibiotic Therapy Type

Characteristics	Macrolide + Beta-Lactam Combination Therapy	Fluoroquinolone Mono-therapy Therapy	P-value
Demographic Variables			
African American/Black, n (%)	376 (20)	239 (19)	0.783
Age, Mean (SD)	65 (17)	67 (16)	0.001+
Male Gender, n (%)	840 (44)	540 (44)	0.797
Medical History			
Active intravenous drug use?, n (%)	31 (2)	10 (1)	0.053+
Alcoholic, n (%)	96 (5)	58 (5)	0.673
Asplenia, n (%)	4 (0)	3 (0)	>0.999
Chronic renal failure, n (%)	120 (6)	80 (6)	0.881
Congestive heart failure, n (%)	481 (25)	343 (28)	0.135+
Cirrhosis, n (%)	16 (1)	4 (0)	0.106+
COPD, n (%)	868 (46)	617 (50)	0.019+
Cerebrovascular disease, n (%)	206 (11)	138 (11)	0.770
Diabetes, n (%)	589 (31)	368 (30)	0.500
HIV, n (%)	25 (1)	16 (1)	>0.999
IV steroids on day 0, n (%)	598 (31)	343 (28)	0.028+
Liver disease, n (%)	127 (7)	71 (6)	0.329
Neoplastic disease (active or within the last year), n (%)	204 (11)	141 (11)	0.56
Renal disease, n (%)	469 (25)	309 (25)	0.833
Nursing home resident, n (%)	74 (4)	102 (8)	<0.001+
Current smoker, n (%)	689 (36)	396 (32)	0.017+
Suspicion of aspiration, n (%)	132 (7)	87 (7)	0.943

+, variables will be included in further analysis as p-value<0.2
**, variables will not be included in analysis due to the inclusion in severity variable

Table 4 continued. Characteristics of Study Population by Antibiotic Therapy Type

Characteristics	Macrolide + Beta-Lactam Combination Therapy	Fluoroquinolone Mono-therapy Therapy	P-value
Physical Findings on Initial Exam			
BMI (kilograms/meter^2), Mean (SD)	29.1 (9)	28.8 (8.6)	0.476
Diastolic blood pressure (mmHg), Mean (SD)	60.8 (17.9)	63.5 (17)	<0.001**
Systolic blood pressure (mmHg), Mean (SD)	121.2 (27.4)	124.1 (25.9)	0.001**
Heart rate (Beats/Minute), Mean (SD)	105.2 (22.1)	102.8 (21.5)	0.002+
Respiratory rate (Breaths/Minute), Mean (SD)	23.7 (6.5)	23 (6.5)	<0.001**
Temperature (Degrees Celsius), Mean (SD)	37.4 (9)	37.4 (0.8)	0.798**
Weight (kilograms), Mean (SD)	82.6 (27)	82 (26)	0.555
Initial Laboratory Findings			
Blood Urea Nitrogen (BUN) (mg/dL), Mean (SD)	22.1 (16.4)	21.2 (13.8)	0.696**
Serum glucose (mg/dl), Mean (SD)	170.4 (88.6)	160.8 (78)	0.012+
Hematocrit(%), Mean (SD)	36.1 (6.1)	36.9 (6)	0.001+
Serum sodium (mEq/L), Mean (SD)	136.7 (5)	136.5 (4.6)	0.297
Severity of CAP			
CAP diagnosis is considered severe, n (%)	602 (32)	333 (27)	0.005+
Altered mental status on admission, n (%)	219 (11)	139 (11)	0.863**
Was the patient admitted directly to an intensive care unit from the emergency department?, n (%)	188 (10)	108 (9)	0.289
Did the patient need vasopressors on day 0?, n (%)	24 (1)	14 (1)	0.868**
Did the patient need ventilatory support on day 0?, n (%)	170 (9)	84 (7)	0.032**

+, variables will be included in further analysis as p-value<0.2
**, variables will not be included in analysis due to the inclusion in severity variable

Variables included in further analysis were as follows: age, cirrhosis, COPD, CHF, history of IV drug use, being in a nursing home, currently smoking, HR, hematocrit, glucose, and severity.

4.2.1 Assessment of Macrolide Combination Therapy and the Effects on Early Clinical Stability: Logistic Regression

Patients on macrolide and beta-lactam combination therapy were less likely to reach ECS than those taking fluoroquinolones, although this is a non significant result (OR 0.901; 95% Confidence Interval (CI) 0.776, 1.047; p-value: 0.173) (Table 5).

In the full model including all the variables that were found to be significantly different (given $p<0.2$) between group 1 and 2 (age, cirrhosis, COPD, CHF, history of IV drug use, being in a nursing home, currently smoking, HR, hematocrit, glucose, and severity) macrolide combination therapy was found to decrease the likelihood of reaching ECS, although this also was non-significant (OR 0.911; 95% CI 0.780, 1.063; p-value = 0.235). Significant variables in this model were COPD (OR 0.747; 95% CI 0.638, 0.875; p-value =<0.001), HR (OR: 0.992; 95% CI 0.988, 0.995; p-value =<0.001), CHF (OR 0.802; 95% CI 0.675, 0.953 ; p-value =0.012), and severity (OR 0.611; 95% CI 0.519, 0.721; p-value =<0.001) (Table 5).

The bidirectional stepwise analysis algorithm yielded the same model results that the data-based method of variable selection did (both algorithms used macrolide combination therapy as the primary predictor variable). The model was as follows: logit P(ECS) = α + β_1(macrolide and beta-lactam combination therapy) + β_2(COPD) + β_3(CHF) + β_4(residence in a nursing home) + β_5(HR) + β_6(severity) + ε. The reduced model was not statistically different from the full model and was thus considered acceptable (Chi-Square P-value = 0.8641289). In the final model, macrolide and beta-lactam use was associated with decreased odds of gaining ECS, although this was once again not statistically significant (OR 0.910; 95% CI 0.780, 1.061; p-value =0.227). The variables in this model that were significantly associated with increased time to clinical stability were COPD (OR 0.735; 95% CI 0.633, 0.854; p-value =<0.001), HR (OR: 0.992; 95% CI 0.988, 0.995; p-value =<0.001), CHF (OR 0.810; 95% CI 0.675, 0.953 ; p-value =0.015), and severity (OR 0.617; 95% CI 0.526, 0.725; p-value =<0.001) (Table 5). The full process for variable selection using a data-based method is presented in Appendix II (ECS: Multivariable Logistic Regression, Data-based Method for Assessment).

Table 5. Multivariable Logistic Regression Models: ECS

Variable	OR	95% CI	P-Value	
Univariate Model				
Macrolide + Beta Lactam Therapy	0.901	0.776, 1.047	0.173	
Full Model				
Macrolide + Beta Lactam Therapy	0.911	0.780, 1.063	0.235	
Age	>0.999	0.995, 1.005	0.984	
Glucose	>0.999	0.999, 1.001	0.756	
Smoking	0.954	0.802, 1.136	0.599	
IV drug use	0.818	0.427, 1.565	0.543	
Cirrhosis	0.738	0.302, 1.805	0.506	
Hematocrit	0.993	0.981, 1.006	0.301	
Residence in nursing home	0.740	0.537, 1.018	0.065	
CHF	0.802	0.675, 0.953	0.012	+
COPD	0.747	0.638, 0.875	<0.001	+
HR	0.992	0.988, 0.995	<0.001	+
Severe	0.611	0.519, 0.721	<0.001	+
Final Model				
Macrolide + Beta Lactam Therapy	0.910	0.780, 1.061	0.227	
Residence in nursing home	0.752	0.548, 1.032	0.078	
CHF	0.810	0.683, 0.959	0.015	+
COPD	0.735	0.633, 0.854	<0.001	+
HR	0.992	0.988, 0.995	<0.001	+
Severe	0.617	0.526, 0.725	<0.001	+

+ statistically significant

4.2.2 Assessment of Macrolide Combination Therapy and the Effects on 30 Day Mortality: Logistic Regression

Assessing the unadjusted effects of macrolide and beta-lactam combination therapy and its effect on 30 day mortality showed that those with macrolide and beta-lactam combination therapy were less likely to have died within 30 days of admission, although this is a non-significant result (OR 0.985; 95% Confidence Interval (CI) 0.746, 1.301; p-value: 0.916) (Table 6).

The full model including all the variables that were found to be significantly different (given p<0.2) between group 1 and 2 (age, cirrhosis, COPD, CHF, history of IV drug use, being in a nursing home, currently smoking, HR, hematocrit, glucose, and severity) macrolide combination therapy was found to decrease 30 day mortality, although this again was non significant (OR 0.911; 95% CI 0.780, 1.063; p-value = 0.235). Significant variables in this model were Age (OR 1.04; 95% CI 1.029, 1.052; p-value =<0.001), HR (OR: 1.014; 95% CI 1.007, 1.020; p-value =<0.001), IV drug use (OR 3.486; 95% CI 1.121, 10.838 ; p-value =0.031), hematocrit (OR 0.950; 95% CI 0.928, 0.973 ; p-value =<0.001), and severity (OR 2.237; 95% CI 1.675, 2.987; p-value =<0.001) (Table 6).

The bidirectional stepwise analysis algorithm produced a different model result than the data-based method variable selection (both algorithms used macrolide combination therapy as the primary predictor variable). Both models

included residence in a nursing home, history of IV drug use, hematocrit lab values, HR, severity, and age. The bidirectional stepwise method included CHF while the data-based method included glucose values. Neither the bidirectional stepwise method nor the data-based method were statistically different from the full model, Chi-Square P-value of 0.3306626 and 0.4590019, respectively. The data-based method model was less different from the full model compared to the bidirectional stepwise method. The model was as follows: logit P(30 Day Mortality) = α + β_1(macrolide and beta-lactam combination therapy) + β_2(residence in a nursing home) + β_3(glucose) + β_4(IV drug use) + β_5(hematocrit) + β_6(HR) + β_7(severe) + β_8(age) + ε.

In the final model, those with macrolide and beta-lactam use were less likely to have died within 30 days of admission, although this was not statistically significant (OR 0.926; 95% CI 0.692, 1.241; p-value =0.608). The variable in this model that was significantly associated with reduced mortality was hematocrit (OR: 0.950; 95% CI 0.928, 0.973; p-value =<0.001). The variables in this model that were significantly associated with increased 30 day mortality were IV drug use (OR 3.548; 95% CI 1.160, 10.854; p-value =0.026), HR (OR 1.013; 95% CI 1.007, 1.019 ; p-value =<0.001), severity (OR 2.290; 95% CI 1.717, 3.052; p-value =<0.001), and age (OR 1.042; 95% CI 1.031, 1.053; p-value =<0.001) (Table 6). The full process for variable selection using a data-based method is presented in Appendix II (30 Day Mortality: Multivariable Logistic Regression, Data-based Method for Assessment).

Table 6. Multivariable Logistic Regression Models: 30 Day Mortality

Variable	OR	95% CI	P-Value	
Univariate Model				
Macrolide + Beta Lactam Therapy	0.985	0.746, 1.301	0.916	
Full Model				
Macrolide + Beta Lactam Therapy	0.929	0.780, 1.063	0.235	
Smoking	0.955	0.663, 1.376	0.804	
COPD	1.068	0.795, 1.435	0.663	
CHF	1.221	0.902, 1.653	0.196	
Residence in nursing home	1.387	0.856, 2.248	0.184	
Cirrhosis	2.486	0.690, 8.963	0.164	
Glucose	1.001	1.000, 1.003	0.094	
IV drug use	3.486	1.121, 10.838	0.031	+
Hematocrit	0.950	0.928, 0.973	<0.001	+
HR	1.014	1.007, 1.020	<0.001	+
Severe	2.237	1.675, 2.987	<0.001	+
Age	1.040	1.029, 1.052	<0.001	+
Final Model				
Macrolide + Beta Lactam Therapy	0.926	0.692, 1.241	0.608	
Glucose	1.001	1.000, 1.003	0.066	
Residence in nursing home	1.390	0.859, 2.249	0.180	
IV drug use	3.548	1.160, 10.854	0.026	+
Hematocrit	0.950	0.928, 0.973	<0.001	+
HR	1.013	1.007, 1.019	<0.001	+
Severe	2.290	1.717, 3.052	<0.001	+
Age	1.042	1.031, 1.053	<0.001	+

+ statistically significant

4.3.1 Propensity Score Creation

The calculated propensity score ranged from 0.2718 to 0.9007 as depicted in the histogram in Figure 5. The mean propensity score was 0.6060 with a standard deviation of 0.0869. Group 1 had a mean of 0.6184 while group 2 had a mean of 0.5868 and were statistically different from one another (p= <0.001) (Figure 6). The propensity scores between the two groups, while visually similar, are not statistically similar, meaning that on average, those who were given fluoroquinolone mono-therapy had a slightly lower probability of being given macrolide and beta-lactam combination therapy.

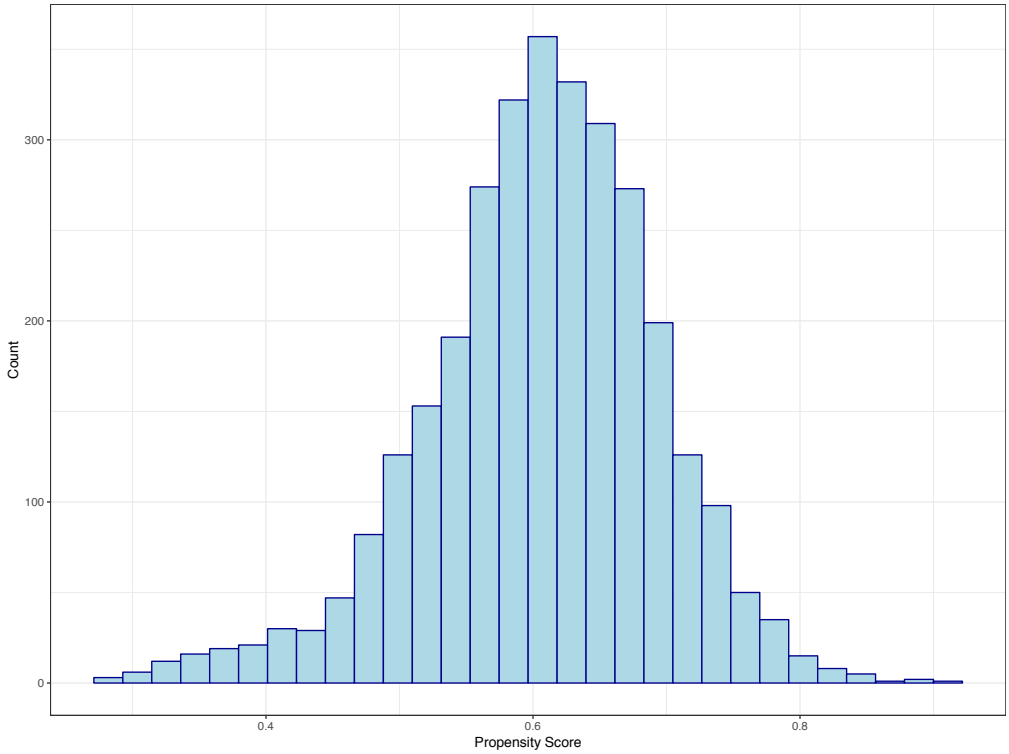

Figure 5. Histogram of Propensity Scores

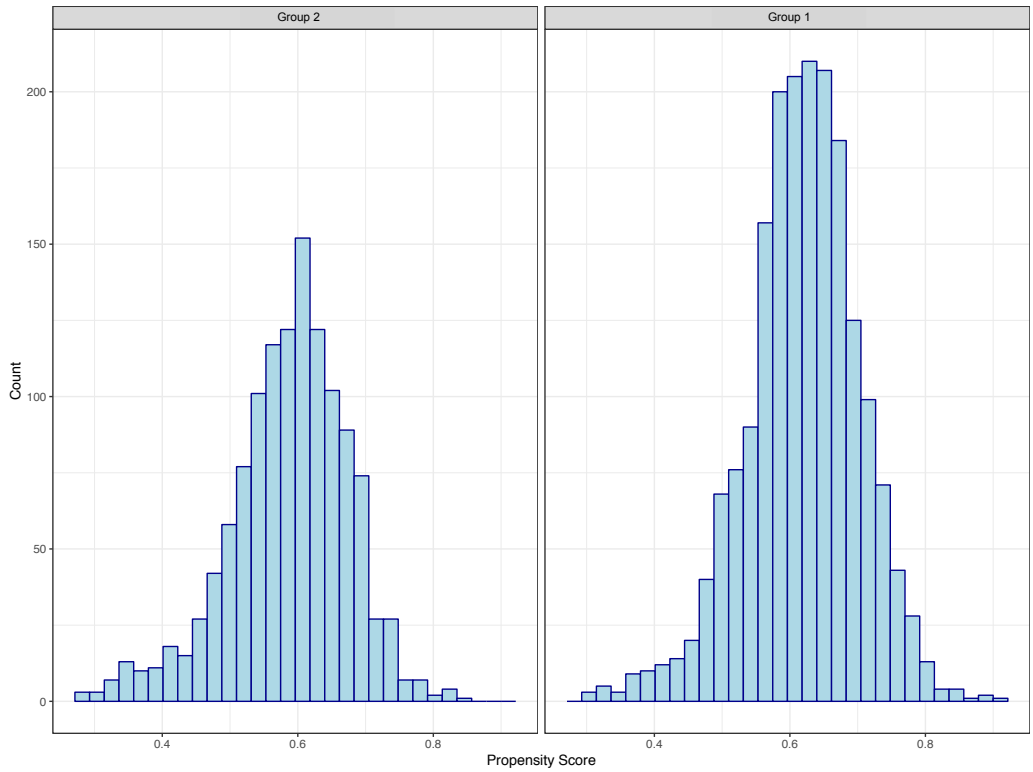

Figure 6. Histogram of Propensity Scores by Treatment Type

Using the calculated propensity score, patients in group 1 were matched with patients in group 2. Nearest neighbor matching with a caliper was used to create the matches. The caliper, 0.02173275, was based on the standard deviation of the propensity score, multiplied by 0.25. Of the original 3142 patients, 1177 matched pairs were created, leaving 61 people in group 2 unmatched and 727 people in group 1 unmatched (Figure 7, Figure 8).

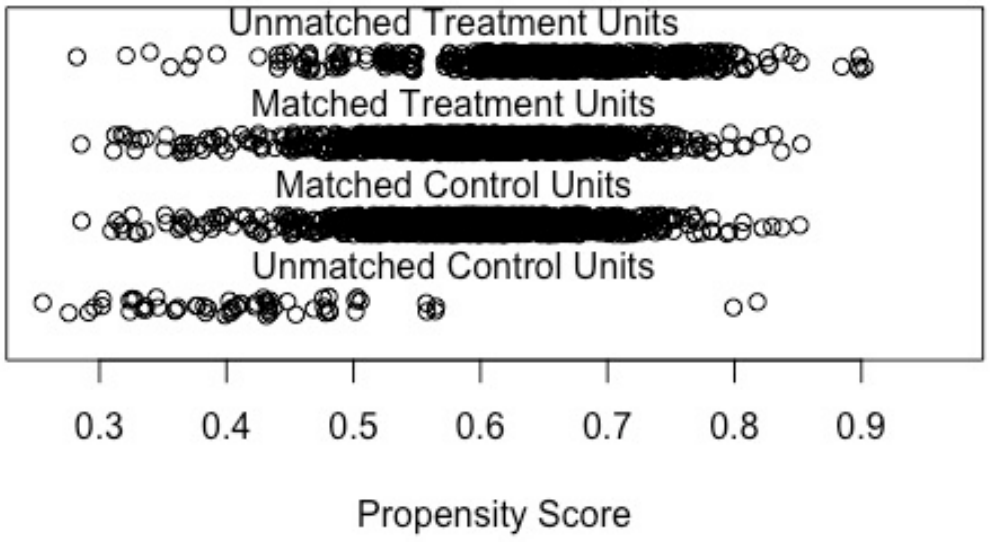

Figure 7: Distribution of Propensity Scores

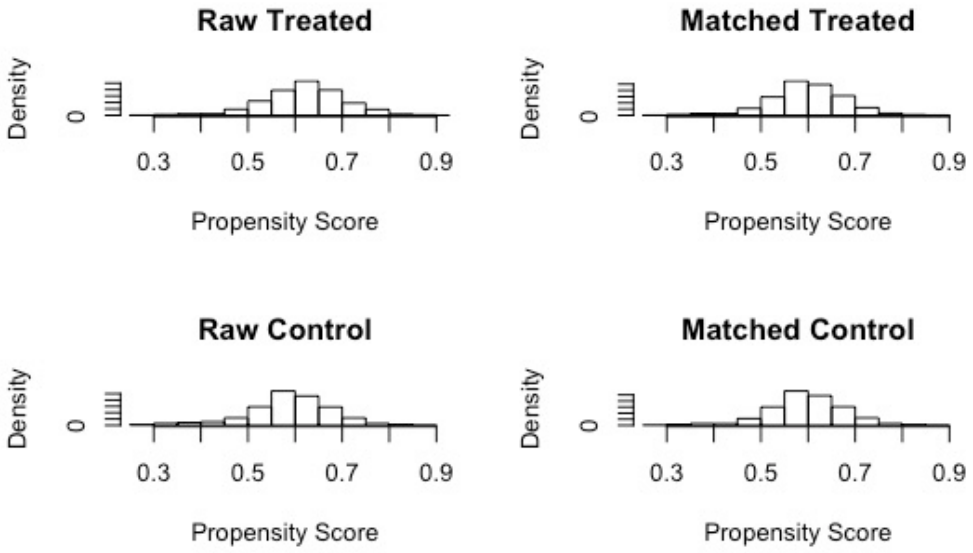

Figure 8: Distribution of Propensity Scores, Matched vs Unmatched

4.3.2 Assessment of Macrolide Combination Therapy and the Effects on Early Clinical Stability: Propensity Score Analysis

Using conditional logistic regression, macrolide and beta lactam usage was found to decrease the likelihood of gaining clinical stability, although this was non-significant (OR 0.885, 95% CI 0.748, 1.048, p-value = 0.156) (Table 7).

When the propensity scores were stratified based on quartile values, the effect of macrolide and beta-lactam combination therapy on ECS was assessed using logistic regression. While none of the values were significant, the effect of macrolide and beta-lactam combination therapy on establishing ECS did change depending on the propensity score value (Table 7).

Table 7. Effects of Macrolide and Beta-Lactam Combination Therapy on ECS, by Propensity Score

Model		OR	95% CI	P-value
Conditional Logistic Regression				
Matched 1:1		0.885	0.748, 1.048	0.156
Stratification by PS				
Q1	0.0001 - 0.5571	0.888	0.660, 1.196	0.435
Q2	0.5572 - 0.6109	0.927	0.684, 1.257	0.625
Q3	0.6110 - 0.6631	1.023	0.755, 1.386	0.884
Q4	0.6632 - 1.0000	0.929	0.679, 1.271	0.646

4.3.2 Assessment of Macrolide Combination Therapy and the Effects on 30 Day Mortality: Propensity Score Analysis

Using conditional logistic regression, macrolide and beta lactam usage was found to decrease 30 day mortality, although this was non-significant (OR 0.848, 95% CI 0.612, 1.174, p-value = 0.321) (Table 8).

When the propensity scores were stratified based on quartile values, the effect of macrolide and beta-lactam combination therapy on 30 day mortality was assessed using logistic regression. While none of the values were significant, the effect of macrolide and beta-lactam combination therapy on 30 day mortality did change depending on the propensity score value, particularly in the third quartile (Table 8).

Table 8. Effects of Macrolide and Beta-Lactam Combination Therapy on 30 Day Mortality by Propensity Score

Model		OR	95% CI	P-value
Conditional Logistic Regression				
Matched 1:1		0.885	0.748, 1.048	0.156
Stratification by PS				
Q1	0.0001 - 0.5571	0.955	0.566, 1.612	0.863
Q2	0.5572 - 0.6109	0.954	0.501, 1.815	0.885
Q3	0.6110 - 0.6631	1.240	0.697, 2.207	0.465
Q4	0.6632 - 1.0000	0.797	0.465, 1.366	0.409

4.4.1 Assessment of Macrolide Combination Therapy and the Effects on Early Clinical Stability: Instrumental Variable Analysis

Instrumental variable analysis was done via a two stage model where the first-stage was a regression of macrolide and beta-lactam combination therapy and other variables on the instrumental variable, ADI. The second-stage was a regression of ECS on the fitted values of the risk factors from the first stage. ADI was considered a strong instrument as the F-statistic was greater than 10 (F-statistic 12.62; p-value <0.001). The model used in this analysis included the variables selected in logistic regression modeling, COPD + CHF + residence in a nursing home + HR + severity.

While the confidence interval was very wide and non-significant, it is interesting to note that macrolide and beta-lactam combination therapy was associated with reaching ECS (OR 1.551; 95% CI 0.778, 3.091; p-value = 0.213). The significant variables in this model were CHF (OR 0.935; 95% CI 0.876, 0.999; p-value = 0.046), COPD (OR 0.915; 95% CI 0.858, 0.976; p-value = 0.007), HR (OR 0.996; 95% CI 0.995, 0.998; p-value = <0.001), and Severity (OR 0.810; 95% CI 0.750, 0.874; p-value = <0.001) (Table 9).

Table 9. Instrumental Variable Analysis with ADI as the Instrument: ECS

Variable	OR	95% CI	P-Value	
Macrolide + Beta Lactam Therapy	1.551	0.778, 3.091	0.213	
Residence in nursing home	0.989	0.824, 1.187	0.907	
CHF	0.935	0.876, 0.999	0.046	+
COPD	0.915	0.858, 0.976	0.007	+
HR	0.996	0.995, 0.998	<0.001	+
severe	0.810	0.750, 0.874	<0.001	+

+ statistically significant

4.4.2 Assessment of Macrolide Combination Therapy and the Effects on 30 Day Mortality: Instrumental Variable Analysis

Instrumental variable analysis was done via the two stage model. ADI was again considered a strong instrument as the F-statistic was greater than 10 (F-statistic 11.03; p-value <0.001). The model used in this analysis included the variables selected in logistic regression modeling, glucose + residence in a nursing home + history of IV drug use + hematocrit lab values + HR + severity + age.

While the confidence interval was non-significant, macrolide and beta-lactam combination therapy was associated with a slight decrease in the likelihood of dying within 30 days (OR 0.958; 95% CI 0.603, 1.522; p-value =0.857). The significant variables in this model were hematocrit (OR 0.995; 95%

CI 0.991, 0.998; p-value = 0.002), HR (OR 1.002; 95% CI 1.001, 1.002; p-value = <0.001), severity (OR 1.108; 95% CI 1.064, 1.154; p-value = <0.001), and age (OR 1.003; 95% CI 1.002, 1.005; p-value = <0.001) (Table 10).

Table 10. Instrumental Variable Analysis with ADI as the Instrument: 30 Day Mortality

Variable	OR	95% CI	P-Value	
Macrolide + Beta Lactam Therapy	0.958	0.603, 1.523	0.857	
Glucose	1.000	1.000, 1.000	0.217	
Residence in nursing home	1.052	0.944, 1.173	0.359	
IV drug use	1.105	0.966, 1.264	0.145	
Hematocrit	0.995	0.991, 0.998	0.002	+
HR	1.002	1.001, 1.002	<0.001	+
Severe	1.108	1.064, 1.154	<0.001	+
Age	1.003	1.002, 1.005	<0.001	+

+ statistically significant

4.2.5 Assessment of Methods Addressing Confounding by Indication: Logistic Regression, Propensity Score Matching, Instrumental Variable Analysis

Figures 8 and 9 compare the results from the three methods for controlling confounding and confounding by indication in a forest plot. Examining the methods used to assess the effects of macrolide and beta-lactam combination therapy on ECS, the OR's of all three methods have non-significant intervals and the OR's from logistic regression and propensity score matching are almost

identical, 0.918 and 0.916 respectively, (Table 9). The methods used to assess the effects of macrolide and beta-lactam combination therapy on 30 day mortality all had similar OR's with non significant intervals (Figure 9, Table 9). The confidence intervals from the instrumental variable analyses preformed are larger than those from logistic regression and propensity score matching.

Table 11. Comparing Logistic Regression, Propensity Score Matching, and Instrumental Variable Analysis

Method	OR	95% CI
ECS		
Logistic Regression	0.908	0.780, 1.059
Propensity Score Match	0.916	0.775, 1.083
Instrumental Variable Analysis	1.551	0.777, 3.091
30 Day Mortality		
Logistic Regression	0.926	0.692, 1.241
Propensity Score Match	0.885	0.748, 1.048
Instrumental Variable Analysis	0.958	0.603, 1.523

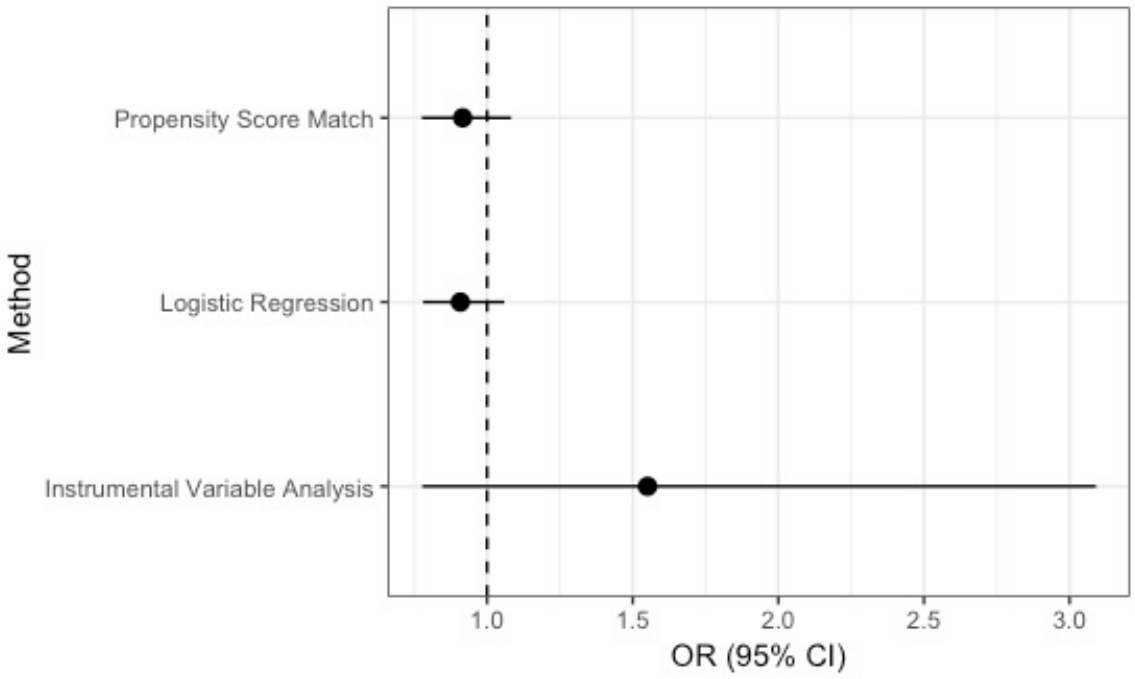

Figure 8: Forest-like Plot, Effect of Macrolide and Beta-Lactam Combination Therapy on ECS

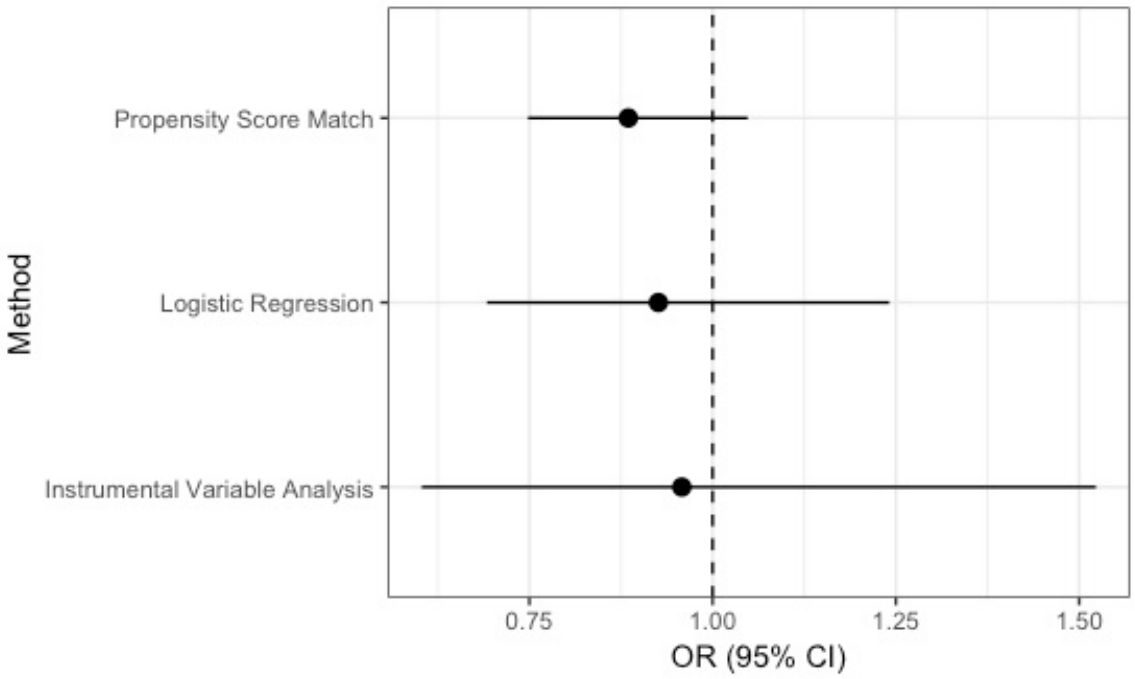

Figure 9: Forest-like Plot, Effect of Macrolide and Beta-Lactam Combination Therapy on 30 Day Mortality

DISCUSSION

5.1 Discussion of Macrolide and Beta-Lactam Combination Therapy and Early Clinical Stability

The first objective of this analysis was to determine whether macrolide and beta-lactam combination therapy usage is appropriate for gold standard treatment in hospitalized CAP though the assessment of ECS. Overall, macrolide and beta-lactam combination therapy was not associated with ECS compared to fluoroquinolone mono-therapy.

When evaluating the effects of macrolide and beta-lactam usage on ECS, there was a difference in the results depending on the method used to address CBI. Analysis with logistic regression and propensity score matching, both addressing measured confounding, showed that macrolide and beta-lactam therapy was not statistically significantly associated with ECS based on confidence intervals and p-values, but both odds ratios were less than 1.0 suggesting protection against establishing ECS. This suggests that, according to these methods for controlling for CBI, macrolide and beta-lactam combination therapy was associated with decreased likelihood of reaching clinical stability by day three. Analysis using ADI in instrumental variable analysis addressed unmeasured confounding and also showed statistically non-significant results. However the calculated odds ratio suggested that macrolide and beta-lactam

combination therapy usage was associated with increasing likelihood of establishing clinical stability on or before day three.

The variation in the odds ratios calculated via the three different methods suggests there may be unmeasured variables that are important in establishing ECS that are not being addressed in logistic regression and propensity score matching. Variables indicated by ADI (a proxy variable) but not actively measured could be playing an important role in establishing ECS. For example those with access to primary care physicians and health insurance that cover “sick” visits may be treated in the outpatient setting for a set time period before the clinician decides to admit to the hospital, while those with lack of access to the same type of primary care provider may be going straight to an emergency room for treatment and be admitted earlier.

There is a difference seen in the results from the methods that analyzed measured confounding vs the method used to analyze unmeasured confounding, nevertheless due to confidence intervals, these results are statistically similar. The confidence intervals from logistic regression and propensity score analysis were narrower than the confidence interval from instrumental variable analysis. The confidence interval from instrumental variable analysis was wider because the instrumental variable, ADI, was a cluster variable. Since the instrumental variable analysis is essentially calculating a separate model in each block group, similar to a multilevel model, the overall sample size can affect the smaller sample seen in each cluster. As the overall sample size is small there isn’t an equal distribution of macrolide and beta-lactam combination therapy usage and

ECS in each block group and the sparse data in some of the census block groups leads to a wider confidence interval. However, even if the sample analyzed was larger, there is no guarantee that the sample would be evenly distributed amongst block groups, and thus the confidence interval could continue to be wide.

5.2 Discussion of Macrolide and Beta-Lactam Combination Therapy and 30 Day Mortality

Another objective of this analysis was to determine whether macrolide and beta-lactam combination therapy usage is appropriate for gold standard treatment in hospitalized community acquired pneumonia though assessment of 30 day mortality. Overall, macrolide and beta-lactam therapy was not associated with 30 day mortality.

In this analysis there was no difference in the calculated OR's from the methods that analyzed measured confounding (logistic regression and propensity score matching) and from the method used to analyze unmeasured confounding (instrumental variable analysis). The three odds ratios were statistically similar, in that each of the the confidence intervals were wide enough to include the OR's from the other analytical methods. However the confidence interval for the instrumental variable analysis was substantially wider than that of the other two analytical methods. This is due to ADI being a cluster variable and the non-equal

distribution of macrolide and beta-lactam combination therapy usage and ECS amongst the census block groups, as discussed previously.

The non-significant OR's of macrolide and beta-lactam combination therapy's effects on 30 day mortality were similar to the results from the meta analyses (88, 120).

Asadi et al, 2012, initially found that macrolide use was associated with a statistically significant lower risk of mortality compared with nonmacrolide use, however there was a large amount of heterogeneity between the studies (88). When they assessed just the randomized control trials, the reduction in mortality was no longer apparent. The analysis also found that there was no significant difference in mortality comparing macrolide and beta-lactam combination therapy versus fluoroquinolone mono-therapy.

Vardakas et al, 2017, reported that mono-therapy regimens were not associated with higher mortality when compared with combination therapies, however the heterogeneity was once again high (120). They found that the retrospective studies reported higher mortality associated with mono-therapy, while both prospective studies and RCTs showed no difference in mortality. There was no difference in mortality between fluoroquinolone mono-therapy and b-lactam/macrolide combination

The concordance between the results from the analytical methods and the findings from the meta analyses give credence to the understanding that there is no difference, with regards to 30 day mortality, between macrolide and beta-lactam combination therapy and fluoroquinolone mono-therapy.

5.3 Discussion of Methods for Analyzing Confounding by Indication

Confidence Interval difference

To compare the odds ratios from the various methods of addressing confounding by indication, the confidence intervals were used as a way to determine similarities. If one confidence interval included the OR's from the other methods, the OR's were determined to be similar. Although this is a useful method, there is no statistical significance attached to the results from this method. There is a lack of analytical methods to compare OR's from various methods of calculation. The assumptions made in the analytical methods do not allow for a simple one-to-one comparison, as is seen in a Wald test.

5.4 Discussion of Macrolide and Beta-Lactam Combination Therapy and Fluoroquinolone Mono-Therapy

Overall, there was no statistical difference between being given macrolide and beta-lactam combination therapy and fluoroquinolone mono-therapy with respect to ECS or 30 day mortality. With these results similar to those seen in other studies it begs the question, why is macrolide and beta-lactam combination therapy considered first line treatment compared to fluoroquinolone mono-therapy? On one side there are the contraindications and complications associated with fluoroquinolones, which shouldn't be ignored. However on the other side there is an increase in the amount of macrolide resistant *S.*

pneumoniae. It is a catch-22 cycle trying to balance side effects with drug resistance.

There needs be increased discernment in the type of antimicrobial given. Empiric antimicrobial therapy within the first 6 hours of admission is known to decrease mortality in patients with CAP. Guidelines also recommend deceleration of antimicrobial treatment once the pathogen is determined, however few cases have a defined causal pathogen. In the study population, only 16.5% of patients had a causal pathogen determined. 85 patients had *S. pneumoniae*, however there were 41 different pathogens, both viral and bacterial, identified.

Physicians should have a greater understanding of the causal pathogens associated with specific risk factors and locations. For example, if a patient has CAP and is from an area that is experiencing an outbreak, there is a greater likelihood of *Chlamydia pneumoniae* or *Legionella* species being the causative pathogen, and so caution against macrolide resistant *Streptococcus pneumoniae* may not be needed. Rapid diagnostic tests could also be beneficial as the pathogen could be understood at an earlier point in the course of CAP and the antimicrobials given could be adjusted accordingly sooner.

CONCLUSION

6.2.1 Conclusion

In this study population, there is no difference in the likelihood of establishing ECS according to whether a patient is given macrolide and beta-lactam combination therapy or fluoroquinolone mono-therapy. The three different methods used to address CBI (logistic regression, propensity score matching, instrumental variable analysis) showed overall similar non-significant results, although instrumental variable analysis, in assessing unmeasured confounding, found different results from the methods addressing measured confounding. There is no statistical difference in the likelihood of 30 day mortality between the antibiotic groups. Logistic regression, propensity score matching, and instrumental variable analysis all found similar non-significant results. Physicians need to have a greater understanding of the causal pathogens associated with specific risk factors and locations. The emergence of macrolide resistant species of Streptococcus pneumoniae give a reason to cautiously examine the antibiotics being empirically given, especially as many studies, including this one, suggest no association between improved clinical outcomes and antibiotic given. There is a need for better rapid diagnostic tests so that the causal pathogen can be understood at an earlier time in the clinical course of CAP.

6.2.2 Strengths

One of the main strengths of this study is that it is a unique data set, having almost 100% coverage of adults hospitalized with community acquired pneumonia in Jefferson County, Kentucky. The HAPPI study also had structural quality control measures (i.e. the entry system would not allow for an age of 500 years to be input, a team of individuals went through the records and assessed for errors, etc.). The study is comprised of a heterogeneous population with regards to ethnicity and socioeconomic status. Three different models were used to evaluate the hypotheses of the study, which led to more informative conclusions. Furthermore, the exposures were verifiable due to inclusion in hospital records .

6.2.3 Limitations

Post-hoc power analysis showed analysis was under powered, although when assessing the outcomes in the study using macrolide use versus non macrolide use (which was fully powered) similar results were seen. There was a potential for random error in the entry of information from hospital records, however this would have been non-differential and so would not have biased results. There was also no accounting for potential diagnostic differences between the various radiologists examining the chest x-rays needed for clinical diagnosis of CAP. However, this would have affected those in both groups, and

so would have been non-differential. The results from the analysis of the effect of macrolide and beta-lactam therapy on early clinic stability an 30 day mortality may not generalizable to the other forms of pneumonia, such as HAP, HCAP, VAP, etc. Also, there is a question of generalizability of the results when it comes to other climates, as Jefferson County, Kentucky is situated in the Ohio River Valley which exposes the patient population to certain environmental exposures that may affect the pathogenicity of CAP. Intra-personal non-modifiable differences (i.e. genetics) were not accounted for as they were beyond the scope of this study.

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APPENDIX I: GLOSSARY

AAFP: American Academy of Family Physicians

ATS: American Thoracic Society

Beta-Lactam: Antimicrobials that are effective against gram positive bacteria and some gram negative bacteria. They act by inhibiting the synthesis of bacterial walls.

BMI: Body Mass Index

BTS: British Thoracic Society

BUN: Blood Urea Nitrogen

CAP: Community Acquired Pneumonia

CBI: Confounding by indication

CHF: Congestive heart failure

Confounding: When a variable has been found to influence both the independent variable (e.g. an antibiotic treatment) and the dependent variable (e.g. a clinical outcome).

Confounding by Indication (CBI): A type of confounding that occurs when a treatment (the primary predictor variable) is selected due to a specific characteristic (e.g. history of a particular disease, provider medication preference) and this characteristic also affects the risk of the outcome variable.

COPD: Chronic obstructive pulmonary disease

Community Acquired Pneumonia (CAP): Characterized by acute symptoms such as dyspnea, cough, fever, or chest pain, it is diagnosed by the presence of pulmonary infiltrate seen on radiography

CURB-65: Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older; Used to predict the need for hospitalization for a patient who has community acquired pneumonia

CVD: Cerebrovascular disease

DBP: Diastolic blood pressure

ECS: Early Clinical Stability

Early Clinical Stability (ECS): The following criteria are met within 3 days of admission; improved symptoms of pneumonia (cough and shortness of breath), lack of fever for at least eight hours, improving leukocytosis (decreased at least 10% from the previous day), and ability to take oral medications

FDA: Federal Drug Administration

Fluoroquinolone: Antimicrobials that work best against aerobic gram-negative bacilli. They are direct inhibitors of bacterial DNA synthesis and bind to the complex of specific enzymes within DNA and thus inhibit progress of the DNA replication leading to bacterial DNA and bacterial cell death.

HAP: Hospital-acquired pneumonia

HAPPI: Hospitalized Adults with Pneumococcal Pneumonia: Incidence Study

HCAP: Healthcare associated pneumonia

HIV: Human immunodeficiency virus

HR: Heart rate

ICU: Intensive care unit

IDSA: Infectious Diseases Society of America

Instrument: Seemingly random variable that is strongly associated with the predictor variable under study but not associated with the outcome.

Instrumental Variable Analysis: Makes use of an IV or an instrument to control for unmeasured variation between confounders.

IV: Intravenous

Logistic Regression: A statistical method for analyzing a dataset in which there are one or more independent variables that determine an outcome. The outcome

is measured with a dichotomous variable (in which there are only two possible outcomes)

Macrolide: Antimicrobials that are used to treat gram positive bacteria, such as S. pneumoniae, and some gram negative bacteria like H. influenzae. Macrolides inhibit protein synthesis in bacteria by binding to the 50S ribosomal subunit and preventing polypeptide elongation and thus protein synthesis.

Pneumonia Severity Index (PSI): Used to predict the need for hospitalization for a patient who has community acquired pneumonia

Propensity Score: Probability of treatment assignment conditional on observed baseline characteristics.

PSI: Pneumonia severity index

SBP: Systolic blood pressure

Severe: This variable was created from a score based on the severity criteria recommended by the ATS/IDSA.

RR: Respiratory rate

VAP: Ventilator-associated pneumonia

30 day mortality: All cause-mortality within 30 days of hospital discharge.

APPENDIX II: ADDITIONAL TABLES

ECS: Multivariable Logistic Regression, Data-based Method for Assessment

Variable	Validity[a]	Precision[b]	Percent Change	
Full Model				
Macrolide and Beta-Lactam + Covariates (dem_age + lab_glucose + smoking.current + hx_ivdruguse + hx_cirrhosis + lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0951	0.0788		
remove age	-0.0951	0.0787	0.01%	
remove glucose	-0.0964	0.0787	1.31%	
remove smoking	-0.0964	0.0787	1.32%	
remove IV drug use	-0.0960	0.0788	0.89%	
remove cirrhosis	-0.0964	0.0787	1.34%	
remove hematocrit	-0.0901	0.0786	5.30%	
remove residence in nursing home	-0.0817	0.0784	14.06%	+
remove CHF	-0.0914	0.0787	3.92%	**
remove COPD	-0.0811	0.0785	14.69%	**+
remove HR	-0.1072	0.0785	12.74%	**+
remove severe	-0.1189	0.0782	24.95%	**+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on ECS
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

ECS: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
Remove dem_age				
Macrolide and Beta-Lactam + Covariates (lab_glucose + smoking.current + hx_ivdruguse + hx_cirrhosis + lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0951	0.0787		
remove glucose	-0.0964	0.0786	1.33%	
remove smoking	-0.0969	0.0787	1.88%	
remove IV drug use	-0.0961	0.0787	1.06%	
remove cirrhosis	-0.0964	0.0787	1.34%	
remove hematocrit	-0.0901	0.0786	5.24%	
remove residence in nursing home	-0.0812	0.0783	14.58%	+
remove CHF	-0.0907	0.0786	4.62%	**
remove COPD	-0.0790	0.0785	16.90%	**+
remove HR	-0.1098	0.0784	15.43%	**+
remove severe	-0.1176	0.0782	23.67%	**+
Remove dem_age + lab_glucose				
Macrolide and Beta-Lactam + Covariates (smoking.current + hx_ivdruguse + hx_cirrhosis + lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0964	0.0786		
remove smoking	-0.0982	0.0786	1.92%	
remove IV drug use	-0.0973	0.0786	0.95%	
remove cirrhosis	-0.0977	0.0786	1.34%	
remove hematocrit	-0.0914	0.0785	5.18%	

a, Beta coefficient for the effect of macrolide + beta-lactam usage on ECS
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

ECS: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
remove residence in nursing home	-0.0825	0.0782	14.41%	+
remove CHF	-0.0929	0.0785	3.56%	**
remove COPD	-0.0813	0.0783	15.68%	**+
remove HR	-0.1127	0.0783	16.99%	**+
remove severe	-0.1206	0.0781	25.20%	**+
Remove dem_age + lab_glucose + smoking.current				
Macrolide and Beta-Lactam + Covariates (hx_ivdruguse + hx_cirrhosis + lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0982	0.0786		
remove IV drug use	-0.0996	0.0785	1.42%	
remove cirrhosis	-0.0996	0.0785	1.39%	
remove hematocrit	-0.0933	0.0784	5.02%	
remove residence in nursing home	-0.0842	0.0781	14.32%	+
remove CHF	-0.0940	0.0784	4.27%	**
remove COPD	-0.0849	0.0783	13.51%	**+
remove HR	-0.1159	0.0782	18.00%	**+
remove severe	-0.1214	0.0780	23.58%	**+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on ECS
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

ECS: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
Remove dem_age + lab_glucose + smoking.current + hx_ivdruguse				
Macrolide and Beta-Lactam + Covariates (hx_cirrhosis + lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0996	0.0785		
remove cirrhosis	-0.1011	0.0785	1.54%	
remove hematocrit	-0.0947	0.0784	4.96%	
remove residence in nursing home	-0.0855	0.0781	14.18%	+
remove CHF	-0.0953	0.0784	4.35%	**
remove COPD	-0.0860	0.0782	13.64%	**+
remove HR	-0.1183	0.0782	18.81%	**+
remove severe	-0.1234	0.0780	23.85%	**+
Remove dem_age + lab_glucose + smoking.current + hx_ivdruguse + hx_cirrhosis				
Macrolide and Beta-Lactam + Covariates (lab_hematocrit + risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.1011	0.0785		
remove hematocrit	-0.0962	0.0783	4.87%	
remove residence in nursing home	-0.0871	0.0780	13.93%	+
remove CHF	-0.0968	0.0784	4.32%	**
remove COPD	-0.0876	0.0782	13.41%	**+
remove HR	-0.1199	0.0781	18.59%	**+
remove severe	-0.1251	0.0779	23.71%	**+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on ECS
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

ECS: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
Remove dem_age + lab_glucose + smoking.current + hx_ivdruguse + hx_cirrhosis + lab_hematocrit				
Macrolide and Beta-Lactam + Covariates (risk_nursinghome + hx_chf + hx_copd + exam_hr + severe)	-0.0962	0.0783		
remove residence in nursing home	-0.0830	0.0779	13.73%	**+
remove CHF	-0.0925	0.0782	3.85%	**
remove COPD	-0.0807	0.0780	16.16%	**+
remove HR	-0.1141	0.0780	18.53%	**+
remove severe	-0.1235	0.0778	28.32%	+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on ECS
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

30 Day Mortality: Multivariable Logistic Regression, Data-based Method for Assessment

Variable	Validity[a]	Precision[b]	Percent Change	
Full Model				
Macrolide and Beta-Lactam + Covariates (smoking.current + hx_copd + hx_chf + risk_nursinghome + hx_cirrhosis + lab_glucose + hx_ivdruguse + lab_hematocrit + exam_hr + severe + dem_age)	-0.0734	0.7426		
remove smoking	-0.0741	0.1495	0.97%	
remove COPD	-0.0767	0.1494	4.59%	

a, Beta coefficient for the effect of macrolide + beta-lactam usage on 30 Day Mortality
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

30 Day Mortality: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
remove CHF	-0.0769	0.1494	4.78%	
remove residence in nursing home	-0.0962	0.1483	31.14%	+
remove cirrhosis	-0.0679	0.1493	7.44%	
remove glucose	-0.0581	0.1491	20.86%	+
remove IV drug use	-0.0668	0.1494	8.91%	**
remove hematocrit	-0.0361	0.1487	50.83%	**+
remove HR	-0.0500	0.1484	31.89%	**+
remove severe	-0.0219	0.1480	70.18%	**+
remove age	-0.0822	0.0822	12.11%	**+
Remove smoking.current				
Macrolide and Beta-Lactam + Covariates (hx_copd + hx_chf + risk_nursinghome + hx_cirrhosis + lab_glucose + hx_ivdruguse + lab_hematocrit + exam_hr + severe + dem_age)	-0.0741	0.1495		
remove COPD	-0.0769	0.1494	3.83%	
remove CHF	-0.0779	0.1494	5.24%	
remove residence in nursing home	-0.0973	0.1482	31.35%	+
remove cirrhosis	-0.0686	0.1493	7.43%	
remove glucose	-0.0588	0.1491	20.60%	+
remove IV drug use	-0.0671	0.1493	9.38%	**
remove hematocrit	-0.0371	0.1486	49.93%	**+
remove HR	-0.0505	0.1484	31.86%	**+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on 30 Day Mortality
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

30 Day Mortality: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
remove severe	-0.0228	0.1480	69.25%	**+
remove age	-0.0921	0.1476	24.34%	**+
Remove smoking.current + hx_copd				
Macrolide and Beta-Lactam + Covariates (hx_chf + risk_nursinghome + hx_cirrhosis + lab_glucose + hx_ivdruguse + lab_hematocrit + exam_hr + severe + dem_age)	-0.0769	0.1494		
remove CHF	-0.0823	0.1492	6.99%	
remove residence in nursing home	-0.1001	0.1481	30.22%	+
remove cirrhosis	-0.0713	0.1492	7.23%	
remove glucose	-0.0622	0.1490	19.11%	+
remove IV drug use	-0.0695	0.1492	9.64%	**
remove hematocrit	-0.0375	0.1484	51.27%	**+
remove HR	-0.0550	0.1483	28.43%	**+
remove severe	-0.0265	0.1479	65.55%	**+
remove age	-0.0968	0.1474	25.88%	**+
Remove smoking.current + hx_copd + hx_chf				
Macrolide and Beta-Lactam + Covariates (risk_nursinghome + hx_cirrhosis + lab_glucose + hx_ivdruguse + lab_hematocrit + exam_hr + severe + dem_age)	-0.0823	0.1492		
remove residence in nursing home	-0.1058	0.1479	28.64%	+
remove cirrhosis	-0.0764	0.1490	7.12%	

a, Beta coefficient for the effect of macrolide + beta-lactam usage on 30 Day Mortality
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

30 Day Mortality: Multivariable Logistic Regression, Data-based Method for Assessment (continued)

Variable	Validity[a]	Precision[b]	Percent Change	
remove glucose	-0.0670	0.1489	18.51%	+
remove IV drug use	-0.0748	0.1490	9.14%	**
remove hematocrit	-0.0421	0.1483	48.87%	**+
remove HR	-0.0602	0.1482	26.82%	**+
remove severe	-0.0330	0.1477	59.83%	**+
remove age	-0.1089	0.1471	32.42%	**+
Remove smoking.current + hx_copd + hx_chf + hx_cirrhosis				
Macrolide and Beta-Lactam + Covariates (risk_nursinghome + lab_glucose + hx_ivdruguse + lab_hematocrit + exam_hr + severe + dem_age)	-0.0764	0.1490		
remove residence in nursing home	-0.0996	0.1477	30.36%	+
remove glucose	-0.0614	0.1487	19.70%	+
remove IV drug use	-0.0686	0.1489	10.23%	**+
remove hematocrit	-0.0375	0.1481	50.96%	**+
remove HR	-0.0543	0.1480	28.90%	**+
remove severe	-0.0258	0.1475	66.19%	**+
remove age	-0.1039	0.1469	35.94%	**+

a, Beta coefficient for the effect of macrolide + beta-lactam usage on 30 Day Mortality
b, Standard error
+, changed the beta coefficient of macrolide + beta-lactam more than 10%
**, statistically significant in full model so will be included in final model

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