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Review

Update on the combination effect of macrolide antibiotics in community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia (CAP) is a leading cause of death from an infectious cause worldwide. Guideline-concordant antibiotic therapy initiated in a timely manner is associated with improved treatment responses and patient outcomes. In the post-antibiotic era, much of the morbidity and mortality of CAP is as a result of the interaction between bacterial virulence factors and host immune responses. In patients with severe CAP, or who are critically ill, there is a lot of emerging observational evidence demonstrating improved survival rates when treatment using combination therapy with a β-lactam and a macrolide is initiated, as compared to other antibiotic regimes without a macrolide. Macrolides in combination with a β-lactam antibiotic provide broader coverage for the atypical organisms implicated in CAP, and may contribute to antibacterial synergism. However, it has been postulated that the documented immunomodulatory effects of macrolides are the primary mechanism for improved patient outcomes through attenuation of bacterial virulence factors and host systemic inflammatory responses. Despite concerns regarding the limitations of observational evidence and the lack of confirmatory randomized controlled trials, the potential magnitude of mortality benefits estimated at 20–50% cannot be overlooked. In light of recent data from a number of trials showing that combination treatment with a macrolide and a suitable second agent is justified in all patients with severe CAP, such treatment should be obligatory for those admitted to an intensive care setting.

Abbreviations: CAP, community-acquired pneumonia; PIS, pneumonia severity index; ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; RFQ, respiratory fluoroquinolone; LPS, lipopolysaccharide; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; MIC, minimum inhibitory concentration; VAP, ventilator-associated pneumonia; IL-8, interleukin 8; ERK, extracellular signal-regulated kinase; NO, nitric oxide; RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; RR, risk ratio

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Contents

1. Introduction

Community-acquired pneumonia (CAP) is the leading cause of death from an infectious cause worldwide. It is a condition that affects, but is not limited to, the lung, and is a systemic disorder that can progress rapidly to shock, multiple organ failure, and death. Those with mild presentations of CAP, and without significant co-morbidities, can often be managed safely in a community or an outpatient setting. Those with moderate or severe presentations are at the greatest risk for developing complications and death; therefore, hospitalization is recommended [1]. Severe CAP is the most common cause of admission to the intensive care unit (ICU) for an infectious condition and has a significant impact on both healthcare costs and utilization.

Predicting who will develop moderate or severe CAP is difficult, as it involves an interplay between bacterial virulence factors, host immune responses, and treatment [2]. The importance of clinical judgment in determining pneumonia severity should not be underestimated; however, physician experience is variable, and clinical signs and symptoms are at times insufficiently accurate. A number of scoring systems have been developed to determine the severity of pneumonia; the commonly used CURB65 and pneumonia severity index (PSI) help predict mortality rates, while the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria are useful for predicting the requirements for admission to the ICU. Potential biomarkers, such as CRP and procalcitonin, can be used to assist the clinical assessments of pneumonia severity and associated systemic inflammatory responses; however, evidence of their efficacy is limited, and there no consensus yet on the use of biomarkers in CAP [3]. Treatment failure in patients with CAP is associated with a high mortality rate; thus, the integration of clinical scoring systems and biomarkers to help predict early and late treatment failure may be of use in its clinical management [4].

The burden of morbidity and mortality in CAP is influenced by a number of factors, including bacterial virulence and pathogenicity, host pathogen interactions, innate and adaptive immune responses, early antibiotic initiation, antimicrobial efficacy, and underlying comorbid disease [2,5].

2. Guidelines for the treatment of CAP

Bacteriologic causes account for the majority of those hospitalized with CAP, although a causative organism is isolated in fewer than 50% of cases [6]. The most frequently isolated bacteria include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In addition, atypical pathogens such as *Mycoplasma pneumoniae*, and intracellular pathogens, such as *Legionella* and *Chlamydophila pneumoniae*, can also be implicated. Viral causes of pneumonia remain common, and testing for influenza is recommended during seasonal outbreaks.

Antibiotic therapy is the cornerstone of CAP treatment. In an ideal clinical scenario, the appropriate antibiotic will be selected against the known causative pathogen; however, in practice, it is not possible to determine causative pathogens at presentation. Early initiation of empiric appropriate antibiotic therapy (e.g., in the emergency department) in moderate/severe CAP is critical, as delays in treatment are associated with increased morbidity and mortality [7].

The published guidelines for the treatment of CAP from the British Thoracic Society, European Respiratory Society/European society of Clinical Microbiology and Infectious Disease, and the ATS/IDSA have remained unchanged for a number of years [3,8,9]. In regions of low macrolide resistance (<25%), macrolide monotherapy can be used for the treatment of mild CAP as an alternative agent to penicillin. However, in moderate/severe CAP, and in patients with risk factors for pathogen resistance, all guidelines recommend broader antimicrobial coverage to lower treatment failure rates. Treatment response rates of 90% or greater can be achieved with the use of a macrolide in addition to a β-lactam (usually a third-generation cephalosporin) or monotherapy with a respiratory fluoroquinolone (RFQ). In severe CAP necessitating ICU admission, guidelines recommend dual antibiotic therapy with a third-generation cephalosporin and either a macrolide (Level II) or a RFQ (Level I) [9].

In the setting of moderate and severe CAP, general adherence to the published guidelines for CAP treatment is poor. Most large studies have found that guideline-concordant therapy is given in fewer than 50% of cases, which may lead to an increased rate of treatment failure and have an adverse effect on patient outcomes [10,11]. Guideline-concordant therapy is an important outcome measure of clinical practice and, when delivered, ensures patients receive the optimal evidence-based treatment [12].

3. Macrolides

Macrolides are a class of antibiotics, first marketed in 1952, for the treatment of pulmonary infections due to their broad