Evidence for use of macrolides in severe CAP

SYSTEMATIC REVIEW

Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis

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ABSTRACT

It is unclear whether in the treatment of community- acquired pneumonia (CAP) beta-lactam plus macrolide antibiotics lead to better survival than beta-lactam alone. We report a systematic review and meta-analysis. Trials and observational studies published in English were included, if they provided sufficient data on odds ratio for all-cause mortality for a beta-lactam plus macrolide regimen compared with beta-lactam alone. Two investigators independently searched for eligible articles. Of 514 articles screened, 14 were included: two open-label randomized controlled trials (RCTs) comprising 1975 patients, one non-RCT interventional study comprising 1011 patients and 11 observational studies comprising 33 332 patients. Random-model meta-analysis yielded an odds ratio for all-cause death for beta-lactam plus macrolide compared with beta-lactam alone of 0.80 (95% CI 0.69–0.92, P = 0.002) with substantial heterogeneity (I^2 = 59%, P for heterogeneity = 0.002). Severity-based subgroup analysis and meta-regression revealed that adding macrolide had a favourable effect on mortality only for severe CAP. Of the two RCTs, one suggested that macrolide plus beta-lactam lead to better outcome compared with beta-lactam alone, while the other did not. Subgrouping based on study design, that is, RCT versus non-RCT, which was almost identical to subgrouping based on severity, revealed substantial inter-subgroup heterogeneity. Compared with beta-lactam alone, beta- lactam plus macrolide may decrease all-cause death only for severe CAP. However, this conclusion is tentative because this was based mainly on observational studies.

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REVIEW

Community-acquired pneumonia: still a major burden of disease

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Macrolides

As discussed above, macrolides are an important component of the antibiotic treatment strategies of patients with severe CAP. It is considered by many that these benefits are not purely because of their antimicrobial activity, but also because of their considerable adjuvant properties that have been attrib- uted to inhibition of synthesis of bacterial virulence factors, counteracting the pro-inflammatory and cytotoxic potential of bactericidal antibiotics that promote disintegration of bacterial pathogens with release of toxins such as pneumolysin (Ply) in the case of the pneumococcus, and the secondary, anti-inflammatory immunomodulatory properties of these agents that target various types of immune and structural cells and their inflammatory mediators [24,25].

Septic shock from community-onset pneumonia: is there a role for aspirin plus macrolides combination?

Intensive Care Med (2016) 42:301–302

The use of macrolides has been previously associated with lower mortality in patients with severe pneumonia, and the administration of clarithromycin has been associated with

restoration of the balance between pro-inflammatory versus anti-inflammatory mediators in patients with Gram-negative sepsis and ventilator-associated pneumonia (VAP). A further double-blind, ran- domized, multicenter trial found that clarithromycin accelerates resolution of VAP, and favors weaning from mechanical ventilation [2].

2. Giamarellos-Bourboulis EJ, Peche`re JC, Routsi C, Plachouras D, Kollias S, Raftogiannis M, Zervakis D, Baziaka F, Koronaios A, Antonopoulou A, Markaki V, Koutoukas P, Papadomichelakis E, Tsaganos T, Armaganidis A, Koussoulas V, Kotanidou A, Roussos C, Giamarellou H (2008) Effect of clarithromycin in patients with sepsis and ventilator- associated pneumonia. Clin Infect Dis 46:1157–1164

Are macrolides now obligatory in severe community-acquired pneumonia?

Intensive Care Med (2010) 36:562–564

That macrolide antibiotics appear to confer a signifi- cant survival advantage in patients with severe community-acquired pneumonia is not a new concept, with multiple observational and retrospective studies demonstrating substantial mortality benefits [2–7]. How- ever, as has been pointed out in many editorials and reviews, none of these studies are prospective, random- ized controlled trials. In the absence of scientifically irrefutable evidence, at what point does the weight of data in favor of using macrolides become so overwhelming that their use is obligatory?

There is substantive evidence for macrolides having an immunomodulating effect on the host immune response [11], and this may be a key factor in their apparent clinical benefit. However, the recent demon- stration that most patients with community-acquired pneumonia and sepsis-related organ dysfunction have high systemic pneumococcal bacterial loads [12] suggests to me that the now well-recognized anti-toxin effects of macrolides, even in macrolide-resistant organisms [13], also play a key role. Importantly, neither fluroquinolones nor tetracyclines were observed to have anti-pneumolysin effects in pneumococci [13].

Given the overwhelming weight of data, I believe that macrolides should be obligatory in all cases of severe community-acquired pneumonia. With odds ratios for death ranging from two to six times greater in non-mac- rolide-treated patients [1, 3, 4, 7], and given the low risk and cost of such treatment, refusal to do so out of scep- ticism of the data is unjustifiable.

Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia

Intensive Care Med (2010) 36:612–620

Objective: To assess the effect on survival of macrolides or fluoroquinolones in intubated patients admitted to the intensive care unit (ICU) with severe community- acquired pneumonia (severe CAP). Methods: Prospective, observa- tional cohort, multicenter study conducted in 27 ICUs of 9 European countries. Two hundred eighteen consecutive patients requiring inva- sive mechanical ventilation for an admission diagnosis of CAP were recruited.

In this cohort, a Cox regression analysis adjusted by severity identi- fied that macrolide use was associated with lower ICU mortality (hazard ratio, HR 0.48, confidence intervals, 95% CI 0.23–0.97, P = 0.04) when compared to the use of fluoroquino- lones. When more severe patients presenting severe sepsis and septic shock were analyzed (n = 92), similar results were obtained (HR 0.44, 95% CI 0.20–0.95, P = 0.03).

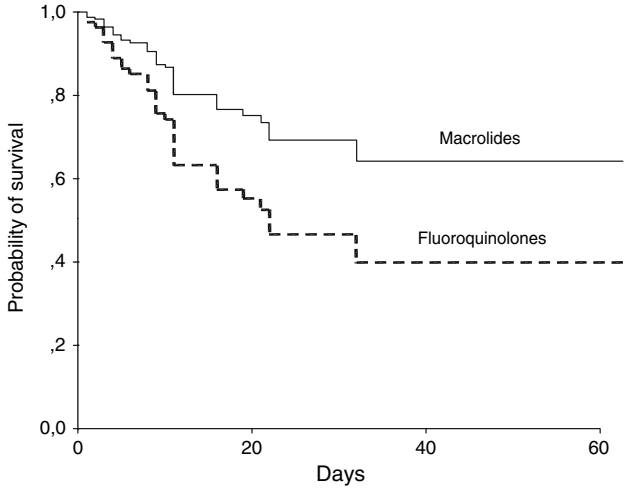

Fig. 2 Survival graph for patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

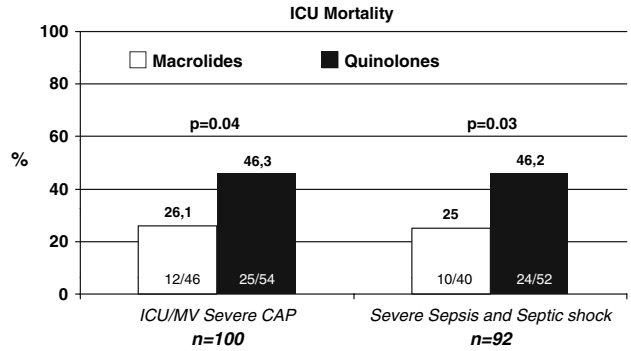

Fig. 1 Intensive care unit mortality among IDSA/ATS guideline-adherent patients according to the treatment in combination with a macrolide or a quinolone

COMMENTARY

Macrolides and community-acquired pneumonia: is quorum sensing the key?

Matt P Wise[1]*, David W Williams[2], Michael AO Lewis[2] and Paul J Frost[1]

Wise *et al*. *Critical Care* 2010, **14**:181

Combination therapy with two antimicrobial agents
is superior to monotherapy in severe community- acquired pneumonia, and recent data suggest that addition of a macrolide as the second antibiotic might be superior to other combinations. This observation requires con rmation in a randomised control trial, but this group of antibiotics have pleiotropic e ects that extend beyond bacterial killing. Macrolides inhibit bacterial cell-to-cell communication or quorum sensing, which not only might be an important mechanism of action for these drugs in severe infections but may also provide a novel target for the development of new anti-infective drugs.

In addition to activity against atypical bacteria, macro- lides have ubiquitous immunomodulatory eðects. Specu- lating how this group of drugs might offer a survival advantage when added to a à-lactam is therefore of interest, and several plausible mechanisms exist.

Moreover, studies limited to pneu- mococcal disease demonstrate that addition of a macro- lide improves survival [8]. It also seems improbable that synergistic killing is responsible, as equivalency with fluoroquinolones would be expected.

Many researchers have focused on the pleiotropic immunomodulatory eðects [9] observed with macrolides as the reason why these agents may be beneficial in CAP. Macrolides, at doses lower than those required for antibacterial activity, alter the production of cytokines and chemokines, and reduce cellular infiltrates and mucous production [9]. e immunomodulatory eðects of macrolides are illustrated by diðuse panbronchiolitis. A chronic progressive lung disease found largely in Japan, diðuse panbronchiolitis is characterised by mixed restrictive and obstructive pulmonary function, inter- stitial infiltrates and *Pseudomonas aeruginosa* infection. Long-term, low-dose macrolide treatment improves lung function and increases 10-year survival rates from around 15 to 90% [9].

Macrolides are now being explored in new therapeutic strategies for a wide range of pulmonary and extra- pulmonary conditions, including asthma, cystic fibrosis, rhinosinusitis, inflammatory bowel disease, psoriasis and rosacea [9].

Quorum sensing describes bacterial cell-to-cell communication that occurs as a function of changing cell density. ese communication pathways are important in the pathogenesis of bacterial species causing human disease, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *P. aeruginosa* [10,11]. Quorum-sensing bacteria produce and release signal molecules or autoinducers, which regulate gene expres- sion within the bacterial population and are closely linked to both biofilm formation and expression of virulence factors. Biofilms are structured populations of bacteria within a polysaccharide matrix, and these growth forms are more resistant to antibiotics.

Macrolides at subminimum inhibitory concentrations have been demonstrated to antagonise quorum sensing in *P. aeruginosa*, resulting in diminished virulence, bio- film formation and oxidative stress response [13].

At a time when few new antimicrobial agents are being commercially developed for clinical use and the burden of infection caused by multiresistant bacteria is increasing, the need for novel approaches to the management of infection is essential. Quorum sensing determines both bacterial virulence and biofilm formation; it is a common pathway for pathogens and represents an attractive new target for the development of drugs in the fight against infection [10].

REVIEW

New aspects in the management of pneumonia

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Prina et al. Critical Care (2016) 20:267

The best antibiotic strategy for the treatment of CAP is currently a subject of debate. For severe CAP, international guidelines suggest the use of two antibiotics such as a β- lactam plus a macrolide or a β-lactam plus respiratory quinolone (levofloxacin or moxifloxacin) [40]. However, many observational studies and a recent meta-analysis have shown that the use of a β-lactam plus a macrolide is the best choice because it is associated with a better outcome and lower mortality in patients with severe CAP, especially in bacteremic pneumococcal CAP. The mechanisms responsible for the favorable effects related to the use of macrolides are not clear and have been attributed in part to their immunomodulatory effect, as observed in some studies [41]. In vitro and in vivo experimental models have shown that macrolides inhibit cytokine secretion by inflam- matory and structural cells of the respiratory tract [42].

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42. Kovaleva A, Remmelts HH, Rijkers GT, Hoepelman AI, Biesma DH, Oosterheert JJ. Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. J Antimicrob Chemother. 2012;67:530–40.

Journal of Antimicrobial Chemotherapy (2007) **60**, 1155–1158
doi:10.1093/jac/dkm338
Advance Access publication 10 September 2007

JAC

Comparison of the effects of macrolides, amoxicillin, ceftriaxone, doxycycline, tobramycin and fluoroquinolones, on the production of pneumolysin by *Streptococcus pneumoniae in vitro*

Objectives: To compare the effects of subinhibitory concentrations of amoxicillin, ceftriaxone, azithromycin, clarithromycin, erythromycin, telithromycin, clindamycin, ciprofloxacin, moxifloxacin, tobramycin and doxycycline on pneumolysin production by a macrolide-susceptible strain and two macrolide-resistant strains [erm(B) or mef(A)] of Streptococcus pneumoniae.

Methods: Pneumolysin was assayed using a functional procedure based on the influx of Ca^{21} into human neutrophils.

Results: Only the macrolides/macrolide-like agents caused significant attenuation of the production of pneumolysin, which was evident with all three strains of the pneumococcus.

Conclusions: Macrolides, at sub-MICs, but not other classes of antibiotic, subvert the production of pneumolysin, even in the presence of (and irrespective of the mechanism of) macrolide resistance in S. pneumoniae.

Macrolides and Mortality in Severe Community-Acquired Pneumonia*

Crit Care Med Feb 2014 Vol 42 No 2

A survival advantage of macrolides is appealing and plau- sible, as in addition to their known antimicrobial activity, mac- rolides have immunomodulatory effects attributed to their 14 and 15 member lactone rings. The clinical evidence of this is classically demonstrated in diffuse panbronchiolitis but also in cystic fibrosis and non-cystic fibrosis bronchiectasis where macrolides have demonstrated benefits that appear to go beyond their antimicrobial activity (7).

Macrolides and Mortality in Critically Ill Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis*

Crit Care Med Feb 2014 Vol 42 No 2

Conclusions: In observational studies of almost 10,000 critically ill patients with community-acquired pneumonia, macrolide use was associated with a significant 18% relative (3% absolute) reduction in mortality compared with nonmacrolide therapies. After pooling data from studies that provided adjusted risk estimates, an even larger mortality reduction was observed. These results suggest that macrolides be considered first-line combination treatment in critically ill patients with community-acquired pneumonia and support current guidelines. (*Crit Care Med* 2014; 42:420–432)

If our findings are not a result of chance, bias, or confound- ing, the mortality differences observed might relate, as men- tioned above, to the non-antimicrobial immune modulatory properties of macrolides, including alterations in pro- and anti-inflammatory cytokines (tumor necrosis factor [TNF-α], interleukin [IL]-1, IL-6, IL-8, and interferon-γ), and decreased neutrophil chemotaxis, adhesion, and/or oxidative metabo- lism (51). In addition, macrolides have been shown to inhibit biofilm formation and decrease mucus hypersecretion, leading to improved mucociliary clearance (51). In a study examin- ing patterns of cytokine gene expression (52) greater proin- flammatory (IL-10 and TNF-α) messenger RNA levels were observed in ICU patients with severe sepsis and septic shock when compared with noncritically ill bacteremic patients or healthy controls. Furthermore, in a recent study in critically ill patients with ventilator-associated pneumonia (53), treatment with clarithromycin restored the balance between pro- and anti-inflammatory mediators in patients with sepsis.

So, what is the clinical relevance of our findings? A random- ized trial might be considered prohibitive, as to demonstrate a 3% absolute mortality difference with a control group event rate of 24% and 80% power would require approximately 6,200 patients in total. Until such a trial is conducted, our anal- ysis represents a synthesis of the best available evidence. Our analysis might also suggest that “enough” observational stud- ies of this question have been conducted and that a morato- rium on nonrandomized studies might be in order. Regardless, based on our results, we would suggest that macrolide therapy may be of benefit in critically ill patients with CAP and should be used in combination as per guidelines.

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Advance Access publication 8 December 2004

JAC

Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions?

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***Background*: It has been recognized for more than 20 years that the macrolides have immunomodulatory effects that are beneficial for those suffering from chronic pulmonary inflammatory syndromes, such as diffuse panbronchiolitis, cystic fibrosis, asthma and bronchiectasis. The macrolides have consistently been associated with decreased length of stay and mortality when used alone or in combination with β-lactam antibiotics. This effect can be demonstrated against combinations consisting of β-lactams and other antibiotics active against 'atypical chest pathogens' when treating community-acquired pneumonia (CAP) in hospitalized patients. As such, it appears that the macrolides' effects in CAP patients are more than just antibacterial in nature.**

***Aims of this review*: This review aims: to give the reader information on the background areas described, as well as related areas; to review the CAP benefits with macrolides and how they may be related to the immunomodulatory properties they demonstrate, albeit in a shorter period of time than previously demonstrated with chronic pulmonary disorders; to use *ex vivo* data to support these extrapolations.**

***Literature search*: A literature search using Medline was conducted from 1966 onwards, searching for articles with relevant key words such as macrolide, diffuse panbronchiolitis, community-acquired pneumonia, biofilm, immunomodulation, cystic fibrosis, erythromycin, clarithromycin, roxithromycin and azithromycin, bronchiectasis and asthma. When appropriate, additional references were found from the bibliographies of identified papers of interest. Any relevant scientific conference proceedings or medical texts were checked when necessary.**

***Conclusions*: (1) Research into macrolide immunomodulation for chronic pulmonary disorders demonstrates consistent positive effects, although of types other than seen with diffuse panbronchiolitis. These effects, together with their inhibitory activity on biofilms, have the potential to make them a useful option. (2) The benefits for CAP are consistent, and higher when a macrolide is given with another atypical agent than if the other atypical agent is given alone, suggesting a non-antibacterial benefit. (3) Recent research of the immunomodulatory properties of azithromycin imply that azithromycin may have a previously unknown short-term biphasic effect on inflammation modulation: enhancement of host defence mechanisms shortly after initial administration followed by curtailment of local infection/inflammation in the following period. (4) Additional *in vivo* research is needed prior to developing any firm conclusions.**

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Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia

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ABSTRACT: Recent studies suggest that macrolides may have beneficial effects for patients at risk for certain infections. The current authors examined the effect of macrolide therapy on 30- and 90-day mortality for patients with severe sepsis caused by pneumonia.

A retrospective cohort study was conducted at two tertiary teaching hospitals. Eligible subjects were admitted with a diagnosis of, had chest radiography consistent with, and had a discharge diagnosis of pneumonia and clinical criteria of severe sepsis. Subjects were considered to be on macrolides if they received at least one dose within 48 h of admission.

Severe sepsis was present in 237 (30.1%) subjects, out of whom 104 (43.9%) received macrolides. Mortality was 20.3% at 30 days and 24.5% at 90 days. In the multivariable analysis, the use of macrolide was associated with decreased mortality at 30 days (hazard ratio (HR) 0.3, 95% confidence interval (CI) 0.2–0.7) and at 90 days (HR 0.3, 95% CI 0.2–0.6) in patients with severe sepsis and in patients with macrolide-resistant pathogens (HR 0.1, 95% CI 0.02–0.5).

Macrolide use was associated with decreased mortality in patients with severe sepsis due to pneumonia and macrolide-resistant pathogens. Confirmatory studies are needed to determine whether macrolide therapy may be protective for patients with sepsis.