

## Prophylactic macrolides for chronic obstructive pulmonary disease in the community:

a decision for GPs

Chronic obstructive pulmonary disease (COPD) is a common progressive respiratory condition with a heavy symptom burden and was the third leading cause of death worldwide in 2019.<sup>1</sup> One tool in the GP's arsenal is prophylactic antibiotics, with macrolides being the most effective. These are thought to both reduce the frequency of infective exacerbations via the antimicrobial effect of neutrophil activation and combat excessive airway inflammation by induction of T helper type 1 lymphocytes, which act to combat inflammation and cause thinning of the bacterial biofilm.<sup>2</sup> The benefits of macrolides have been proven, but which patients are most likely to benefit from them, and which healthcare providers are best placed to identify them?

### PATIENTS WITH MILD OR SEVERE DISEASE

The first question to explore is whether prophylactic macrolide use could be of most benefit to those with mild COPD or those with moderate-to-severe disease. A meta-analysis examining the effect of macrolide prophylaxis in the moderate-to-severe disease cohort has shown a significant reduction in the number of exacerbations with macrolide use versus placebo across all 14 studies examined.<sup>3</sup> Furthermore, six of seven studies within this analysis showed the time to first exacerbation was significantly lengthened in the treatment groups.<sup>3</sup> However, participants who had already been experiencing exacerbations requiring hospitalisation showed no significant reduction in the frequency of hospitalisation with macrolide use (Figure 1). It may be that this cohort's disease had progressed to the point where prophylactic treatment could provide minimal benefit.

In mild disease, there is a gap in the literature addressing macrolide prophylaxis use, with no specific recommendations currently in place. Interestingly, the meta-analysis showed that the odds ratio for having

one or more exacerbations on prophylactic macrolide therapy versus placebo was 0.31 (0.13–0.72). This suggests that the number of patients with mild disease having zero exacerbations in a year is increased with the use of prophylactic macrolides.

### PATIENTS WITH COEXISTING ASTHMA

Given that severe COPD may not be as strong an indication for the use of prophylactic macrolides as was previously thought, their utility in the patient cohort with respiratory comorbidities such as asthma should be considered. A review of the literature shows evidence of a benefit to long-term macrolide therapy in these patients, who may be classified as having 'COPD–asthma overlap syndrome'.<sup>4</sup> Given that this syndrome is a predictor for lower quality of life (QoL),<sup>5</sup> interventions that might specifically benefit these patients are needed. In several small cohort studies,<sup>6–7</sup> patients with asthma saw a benefit in pulmonary function tests (PFTs) and QoL after a 6-week course of macrolides. Could this effect be applied to COPD patients who show asthmatic features?

Improvement in PFTs and QoL are very important markers for COPD therapy, but the use of prophylactic macrolides may have even more utility as a steroid-sparing agent for patients who require frequent prescriptions for oral corticosteroids. This effect was first observed in the 1970s in a group of patients with prednisolone-responsive asthma.<sup>8</sup> In this double-blind placebo-controlled crossover trial, 85% of participants saw improvements not just in corticosteroid requirement, but also in sputum production, PFTs, and bronchodilator requirements. More recently, a small case series showed that within 3 to 6 months of initiation of treatment with clarithromycin, and throughout the 12-month follow-up, two of three patients discontinued prednisolone therapy altogether, while the third patient displayed improved spirometry readings

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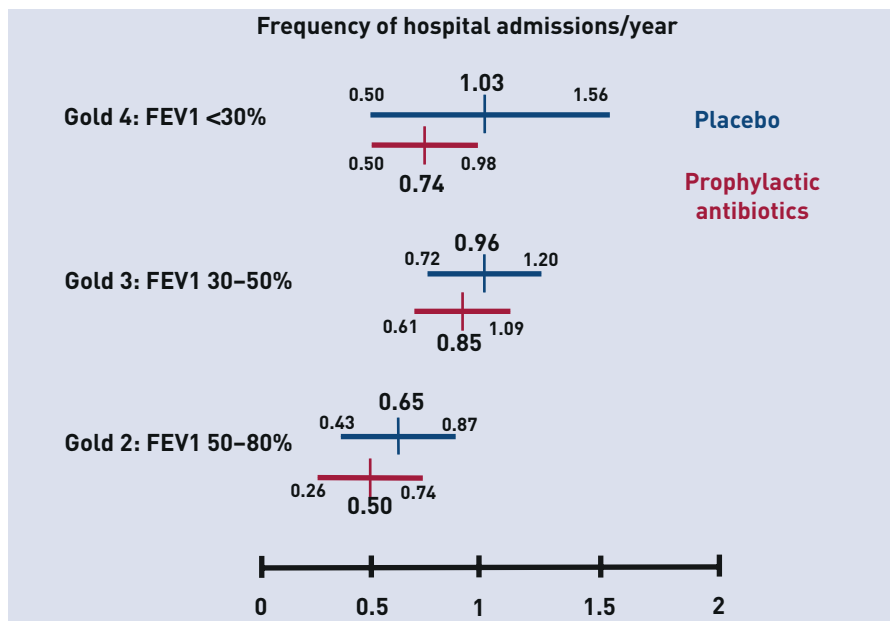
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**Figure 1. Comparison of frequency of exacerbations requiring hospital admissions in patients with Gold stages 2, 3, and 4 disease on prophylactic antibiotics versus placebo: no significant reduction.**

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and increasingly better QoL.<sup>7</sup>

This guidance can be applied effectively to clinical practice to improve outcomes for COPD patients who show asthmatic features. The evidence suggests that this group would likely see improvements in pulmonary function regarding their asthma, while synergistically improving QoL by reducing the frequency of infective exacerbations by the antimicrobial effect.

## PATIENTS WITH GENERAL COMORBIDITIES

COPD is a complex condition, made even more complex by the high likelihood of non-respiratory comorbidities. Common non-respiratory conditions that may be impacted by long-term macrolide therapy are type 2 diabetes mellitus and cardiac arrhythmias such as atrial fibrillation.

### Type 2 diabetes mellitus

As mentioned previously, prophylactic macrolide therapy may have some utility as a steroid-sparing agent in patients with asthma,<sup>7–8</sup> and this may be applicable to patients with COPD who show asthmatic features. Hospital admissions for COPD exacerbations frequently incorporate a course of oral corticosteroids to achieve full resolution of the flare, but this is likely to lead to glucose spikes, which may take some time to resolve. In the later stages of type 2 diabetes, these glucose spikes can have catastrophic consequences.

In this group, prophylactic macrolides may play an important role in optimising long-term glycaemic control.

## Cardiac arrhythmias

Macrolides have long been associated with the risk of QTc prolongation and arrhythmia when prescribed, an association that is higher in those with underlying cardiac risk factors and who have multiple comorbidities requiring polypharmacy. A cohort study screening QTc changes in 47 patients with COPD showed 38 patients (80.1%) had at least one contraindication to azithromycin prophylaxis. These included pre-existing QTc prolongation, congestive cardiac failure diagnosis, and prescribed medications that may interact with azithromycin.<sup>9</sup> Taking this into account, a baseline echocardiogram and review of patient medications and comorbidities should be considered before prescribing macrolide prophylaxis.

## CONCLUSION

COPD is a complex syndrome that requires nuanced management in the community to prevent recourse to tertiary care. Prophylactic macrolides are a useful adjunct to traditional inhaled therapies to reduce the frequency of exacerbations in patients with mild-to-moderate disease, but there is insufficient evidence for their ability to reduce exacerbations leading to hospital admissions in severe disease. With most patients being managed in the community with mild-to-moderate disease, they could be best placed to benefit from the introduction of macrolides from their primary care physician.

The efficacy of macrolides in patients with asthma suggests that patients with COPD–asthma overlap syndrome may benefit more than patients with more traditional phenotypes. Their use as a steroid-sparing agent in type 2 diabetes should not be underestimated, but, in the significant proportion with underlying cardiac arrhythmias, the risks associated with QTc prolongation must be considered. Ultimately, the GP will be able to weigh up the risks and benefits of this therapy because of their close and longstanding relationship with the patient.

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