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CLINICAL FOCUS: PULMONARY AND RESPIRATORY CONDITIONS
REVIEW

Immunomodulatory indications of azithromycin in respiratory disease: a concise review for the clinician

Cassondra L. Cramer, Allie Patterson, Abdulrazak Alchakaki and Ayman O. Soubani

Division of Pulmonary, Critical Care and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI, USA

ABSTRACT

Azithromycin has a well-characterized bacteriostatic activity. However, it also has a robust immunomodulatory effect that has proven beneficial in a variety of chronic illnesses. This effect results in decreased production of pro-inflammatory cytokines in the acute phase and promotes resolution of chronic inflammation in the later phases. Specifically, azithromycin has direct activity on airway epithelial cells to maintain their function and reduce mucus secretion. These characteristics have resulted in the use of azithromycin in the management of a variety of chronic lung diseases including chronic obstructive pulmonary disease, cystic fibrosis (CF), non-CF bronchiectasis, bronchiolitis obliterans syndrome, diffuse panbronchiolitis, and asthma. In this review, we present the evidence supporting the role of azithromycin in these conditions with an emphasis on the clinical aspects for the practicing physician.

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1. Introduction

Macrolide antibiotics have been used extensively for a variety of respiratory pathogens due to their good oral availability, and broad activity against a variety of gram-positive and -negative lung pathogens [1]. Interest in nonantibiotic uses of macrolides began with treatment of diffuse panbronchiolitis in the 1980s and since has grown to include several chronic respiratory conditions. It was discovered in studying erythromycin use in diffuse panbronchiolitis that certain macrolides possess immunomodulatory functions, relating to decreased airway secretions [2] and reduced production of pro-inflammatory cytokines [3,4]. The focus of current research in immunomodulatory actions of macrolides has shifted to azithromycin, which is widely used for a variety of indications, and has a better side effect profile [5] (Table 1). The purpose of this review is to examine the clinical indications for azithromycin immunomodulatory use in a variety of chronic lung conditions, such as diffuse panbronchiolitis, cystic fibrosis (CF), non-CF bronchiectasis, chronic obstructive pulmonary disease (COPD), asthma, and posttransplant bronchiolitis obliterans syndrome (BOS). The risks and benefits will be reviewed for each condition, and the reviewer will understand current clinical practice regarding azithromycin immunomodulatory use.

2. Mechanism of action

2.1. Antibiotic effects

Macrolide antibiotics like azithromycin exhibit bacteriostatic activity by inhibiting protein synthesis through disturbance of the 50S large ribosomal subunit and subsequent interruption of protein synthesis [6]. Azithromycin is notable among the macrolide class for its lack of inhibition of CYP3A4 and its high cellular accumulation, particularly in phagocytes where azithromycin accumulation is 200-fold higher compared to serum [7]. Subsequently, high concentrations of azithromycin are targeted to sites of infection and inflammation [8]. Finally, azithromycin reduces biofilm growth of bacteria such as *Pseudomonas aeruginosa* by impairing quorum-sensing signals [9].

2.2. Immunomodulatory function

Beyond the simple bacteriostatic function of azithromycin lies its well-studied immunomodulating activity (Figure 1). These effects can be described as an acute phase of inhibition of inflammation and a late phase of resolution of chronic inflammation. In the acute phase, azithromycin use has been shown to decrease production of pro-inflammatory cytokines, such as IL-8, GM-CSF, IL-6, MMPs, and TNF-α [10–13]. These cytokines serve to signal neutrophils, macrophages, and other phagocytic cells to the site of inflammation [12]. In the late phase, azithromycin has been shown to decrease the oxidative burst of neutrophil killing cycle, and increase neutrophil apoptosis [14]. In the study by Murphy et al. [10], azithromycin diminished T helper-1 cell (Th-1) responses following lipopolysaccharide activation of alveolar macrophages, largely through modulation of the pro-inflammatory cytokine signals already described. This effect serves to shift the inflammatory milieu to favor anti-inflammatory phenotype of Th-2 cells, which promotes healing and repair following inflammation [15].

CONTACT Ayman O. Soubani asoubani@med.wayne.edu

Table 1. Common upper and lower respiratory indications of azithromycin.

Antibacterial indications
– Acute bacterial sinusitis
– Acute bacterial otitis media
– Pharyngitis, tonsillitis
– Acute exacerbation of chronic bronchitis
– Community-acquired pneumonia
– *Mycobacterium avium* complex prophylaxis (and part of treatment regimen)
Immunomodulatory indications
– CF
– Diffuse panbronchiolitis
– Posttransplant BOS
– Non-CF bronchiectasis
– COPD

Azithromycin's role in this process can be explained by its inhibition of the transcription factor nuclear factor-kappa B, which functions to activate transcription of many pro-inflammatory cytokines, including IL-8 [16]. Thus, the many immunomodulating effects of azithromycin treatment serve to reduce acute inflammation and to promote long-term healing and repair.

2.3. Clinical effects

Understanding the biochemical processes affected by azithromycin hint at the implications for its usage in medicine. Azithromycin has a role in many organ systems but its employment in pulmonary diseases has been particularly well characterized. Azithromycin acts directly on airway epithelial cells to reduce airway secretions, decreasing mucus formation and increasing the integrity of the airway epithelium [17]. Azithromycin has also been studied in several pulmonary diseases characterized by chronic inflammation. COPD is one such disease where azithromycin has made some impact. Cells from sputum samples of COPD patients which have been treated with azithromycin have shown to exhibit decreased pro-inflammatory cytokine release [18], as well as improved alveolar phagocytosis of apoptotic polymorphonuclear cells [19], thereby promoting resolution of inflammation. In a similar way, azithromycin has revolutionized the treatment of diffuse panbronchiolitis and shows promise in the treatment of BOS [15]. CF airway epithelial cells are characterized by a higher production of IL-8 and a heightened response to bacteria [20], making it a prime target for therapy with azithromycin, and indeed azithromycin exerts a benefit for CF patients as well. In other bronchiectatic diseases, azithromycin has a special role in reduction of biofilm growth, likely mediated by interruption of quorum-sensing proteins [21]. The combination of the immunomodulatory effects of reduced acute inflammation and promotion of healing and repair, plus the pulmonary effects of reduced mucus production and increased airway epithelium integrity, explains the basis for the variety of benefits observed.

3. Disease-specific indications

3.1. Cystic fibrosis

CF is a disease characterized by a constellation of symptoms but the involvement of the upper and lower airways has the greatest impact on quality of life and survival. It is postulated that repeated respiratory infections and impaired mucociliary clearance contribute to the picture of chronic inflammation in CF [22]. Sputum biomarkers show a neutrophil predominance in CF, and the observed decline in lung function is likely due to pro-inflammatory cytokines and inflammatory cell recruitment promoted by neutrophils [23]. *P. aeruginosa* is a common pathogen in later stages of CF, which exerts its virulence by altering cell permeability and secreting mucin, along with several other pro-inflammatory cytokines [24]. *P. aeruginosa*

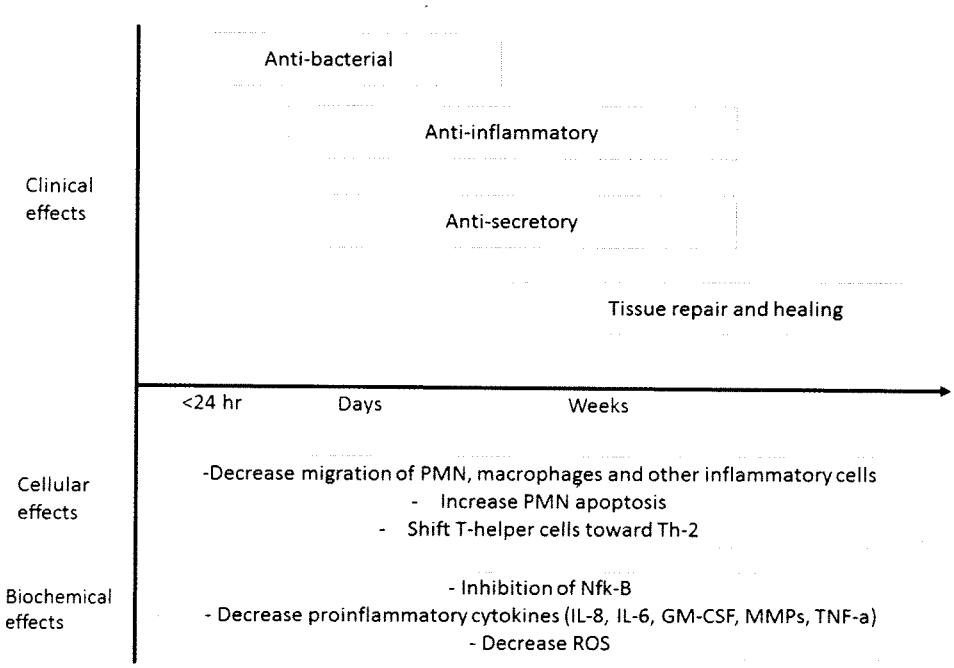

Figure 1. Proposed timeline for the elements involved in the bacteriostatic and immunomodulatory actions of azithromycin.

adapts to the harsh environments of CF by a biofilm form of growth that is very difficult to eradicate with antibiotics [25].

The immunomodulatory properties of azithromycin make it a prime therapy for CF [26]. In the case of *P. aeruginosa* infection, azithromycin reduces mucin secretion and biofilm formation, as well as increases *P. aeruginosa* susceptibility to other antibiotics [27]. Additionally, a recent Cochrane review identified five studies including 549 patients showing that azithromycin therapy versus placebo demonstrated an improvement in FEV1 (mean difference at 6 months was 3.97% with 95% confidence interval (CI): 1.74–6.19) [28]. In one of the included studies, this difference in FEV1 (forced expiratory volume in one second) equated to be 0.097 L improvement with azithromycin treatment at 6 months [29]. Patients in these studies were approximately free from pulmonary exacerbation about twice as long as control patients (odds ratio 1.96, 95% CI: 1.15–3.33) [28]. Most of the studies included in the review used a three-times-weekly azithromycin dosing schedule where individuals <40 kg received 250 mg and those >40 kg received 500 mg. Not only do more severe CF patients with *P. aeruginosa* infection benefit, patients with CF who are not infected with *P. aeruginosa* also experience lower rate of exacerbations, decreased antibiotic use, and increased weight gain [29]. Prolonged treatment with azithromycin has not been proven to be beneficial. In fact, in the study done by Samson et al., treatment benefits began to decline with greater than 12 months of therapy and at 36 months of therapy, the rate of exacerbations and improvements in FEV1 are similar to pretreatment levels [30]. However, current practice recommendations from the Cystic Fibrosis Foundation advocates for the use of chronic azithromycin for CF patients aged ≥6 years or older with persistent *P. aeruginosa* airway cultures to improve lung function and reduce exacerbations (level of evidence – fair) [31].

3.2. Diffuse panbronchiolitis

Diffuse panbronchiolitis is a disease characterized by bronchiolitis and chronic sinusitis. It is mainly described in patients of Asian descent, but has also been rarely reported in patients from other races [32]. Without the appropriate treatment, the disease is fatal. The etiology of diffuse panbronchiolitis is not known; however, genetic factors may play a role. It is characterized by the presence of chronic inflammatory infiltrates by lymphocytes, plasma cells, and histiocytes involving all the respiratory bronchioles (diffuse) and all layers of the bronchiolar walls and peribronchial tissue (pan) [32]. The symptoms including persistent cough, dyspnea, and purulent sputum mimic other common respiratory diseases, so diagnosis of diffuse panbronchiolitis is based upon multiple criteria such as diffuse nodular shadows on chest x-ray, pulmonary function as a measurement of FEV1/FVC (forced vital capacity) <70% and PaO_2 < 80 mmHg, and course crackles on physical exam [33]. While some cases of diffuse panbronchiolitis are complicated by bacteria, most commonly *P. aeruginosa*, macrolides have been shown to improve lung function even when no bacteria are cultured from sputum samples, presumably because of the immunomodulatory functions of the drug [32]. According to a review by Lin et al., only one randomized controlled trial has been published that used a macrolide to treat diffuse panbronchiolitis, and the study had limitations both in the design and in the small number of participants, which rendered the results unreliable for creating guidelines [34]. There have, however, been numerous case reports and retrospective studies which have shown that macrolides have increased the 10-year survival from <50% before macrolides were introduced to >90% with chronic macrolide therapy in patients with diffuse panbronchiolitis, thereby justifying the current recommendations [35]. Macrolides been the mainstay of treatment for diffuse panbronchiolitis since the retrospective study by Kudoh et al. showed that erythromycin treatment is associated with marked symptomatic improvement, and importantly patients with this therapy are living longer [36].

Earlier studies on the benefits of macrolides in the management of diffuse panbronchiolitis were primarily using erythromycin. However, given its side effect profile and daily dosing, there has been more interest in the azithromycin as a therapeutic alternative. A retrospective study by Hui et al. indicated that out of the 29 case studies of patients with diffuse panbronchiolitis using azithromycin 500 mg once daily for at least 1 year, 28 showed improvement in pulmonary function testing and high-resolution computed tomography scans [37]. A larger retrospective study of 51 cases of diffuse panbronchiolitis indicated that azithromycin had a comparable survival rate to erythromycin in addition to the statistically significant improvement in FEV1 and PaO_2 after treatment [38]. Therefore, we can conclude that azithromycin is a reasonable option for the treatment of diffuse panbronchiolitis based on its efficacy, mild side effect profile, and infrequent dosing (twice or thrice weekly).

3.3. Posttransplant BOS

BOS is a condition defined as new airflow limitation in the absence of infectious etiology and imaging evidence of bronchiolitis in patients who received allogeneic hematopoietic stem cell transplantation or lung transplant. Histopathology findings of small airway inflammation and scarring are characteristic of BOS [39]. It is manifested on pulmonary function tests with FEV1/FVC <0.7 and drop in FEV1 > 20% from baseline or best following lung transplant [40–48]. BOS occurs in the setting of chronic transplant rejection following almost half of lung transplants in the first 5 years [49] and following 6–20% of allogeneic hematopoietic stem cell transplantation [50]. In lung transplant patients, a meta-analysis by Kingah et al. [40] described a significant improvement in overall lung function with a mean increase in FEV1 of 8.8% (95% CI: 5.1–12.47, $p < 0.001$) after an average follow-up period of 7 months with a pooled hazard ratio (HR) of 0.25 (95% CI: 0.06–0.56; $p = 0.041$). Importantly, they showed a lower mortality in patients who received azithromycin [40]. A randomized controlled study by Corris et al. [41] found that zero patients in the placebo group reached an increase in FEV1 as much as 10%; however, nine patients taking azithromycin had an increase in FEV1 of at least 10% ($p = 0.002$). The contemporary literature supports the current practice of using

azithromycin (250 mg thrice weekly) post lung transplant to reduce decline in lung function and mortality [40,41,50].

In patients with allogeneic hematopoietic stem cell transplantation, BOS can manifest as a form of chronic graft versus host disease [42]. There is interest in what role azithromycin might play in treatment but as of yet, the evidence of azithromycin benefit is still anecdotal. The pooled data from a recent meta-analysis by Yadav et al. showed that azithromycin therapy has neither significant improvement in FEV1, which increased by +30 ml (95% CI: −260 to +330 ml; $p = 0.82$), nor any added mortality benefit. Recently, an analysis of allogeneic hematopoietic stem cell transplantation patients with BOS who were treated with azithromycin-based regimen showed stabilization of FEV1 after diagnosis [43]. There are several limitations to the studies that compiled the analysis above, but in general, the stability of lung function is adequate to recommend the therapy [43–46]. Until further long-term studies measuring quality of life, pulmonary function and outcomes are available, azithromycin-based regimen is favored.

3.4. Non-CF bronchiectasis

Non-CF bronchiectasis is a chronic inflammatory lung condition characterized by irreversible dilatation of the bronchi and bronchioles due to a wide variety of causes including recurrent or old infections, immunodeficiency, autoimmune conditions, connective tissue disease, and idiopathic disease [48]. Repeated infections are associated with a chronic state of inflammation leading to airway dilatation, bronchial wall thickening, and mucus plugging on high-resolution computed tomography, which is the gold standard for diagnosis [51]. While almost all patients experience chronic cough and sputum production, recurrent bacterial infections lead to a decline in lung function and a poor prognosis, especially when complicated with *P. aeruginosa* [52]. Many treatment options used in the management of CF aimed at symptom control have been applied to patients with non-CF bronchiectasis, such as inhaled recombinant deoxyribonuclease, hypertonic saline, mucolytic agents, bronchodilators, and exercise; however, none of these have been proven to reduce the frequency of exacerbations [53,54]. Macrolides, on the other hand, have shown benefit in both CF and non-CF bronchiectasis [53].

Non-CF bronchiectasis has suffered from a lack of clinically proven treatment options, but two major randomized controlled trials have studied the effect of azithromycin in the disease with good outcomes [54]. The EMBRACE study examined patients who had at least one pulmonary exacerbation requiring antibiotics in the past year and showed that by taking 500 mg of azithromycin 3 days a week for 6 months, exacerbations were reduced by 62% ($p < 0.0001$) [55]. This difference was maintained for 6 months following the treatment period at 42% reduction in exacerbations ($p < 0.0001$) [55]. The number needed to treat (NNT) to prevent one exacerbation in 12 months is 5 [55]. The BAT study included more severely affected patients with three pulmonary exacerbations requiring antibiotics and one positive sputum culture in the last year and they found that by taking azithromycin 250 mg daily for 12 months, the NNT to prevent one exacerbation in 12 months was reduced to 3 [56]. In addition to the significant decrease in exacerbations, this trial showed an increase in FEV1 by 1.03 every 3 months while taking azithromycin ($p = .047$) and an increase in quality of life compared to those taking placebo ($p = .046$), as measured by St. George's Respiratory Questionnaire [56]. The current evidence suggests that azithromycin decreases the frequency of exacerbations, improves lung function, and quality of life in patients with non-CF bronchiectasis who have at least one exacerbation in the past year [56].

3.5. Chronic obstructive pulmonary disease

COPD is a major public health problem that is characterized by long-standing pulmonary inflammation. Acute exacerbations of COPD (AECOPD) are a major source of patient mortality and healthcare expenditure [57]. Each year, up to one-third of patients diagnosed with COPD experience an exacerbation, which is not only a major source of patient mortality and reduced quality of life but also accounts for a large percentage of the costs associated with treating COPD [58,59]. Prevention of AECOPDs is therefore of utmost importance. Several studies have shown benefits in prophylactic use of azithromycin to reduce AECOPDs; a recent meta-analysis by Ni et al. [60] includes 1614 participants and shows that prophylactic long-term macrolide treatment significantly reduced the exacerbations in comparison with the control group (relative risk [RR] = 0.70; 95% CI: 0.56–0.87; $p < 0.01$).

Two of the studies described in the meta-analysis include Albert et al. [61] who included patients aged 40 and older with at least one exacerbation, and Uzun et al. [62] who included patients aged 18 and older and with at least three exacerbations. Both papers showed a benefit in these patient populations, with Albert et al. describing an increased median time to first exacerbation in the azithromycin group compared to placebo (266 days compared to 174 days, respectively $p < 0.01$) and fewer exacerbations per patient, with the NNT to prevent one exacerbation calculated at 2.86 [61]. Even in the very severe COPD patients requiring tracheostomy studied by Blasi et al. [63], there was a decreased rate of exacerbations and hospitalizations with azithromycin prophylaxis. Importantly in these studies, the effects were realized with treatment of 250 mg daily azithromycin over the course of 1 year, this differs from earlier studies that reported conflicting results regarding prophylaxis and evaluated treatment at shorter time courses. In conclusion, prophylactic long-term azithromycin therapy may decrease the frequency of AECOPD in selected patients with frequent exacerbations despite optimal maintenance inhaler therapy [59–63].

3.6. Sepsis and acute respiratory distress syndrome (ARDS)

Given the extensive research into the role of azithromycin in chronic inflammation, it is not surprising that interest has grown in studying azithromycin in systemic inflammatory conditions such as sepsis and ARDS. Both sepsis and ARDS are common conditions in any intensive care unit and represent a high mortality for the patient. They are characterized by a major activation of inflammatory mechanisms with systemic

involvement. Walkey et al. demonstrated a mortality benefit for patients who received macrolide antibiotics within 24 h of identifying acute lung injury (HR = 0.46; 95% CI: 0.23–0.92; p = 0.028), as well as a shorter time to discontinuation of mechanical ventilation (HR = 1.93; 95% CI: 1.18–3.17; p = .009) [64]. This effect is echoed in a study by Kawamura et al. who showed that in patients with sepsis-related ARDS, azithromycin use was associated with a lower 60-day mortality and a shorter time to discontinuation of mechanical ventilation [65]. Further studies are needed to explore the role of azithromycin in these conditions and document whether the benefits reported are related to its immunomodulatory properties.

3.7. Asthma

There was also interest in use of macrolides in management of asthma given it is an inflammatory airway disease and there is evidence in some patients of a chronic infection by atypical bacterial infection such as *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. A meta-analysis of seven studies failed to show benefit for this purpose [66]. A recent study of adding azithromycin to the standard treatment of asthma found no clinical benefit [67]. At this time, there is minimal evidence to support the use of azithromycin in this patient population. Similarly, azithromycin is not recommended in the management of patients with chronic rhinosinusitis with no confirmed or suspected infection [68].

3.8. Non-respiratory indications for azithromycin

Although the focus of this review is on the indications of azithromycin for chronic pulmonary diseases, it deserves mention that the antibiotic and immunomodulatory properties of aizthromycin have important applications in several other diseases. For example, azithromycin prophylaxis in doses of 1200 mg weekly reduces the risk of disseminated *Mycobacterium avium* complex in patients with acquired immunodeficiency syndrome [69]. Azithromycin, like erythromycin, possess the same motilin agonist properties that make it a suitable treatment for gastroparesis [70]. Finally, there has been extensive historical interest in the association between *C. pneumoniae* infection and atherosclerosis and the potential role for antibiotic treatment to prevent coronary artery disease. In a large trial, this question was examined using weekly azithromycin dosing for 1 year and there was no mortality benefit associated with this treatment [71].

4. Adverse effects and precautions

Chronic use of azithromycin therapy is not without its drawbacks. As would be expected, bacterial resistance increases substantially with chronic antibiotic use. A meta-analysis of six trials was done studying the effects of azithromycin therapy in chronic lung diseases such as asthma, COPD, and CF, which showed that the risk of bacterial resistance was 2.6 times higher in the treatment group (RR = 2.59; 95% CI: 1.294–5.31; p = 0.007) [5]. In one study of pediatric patients with CF, macrolide-resistant strains of *Staphylococcus aureus* increased to 83% in the first year of therapy, 97% in the second year, and 100% in the third year after azithromycin was initiated [72]. Also, patients at increased risk for nontuberculous mycobacterial infections, such as patients with CF, should be screened for these infections prior to starting and during chronic azithromycin treatment to avoid inducing resistant mycobacteria [73]. In view of the concern for increasing antibiotic resistance, exciting new research is being done studying azithromycin analogues that possess comparable immunomodulatory properties without antibiotic activity [74].

Unsurprisingly, the side effects commonly reported with macrolide antibiotics are often reported with long-term azithromycin therapy. Gastrointestinal discomfort has a well-known association with macrolides [75] and is a commonly cited reason for why study participants cannot tolerate the drug. Hearing decrement was observed in the study conducted by Uzun et al. [62] in COPD patients treated with azithromycin for 1 year compared to placebo (25% vs. 20%, respectively, p = 0.04), which partially resolved upon discontinuation of the drug.

Macrolide antibiotics have a known side effect of QTc prolongation. It is thought that erythromycin and clarithromycin have a stronger effect, although recent reports have certainly linked azithromycin to QTc prolongation as well [76–78]. Ray et al. conducted a comprehensive observational study of patients in the Tennessee Medicaid program and showed that patients taking azithromycin were two to three times more likely to experience cardiovascular death compared to controls [77]. However, this formidable statistic has been called into question by many because of the high percentage of comorbid conditions in the study population. In a subsequent study, Svanstrom et al. examined a population of Danish adults aged 18–64 and showed no associated increased risk of cardiovascular death in patients treated with azithromycin compared to penicillin V (RR = 0.93; 95% CI: 0.56–1.55) [78]. What is missing from both of these studies is a review of the cardiovascular risks of chronic azithromycin treatment, for in both cases the risks were studied in patients receiving a 5-day treatment course. More research is needed to fully understand the cardiovascular risks associated with azithromycin, but it seems that for patients who have a higher baseline risk of cardiovascular death, caution is indicated.

Azithromycin is a generally well-tolerated antibiotic; however, given the potential adverse effects, chronic treatment should be individualized and benefits weighed against potential risks. Also, patients should be monitored during treatment for any of the aforementioned adverse effects.

5. Conclusion

In addition to its bacteriostatic effects, azithromycin has significant immunomodulatory properties. Due to the acute effects of reduced production of pro-inflammatory cytokines and longer-term effects of resolution of ongoing inflammation, azithromycin has a role in conditions ranging from sepsis to lifelong conditions like CF. For many of the conditions described in this review, azithromycin has shown to improve patient survival, lung function, quality of life, and healthcare expenditure. Knowledge of the immunomodulatory and long-

term indications, as well as potential adverse effects and precautions of this medication, is important for the contemporary healthcare provider.

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Declaration of interest

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